Pioneers of Egyptian Cardiology

الأستاذ الدكتور حسن عز الدين

الجليسة إلى أوراقنا أكتب نبذة عن رجل من أحب الناس إلى قلبي. الرجل الذي يرحل كثيرون ولكنه ترك إرثًا لا يتركه إلا قليلون... أستاذ دكتور حسن عز الدين كمن بعده عندما نسب نفسه إليه. وكمن أقدر أن أنساب إليه وأشعر بصماليته في عمله وفي شتى نواحي حياتي. لقد تعلمت منك إن الأستاذ ليس وظيفته في سلك الوظائف ولكن الأستاذ هو المعلم وهو الببراس والملك الأعلى.

لقد عهد الجميع فيك ثلاث خصال جعلتك مثلًا للأستاذ الجامعي كما ينبغي أن يكون هو الأنتظام والصداقة وحب المعرفة. الأنتظام بالمعايير الأخلاقية للطبيب. الأنتظام بالمناهج العلمية والقواعد الطبية الأساسية. الأنتظام في الوعود والأنتظام في الموعد وهي جملة تبني عليها الحضارات. أما الصداقة فكانت مفتاح شخصيته والمصداقيته هي الأمانة هي حفظ الكلمة هي الوقوف إلى جانب الحق وعدم المحاباة وأعطاء الأولوية للمصلحة العام. ولهذا نستطيع أن نقول إنك من أثراء الفي بحارنا ثم نستطيع أن نقول إنك من أثراء الفي بحارنا ثم نستطيع أن نقول إنك من فكره. وضعك من عروقنا إن الدكتور حسن عز الدين كان رجلاً مشهورًا له بالأنتظام والمصداقيه والأمانة شغفًا بالمعرفة والقراءة في شتى المجالات لم يعتلي بعضاته.


القسم الذين يكونون ولد وفاته برغم قصر الفترة التي عاشوها فيها.
يقول عنه الأستاذ الدكتور على رمزى والذي كانت تتميز علاقته خاصه وصداقه قديمه بالدكتور حسن. كان حسن عز الدين شخصية فريده بحق، عملنا معه معا منذ أن كنا أطباء مقيمين بالقسم كان حسن عز الدين زميلنا وصديقا فريدا في نفقاته وامانته. كانت له أبحاث عديدة في حالات ارتفاع ضغط الدم الشريان الرئوي وكان معظمها في هذا الوقت نتجت للبيروسي. بدأ اهتمامه بقضية القلب في منتصف السبعينيات وأعطى جهدًا كبيرًا لأجروا معمل قسطرة القلب الأول بالمستشفى ودرب الكواذر الأولى للقسطرة والرعاية المركزة في أوائل السبعينيات.

يقول عنه الأستاذ الدكتور مختار جمعه كان للدكتور حسن عز الدين معرف معه متدت بعدا عن الطب وكان متحدثا جدًا يقص الكثير من الطرائف والمواقف ل ولم ان تجلس تستمع إليه.

أما المهندس كمال علام الصديق الأقرب للأستاذ الدكتور حسن عز الدين فيقول "كان د. حسن عز الدين صديق عمري، عرفته منذ أول يوم داخلنا في رياض الأطفال بمدرسة المحلة بمصر الجديدة ونشأت صداقة قوية منذ ذلك الحين أي منذ ما يقرب من 25 عاما إلى يوم وفاته الذي كنت بجانبه لحظتها. لم نتفق أبدا طوال هذه الفترة... منذ رياض الأطفال والمدرسة الأبتدائية والثانوية بمصر الجديدة. انضم إلى كلية الطب وأنا لهندسه، تفوق في مجاله وتفوق أيضاً في مجاله حيث أنه من الأشخاص الذين إذا قرأني نيج وإذا درس متفوق وإذا لجأت إليه يتفانى في خدمته.

وتقول عن شبكة حياته زوجته أ.د. شا خليل "كان حسن عز الدين يرتسم بالطيبه الفائقة بارغم من مظهره الجاد فكان حنواً إلى أقصى درجة على عائلته ومرضاه وأصدقائه مراياً للصلة الرحم وكان دائما يردد قول رسول الله (ص) "إن الله يحب إذا عمل أحدكم عملاً أن يتقنها".

إن الأستاذ الدكتور حسن عز الدين شخص لا يستقل من ذاكرتك بمجرور الوقت فإن مرضاه مع أكثر من شعر بمرارة فراقه وكانوا دائما يذكرون لي أنه ليس من السهل إشباعه بطبيب آخر. أول مرة جلست بجواره في عيادته وهو يكشف على أحد مرضاه لنصحته النصيحة التي لا يمكن أن تنساه "كن أمينا دائما مع مرضيك ولا تكذب عليه أبدا ولا تخجل أن تقول لا أعلم أن كنت لا تعلم". إن ذكرت بإذن كنت أحد تلاميذه وإن الأشياء التي غرسها في تعلمه حياً ستشكل. وأرجو من الله أن أستطيع أن أتلق ولع ببعضها من أجالي قادم.

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Coronary Flow in Patients with Coronary Artery Ectasia and the Effect of Intravenous Nitroglycerin on Flow as Assessed by Transoesophageal Echocardiography

TAREK M KHAIRY ABD EL-DAYEM, MD*; WAEL M EL-NAMMAS, MD*; AHMED M EL-MAHMOUDY, MS*; MONA MOSTAFA RAYAN, MD*; RAMZY H EL-MAWARDY, MD*

**Background:** There is no consensus about the etiology, pathophysiology, prognostic significance and morbidity related to coronary artery ectasia (CAE).

**Aims:** We sought to assess basal coronary flow in patients with coronary artery ectasia and to study the effect of intravenous nitroglycerin on coronary flow using transesophageal echocardiography (TEE).

**Patients and Methods:** Forty subjects were consecutively included in the study, all underwent elective coronary angiography. Subjects were divided according to the result of elective coronary angiography into two groups; group I: included 30 patients with documented CAE without stenosis in the left anterior descending coronary artery (LAD) and group II: included 10 subjects with angiographically normal coronaries (this served as a control group). All subjects underwent TEE using pulsed wave Doppler to measure peak systolic and diastolic velocities (m/sec), systolic, diastolic & total velocity time integrals (cm) and the systolic, diastolic & total coronary blood flow (cm/min). All subjects subsequently underwent re-assessment of the previous parameters after intravenous injection of 0.3 mg (300µgm) of nitroglycerin (NTG).

**Results:** Patients with CAE were younger with male predominance and the incidence of diabetes mellitus was significantly low among them. No statistically significant difference was found between the two study groups as regards baseline systolic, diastolic & total velocity time integrals. A statistically higher systolic, diastolic and total basal coronary blood flow was found in group I compared to group II (46.09±34.33 versus 23.05±8.21, 123.98±73.33 versus 68.06±21.6, 170.07±97.88 versus 91.10±26.82, respectively, *p* value <0.05). In group I intravenous injection of NTG caused a statistically significant decrease in peak diastolic velocity, systolic, diastolic & total velocity time integrals and a statistically significant decrease in diastolic & total coronary blood flow. Meanwhile, in group II, intravenous injection of NTG caused a statistically significant increase in total coronary blood flow. The percent increase in cross sectional area after NTG was higher in group II.

**Conclusion:** Ectatic coronary arteries are more common in the young and are uncommonly associated with diabetes. They are characterized by a higher basal coronary flow as compared to normal arteries. Intravenous administration of nitroglycerin causes significant reduction of flow parameters in ectatic coronary arteries, as opposed to its augmentation of flow in normal coronary arteries.

**Key Words:** Coronary artery ectasia – Coronary flow – Vasodilators – Transoesophageal echo – Diabetes.
Patients and Methods

Forty patients were included in the study, who underwent elective coronary angiography at Ain Shams University Hospital, within the period between February 2006 and February 2008.

Patient Selection: Patients were divided into two groups:

Group I: Included 30 patients with angiographically documented pure ectasia without stenosis in the left anterior descending coronary artery (LAD). Ectasia was defined as luminal dilatation 1.5 times that of the adjacent angiographically normal coronary artery segment or the diameter of the corresponding coronary artery of the control group if there was no normal segment [1].

Group II: Included 10 subjects with angiographically normal coronaries (This served as a control group).

Exclusion criteria:
1- Contraindications to TEE such as: esophageal or pharyngeal obstruction, esophageal varices or diverticulae, suspected or known perforated viscus, gastrointestinal bleeding, oro-pharyngeal distortion, instability of cervical vertebrae, cervical arthritis, bleeding diathesis or over anticoagulation (defined as INR >5 or PTT >100 sec, platelets <50,000/ mm$^3$), or uncooperative patient.
2- Improper visualization of the LAD by TEE.
3- Patients with coronary artery stenosis in the examined artery.

Methods:
All the patients included in the study were subjected to:
1- Thorough history taking with emphasis on coronary risk factor distribution (age, gender, smoking, hypertension, diabetes mellitus, dyslipidemia, family history for coronary artery disease), symptoms suggestive of ischemic heart disease and contraindications for TEE.
2- Careful clinical examination.
3- Twelve lead surface ECG.
4- Trans-esophageal echocardiography (TEE):

Echocardiographic study was performed using a Vivid Five system (Vingmed Technology, USA) cardiac ultrasound machine. A 5MHz multi-plane phased-array probe was used to obtain 2D views and Doppler measurements. The probe was introduced till about 30 cm from the incisor teeth at which level the aortic cusps could be seen (basal short axis view at the level of the aortic valve). It was withdrawn slowly till the opening of the left main coronary artery was clearly visible. Fine adjustments with rotation and flexion were made to obtain an optimal image of the left anterior descending coronary artery. The opening of the left main coronary artery could be seen at the 2 o’clock position of the aortic ring. The bifurcation of the left main coronary artery was usually Y-shaped, with the left circumflex artery appearing as a continuation of the left main coronary artery, and the left anterior descending coronary artery lying in a plane almost perpendicular to that of the left main & left circumflex coronary arteries.

* Measurement of the diameter of the examined artery (in cm) by 2D was done.

* The pulsed wave sample volume was placed over the proximal portion of the LAD and the direction of the sample volume was made as parallel as possible to that of the LAD then spectral recording of the flow velocity was made and the following parameters were calculated:
  1- Peak systolic velocity (m/sec).
  2- Peak diastolic velocity (m/sec).
  3- Systolic velocity time integral (cm).
  4- Diastolic velocity time integral (cm).
  5- Total velocity time integral (cm).

* The coronary blood flow (systolic, diastolic & total) was calculated using the following formula: Coronary cross section area x Velocity time integral x heart rate (Fig. 1).

* Intravenous injection of nitroglycerin (NTG) 0.3 mg bolus was injected via a large bore cannula.

* Heart rate, blood pressure and all previously mentioned measurements were reassessed within 5 minutes after the injection of NTG (Fig. 2).

* At the end of the procedure the probe was inspected for any bites, washed with running water, then immersed in Cidex® for 20 minutes then rewarshed again with running water. The patient was followed up for half an hour to monitor blood pressure and heart rate before transfer to the ward or discharge.

Statistical analysis:
Data were collected, verified and revised. Categorical variables were expressed as their absolute and relative frequencies (percentage), while con-
Continuous variables were presented as mean values ± standard deviation. Comparisons were made between the 2 groups using the t-test for continuous variables and the chi square test & Pearson correlation coefficient for categorical variables.

Statistical analysis was performed using statistical package for social sciences (SPSS) version 12. Differences were considered statistically significant at a p value <0.05 level and highly significant at a p value <0.001.

Results

The mean age of the study group was 48.55±7.95 years. Thirty nine patients were males (97.5%). Twenty two patients (55%) were hypertensive, nine patients (22.5%) were diabetics and twenty seven patients (67.5%) were smokers. Dyslipidemia was documented in ten patients (25%) and six patients (15%) had positive family history for premature coronary artery disease. The baseline characteristics of the whole cohort and the two study groups are shown in Table (1). The two study groups were comparable as regard age, sex, risk factors for coronary artery disease, with no statistically significant difference between them.

When the two groups were compared as regards HR (bpm) and BP, before and after, nitroglycerin injection, no statistically significant difference was found as shown in Table (2).

Table (3) presents baseline Doppler flow velocity data recorded for the 2 study groups. There was no statistically significant difference between both groups as regards peak systolic and diastolic velocities or systolic, diastolic & total velocity time integrals.

A statistically higher systolic, diastolic and total coronary blood flow was found in group I than group II (46.09±34.33 versus 23.05±8.21,
Coronary Flow in Patients with Coronary Artery Ectasia

123.98±73.33 versus 68.06±21.6, 170.07±97.88 versus 91.10±26.82, respectively, *p* value <0.05).

In group I intravenous injection of nitroglycerin caused a statistically significant decrease in peak diastolic velocity, systolic, diastolic & total velocity time integrals and in diastolic & total coronary blood flow (Table 4, Fig. 3).

Meanwhile, in group II, intravenous injection of nitroglycerin caused a statistically significant increase in total coronary blood flow, while changes in other parameters did not meet statistical significance, (Table 5, Fig. 4).

### Table 2: Comparison of vital signs of the two groups before and after nitroglycerin injection.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total cohort</th>
<th>Group I (N=30)</th>
<th>Group II (N=10)</th>
<th><em>p</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BP before NG:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>122±20.72</td>
<td>119±16.63</td>
<td>&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>77.33±10.48</td>
<td>73.62±9.49</td>
<td>&gt;0.05</td>
<td></td>
</tr>
<tr>
<td><strong>HR before NG (bpm)</strong></td>
<td>87.07±19.33</td>
<td>93.90±18.86</td>
<td>&gt;0.05</td>
<td></td>
</tr>
<tr>
<td><strong>BP after NG:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>124±22.72</td>
<td>120±16.63</td>
<td>&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>78.45±10.48</td>
<td>75.22±9.49</td>
<td>&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>HR after NG (bpm)</td>
<td>90.67±16.71</td>
<td>96.10±20.72</td>
<td>&gt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3: Comparison between the two study groups as regards Doppler parameters.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I (N=30)</th>
<th>Group II (N=10)</th>
<th><em>p</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak systolic velocity (m/sec)</td>
<td>0.22±0.11</td>
<td>0.22±0.09</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Peak diastolic velocity (m/sec)</td>
<td>0.39±0.15</td>
<td>0.47±0.14</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Systolic velocity time integral (cm)</td>
<td>3.01±1.89</td>
<td>2.79±1.20</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Diastolic velocity time integral (cm)</td>
<td>8.24±4.31</td>
<td>8.56±4.75</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Total velocity time integral (cm)</td>
<td>11.26±5.54</td>
<td>11.37±5.69</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Systolic coronary blood flow (cm³/min)</td>
<td>46.09±34.33</td>
<td>23.05±8.21</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diastolic coronary blood flow (cm³/min)</td>
<td>123.98±73.33</td>
<td>68.06±21.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Total coronary blood flow (cm³/min)</td>
<td>170.07±97.88</td>
<td>91.10±26.82</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

### Table 4: Comparison of Doppler parameters in group I before and after nitroglycerin injection.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I Basal</th>
<th>Group I after nitroglycerin</th>
<th><em>p</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak systolic velocity (m/sec)</td>
<td>0.22±0.11</td>
<td>0.20±0.10</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Peak diastolic velocity (m/sec)</td>
<td>0.39±0.15</td>
<td>0.29±0.14</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Systolic velocity time integral (cm)</td>
<td>3.01±1.89</td>
<td>2.45±1.52</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diastolic velocity time integral (cm)</td>
<td>8.24±4.31</td>
<td>5.88±3.83</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Total velocity time integral (cm)</td>
<td>11.26±5.54</td>
<td>8.33±4.74</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Systolic coronary blood flow (cm³/min)</td>
<td>46.09±34.33</td>
<td>43.19±30.55</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diastolic coronary blood flow (cm³/min)</td>
<td>123.98±73.33</td>
<td>105.58±78.02</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Total coronary blood flow (cm³/min)</td>
<td>170.07±97.88</td>
<td>148.81±98.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
Figure 3: Comparison of Doppler parameters in the coronary artery ectasia group before and after nitroglycerin injection.

Figure 4: Comparison of Doppler parameters in group II (angiographically normal coronaries) before and after nitroglycerin injection.

PSV = Peak systolic velocity.
PDV = Peak diastolic velocity.
SysVTI = Systolic velocity time integral.
DiasVTI = Diastolic velocity time integral.
TotVTI = Total velocity time integral.
SysFLOW = Systolic flow.
DiasFlow = Diastolic flow.
TotFLOW = Total flow.
Coronary Flow in Patients with Coronary Artery Ectasia

Table 5: Comparison of Doppler parameters in group II before and after nitroglycerin injection.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group II Basal</th>
<th>Group II nitroglycerin</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak systolic velocity (m/sec)</td>
<td>0.22±0.09</td>
<td>0.21±0.06</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Peak diastolic velocity (m/sec)</td>
<td>0.47±0.14</td>
<td>0.40±0.19</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Systolic velocity time integral (cm)</td>
<td>2.79±1.20</td>
<td>2.468±7.77</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Diastolic velocity time integral (cm)</td>
<td>8.56±4.75</td>
<td>8.05±5.22</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Total velocity time integral (cm)</td>
<td>11.37±5.69</td>
<td>10.52±5.39</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Systolic coronary blood flow (cm³/min)</td>
<td>23.05±8.21</td>
<td>27.43±8.16</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Diastolic coronary blood flow (cm³/min)</td>
<td>68.06±21.60</td>
<td>87.86±45.93</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Total coronary blood flow (cm³/min)</td>
<td>91.10±26.82</td>
<td>115.30±46.75</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Discussion

The main coronary angiographic characteristics of CAE are delayed antegrade coronary dye filling, segmental back flow phenomenon (milking phenomenon) and stasis with local deposition of dye in dilated coronary segments [3].

Several studies have evaluated the traditional cardiovascular risk factors profile in patients with CAE.

In this study all CAE patients were males and relatively young. This finding is concordant with Giannoglu et al (2006), who reported a male dominance in patients with CAE [4]. This gender difference was reported previously and was supposed to be due to the lower incidence of CAD in women, although the relation between CAE and CAD is not fully understood [4-6]. Moreover, the higher likelihood of males having CAE compared to women is generally consistent with a study in Spain in which male gender was demonstrated as an independent factor that increased the hazard of CAE [7].

Age was shown to constitute a significant factor that is inversely associated with the presence of CAE [4]. A similar finding of significantly younger age among patients with CAE as compared to those without, was previously described [7,8]. This finding is contradicted by the study of Markis et al (1976), who reported comparable sex and mean age in patients with CAE and patients with stenotic CAD [9].

In the present study, nineteen patients were smokers, hypertension was found in sixteen patients and dyslipidemia was found in eight patients. These data agree with the study of Gardiner and Lindop (1989), who reported that hypertension and dyslipidemia were implicated in the pathogenesis of CAE [10]. Bermudez et al, (2003) reported that smoking was more common in patients with CAE than in those with stenotic CAD [7].

Diabetes mellitus is a well known risk factor positively associated with coronary atherosclerosis and its complications [11,12]. In the current study, diabetes mellitus was found in 20% of CAE patients. This is concordant with the studies of Bermudez et al, (2003) and Androulakis et al, (2004) who reported a significant independent and inverse association between CAE and diabetes mellitus [7,13]. Supporting this inverse association, demographic data have been provided in studies confirming a low prevalence of diabetes in CAE patients [14]. It may be reasonable to expect such an inverse association between diabetes mellitus and CAE, because diabetes mellitus is known to promote negative remodeling in the arterial wall and to impair compensatory arterial enlargement during the course of the atherosclerotic process [15].

In the present study, there was no statistically significant difference at baseline between both groups as regard peak systolic and diastolic velocities. These data are concordant with Akyurek et al, (2003) who found that peak velocities of coronary blood flow at baseline were similar in both ectatic and normal vessels with lower resting blood flow velocity in patients with isolated CAE [1].

However, our results are discordant with Mavrogeni et al, (2005) who found that controls had significantly higher peak flow velocity and lower TIMI frame count in both RCA and LAD as compared to patients with CAE. This difference may be explained by the use of different modalities for assessment of coronary artery flow [16].

In the present work there was a significantly higher resting coronary blood flow (systolic, diastolic and total) in ectatic vessels. This finding is...
concordant with Akyurek et al who found volumetric coronary blood flow was significantly higher in the CAE group than in their control group [1].

Occurrence of ischemia despite higher resting coronary blood flow in CAE patients could be explained by several possible pathophysiologic mechanisms:

1- The larger lumen causes a conversion from laminar to turbulent coronary flow in the dilated segments [17].

2- Decreased blood flow velocity according to Hagen-Poiseuille’s law: (blood flow velocity decreases with an increasing vessel diameter).

However, this physical law is valid only in the case of laminar flow of a homogeneous fluid [18].

3- Increased viscosity; blood has specific flow properties (Reynold’s law); which means that below a critical blood flow velocity, viscosity increases leading to erythrocyte aggregation and/or activation of platelets and the coagulation system with possibly distal resultant microembolization [19].

4- Lower coronary flow reserve, possibly due to impaired production of NO. This has been demonstrated by intracoronary administration of papaverine, which is a potent hyperemic stimulus, the coronary flow reserve was 1.51 in CAE compared with 2.67 in control arteries, suggesting endothelial and/or microvascular dysfunction as the cause of myocardial ischemia [1].

In this study, the intravenous injection of nitroglycerin in patients with coronary artery ectasia caused statistically significant decreases in peak diastolic velocity, velocity time integrals (systolic, diastolic & total) and in diastolic & total coronary blood flow and a non statistically significant decrease in peak systolic velocity and systolic coronary blood flow. These findings are in agreement with Kruger et al, (1999) who found that nitroglycerin leads to an aggravation of exercise-induced coronary ischemia and is therefore of no therapeutic benefit [3]. This finding is not concordant with Kim et al, (2006) who found that the value of Fractional Flow Reserve (FFR) in patients with CAE was not reduced through the injection of nitrates. However, their study was conducted on only 10 patients [21].

The significant decrease in diastolic and total blood flow despite an increase in measured cross-sectional area (CSA) could be explained by the significantly higher percent increase of CSA in patients with normal coronaries. Dunker et al, (1995) previously reported that the magnitude of arterial dilatation is inversely correlated to the baseline diameter [22]. Other possible mechanisms, are the impaired production of/or response to nitric oxide, or to the destruction of the arterial media in patients with CAE proposed by Aksoy et al, (2006), leading to impaired arterial responsiveness [23].

Conclusion:

This study shows that, compared to stenotic coronary arteries, CAE is more common in the young, and less common in diabetic patients.

Intravenous administration of nitroglycerin causes significant reduction of flow parameters in ectatic coronary arteries, as opposed to its augmentation of flow in normal coronary arteries. Ectatic coronary arteries are characterized by a relatively higher basal coronary flow as compared to normal arteries, but with impaired reserve.

Thus the routine use of nitroglycerin in CAE patients should be avoided, due to the potential for worsening of myocardial perfusion.

Limitations:

The use of Doppler flow wire to assess coronary flow is a more established method; however this would have eliminated the possibility of measuring volume of flow [20]. TEE evaluation of coronary flow reserve has been validated previously. On the other hand, using TEE limited the inclusion of CAE patients due to the necessity of LAD affection. This resulted in the elimination of a large number of patients with isolated ectasia of the RCA.

References


Coronary Flow in Patients with Coronary Artery Ectasia


Coronary Artery Ectasia: Clinical, Echocardiographic and Angiographic Characteristics (Cardiovascular Department, Catheterization Laboratory, Mansoura University)

HELMY M BAKR, MD; EID M DAoud, MD; AHMED W SOLIMAN, MD; MAGED Z AMER, MD; NADER EL-SHAHAT, MD; AYMAN A ABD-ELAZIZ, MD; WAEL R RIFAIE, MD

Background: Coronary artery ectasia (CAE) is defined as a discrete or fusiform arterial dilatation with a diameter of at least 1.5 times the diameter of an adjacent normal coronary segment. CAE is an uncommon finding with estimates of its incidence varying from 1.2 to 4.9% in large angiographic series.

Objectives: To investigate the prevalence as well as different clinical, echocardiographic and angiographic characteristics of the patients with CAE in Mansoura Cardiovascular Department, Catheterization Laboratory.

Patients and Methods: A retrospective study enrolled 900 patients gathered from Mansoura Medical Specialized Hospital, Cardiology Department, Cardiac Catheterization Laboratory at the period between June 2007 and July 2008. They were classified according to presence or absence of ectasia into 90 patients with angiographic evidence of ectasia of one or more of coronary arteries (group I) and 810 patients without angiographic evidence of such pathology, 208 patients with normal coronary angiography were excluded from our study, the remaining 602 patients with angiographic evidence of atherosclerotic lesion(s) considered as group II. Both groups underwent the followings: Thorough history, physical examination, 12 lead ECG, laboratory, echocardiographic and angiographic examination.

Results: Nine hundred patients underwent coronary angiography and 90 patients of these presented with CAE which represent a prevalence of 10%. There was more prevalence of diabetes among CAE group (42.2% versus 37.5%) when compared with group II, also there was significant increase in SWMA in group I than group II (p=0.001). The RCA artery was most frequently affected (30%) followed by LAD (25.6%), LCx (17.7%) and LMCA (7.8%), diffuse ectasia was found in 17 patients (18.9%). Multivariate logistic regression analysis revealed the age, male sex, presence of diabetes mellitus are independent predictors of presence of coronary artery ectasia.

Conclusion: The prevalence of coronary artery ectasia in patients referred for angiography in Mansoura cardiovascular department catheterization laboratory from June 2007 to July 2008 was 10%. Coronary artery ectasia was prevalent in male sex and associated with classic risk factors especially diabetes mellitus which was independent predictor for presence of CAE.

Key Words: Coronary artery ectasia – Angiography – Diabetes mellitus – SWMA.
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by atherosclerotic plaque. Dilatation of the artery can be severe enough to disrupt the normal flow patterns, leading to delayed filling, segment backflow, turbulence and blood pooling. These arteries are subjected to thrombus formation, spasm and intracoronary dissection, leading to myocardial infarction in up to one third of cases [5].

Patients and Methods

This retrospective study enrolled 900 patients gathered from Mansoura Medical Specialized Hospital Cardiology Department, Cardiac Catheterization Laboratory at the period between June 2007 and 2008. They were classified according to presence or absence of ectasia into 90 patients with angiographic evidence of ectasia of one or more of coronary arteries (group I) and 810 patients without angiographic evidence of such pathology, 208 patients with normal coronary angiography were excluded from our study, the remaining 602 patients with angiographic evidence of atherosclerotic lesion(s) considered as group II. Both groups underwent the followings:

1- Through history taking and physical examination with special emphasis on the age, sex, special habits, history of hypertension, diabetes and dyslipidemia.

2- 12 lead electrocardiographic recording with special emphasis on ST elevation and depression, ST-T changes and basic rhythm.

3- Basic laboratory profiles especially CPK-MB fraction, SGOT SGPT, INR and total cholesterol.

4- Echocardiographic Doppler study:
All patients had undergone 2 dimensional echo Doppler studies in the periangiography period according to American society of echocardiography guidelines [6] to assess for left atrial diameter (LAD), left ventricular end systolic (LVESD) and end diastolic dimensions (LVEDD), ejection fraction (EF), global LV systolic function and presence or absence of systolic wall motion abnormalities (SWMA).

5- Coronary angiography:
Left heart catheterization and coronary angiography were done according to guidelines described elsewhere using standard Judkin left and right coronary catheters and percutaneous femoral approach [7].

Patients with marked concentric LVH and advanced chronic renal impairment were excluded from the study.

Statistical analysis:
Statistical analysis was done using computer software SPSS version 12. Data were expressed as mean & standard deviation. Parametric 2 unrelated samples student t test was done for two group’s comparison assuming normally distributed values of the corresponding variables in every group studied. Spearman rank correlation coefficient was calculated to analyze univariate correlation between two variables at a time. Multivariate logistic regression was done for variable that showed significant correlation with coronary artery ectasia by univariate analysis.

Results

Nine hundred patients underwent coronary angiography and 90 patients of these presented with CAE which represent a prevalence of 10% (Fig. 1).

Clinical characteristics:
Clinical characteristics of patients with and without CAE appear in Table (1) & Fig. (2).

More prevalence of diabetes and smoking among CAE group (42.2% Vs 37.5%, p=0.007) and (65.5% Vs 44.2%, p=0.001) respectively.

No statistically significant difference between both groups as regard prevalence of hypertension, dyslipidemia and family history of CAD.

Patients with CE showed a lower prevalence of prior revascularization, whether by PCI (7.7% Vs 15%, p<0.001) or CABG (2.2% Vs 5.1%, p=0.01).

Laboratory findings:
Significant increase of CPK and CPK-MB among group I when compared with group II (Table 2).
**Echocardiographic characteristics:**

As shown in Table (3) & Fig. (3) there were no significant differences between both groups as regard ARD and LAD.

Significant increase in LVESD, LVEDD & SWMA in group I than group II.

**Angiographic characteristics:**

Twenty nine patients (32.2%) presented with CE but without significant stenotic lesions to coronary arteries. In contrast, results of the coronary angiograms indicated that most patients with CE (68.8%) presented significant stenosis in one, two or three coronary arteries.

The RCA artery was most frequently affected (30%) followed by LAD (25.6%), LCx (7.7%) and LMCA (7.8%), diffuse ectasia was found in 17 patients (18.9%) (Table 4 & Fig. 4).

Multivariate logistic regression analysis revealed the age, male sex, presence of diabetes mellitus were independent predictors for presence of CAE (Table 5).

---

**Figure 1:** Classification of patients according to presence or absence of CAE and angiographic significant lesion.

**Table 1:** Clinical characteristics of studied groups.

<table>
<thead>
<tr>
<th></th>
<th>Patients with CAE (n=90)</th>
<th>Patients without CAE (n=602)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>55.6±7.9</td>
<td>50.9±8.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Male</td>
<td>73 (81.1%)</td>
<td>447 (74.2%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168.5±5.9</td>
<td>166.5±6.3</td>
<td>0.444</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.5±7.7</td>
<td>77.5±7.5</td>
<td>0.515</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.9±1.7</td>
<td>27.9±1.8</td>
<td>0.446</td>
</tr>
<tr>
<td>HR (B/min)</td>
<td>82.4±8.1</td>
<td>80.9±11.0</td>
<td>0.971</td>
</tr>
<tr>
<td>Smoking</td>
<td>59 (65.5%)</td>
<td>266 (44.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HPN</td>
<td>54 (60%)</td>
<td>353 (58.6%)</td>
<td>0.433</td>
</tr>
<tr>
<td>DM</td>
<td>38 (42.2%)</td>
<td>226 (37.5%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>43 (47.7%)</td>
<td>298 (49.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Family history</td>
<td>10 (11.1%)</td>
<td>71 (11.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>History of angina (S &amp; US)</td>
<td>56 (62.2%)</td>
<td>364 (60.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>History of Myocardial infarction (MI)</td>
<td>34 (37.8%)</td>
<td>238 (39.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>7 (7.7%)</td>
<td>87 (14.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>2 (2.2%)</td>
<td>31 (5.1%)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**BMI** = Body mass index.  
**HR** = Heart rate.  
**HPN** = Hypertension.  
**DM** = Diabetes mellitus.  
**S** = Stable.  
**US** = Unstable.  
**PCI** = Percutaneous coronary intervention.  
**CABG** = Coronary artery bypass graft.
Coronary Artery Ectasia

**Figure 2:** Risk factors difference between both groups.

**Table 2:** Laboratory findings of studied groups.

<table>
<thead>
<tr>
<th></th>
<th>GP I (n=90)</th>
<th>GP II (n=602)</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine</td>
<td>0.98±0.24</td>
<td>1.0±0.22</td>
<td>3.4</td>
<td>0.064</td>
</tr>
<tr>
<td>INR</td>
<td>1.19±0.14</td>
<td>1.2±0.18</td>
<td>1.37</td>
<td>0.242</td>
</tr>
<tr>
<td>CPK</td>
<td>182.1±49.9</td>
<td>166.0±29.69</td>
<td>9.4</td>
<td>0.002</td>
</tr>
<tr>
<td>CPK-MB</td>
<td>22.5±9.1</td>
<td>19.2±6.9</td>
<td>17.7</td>
<td>0.000</td>
</tr>
<tr>
<td>LDH</td>
<td>431.8±90.9</td>
<td>399.6±82.5</td>
<td>1.7</td>
<td>0.193</td>
</tr>
<tr>
<td>Cholesterol (Total)</td>
<td>195.2±29.4</td>
<td>193.1±33.1</td>
<td>20.2</td>
<td>0.156</td>
</tr>
</tbody>
</table>

**Table 3:** Descriptive and comparative analysis of some echocardiographic variables between coronary artery ectasia (group I) and non ectasia (group II) groups.

<table>
<thead>
<tr>
<th></th>
<th>M ± SD</th>
<th>M ± SD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARD</td>
<td>3.24±0.651</td>
<td>3.22±0.638</td>
<td>0.735</td>
</tr>
<tr>
<td>LAD</td>
<td>3.97±0.909</td>
<td>3.97±0.884</td>
<td>0.965</td>
</tr>
<tr>
<td>LVEDD</td>
<td>5.38±0.75</td>
<td>5.19±0.76</td>
<td>0.042</td>
</tr>
<tr>
<td>LVESD</td>
<td>3.73±0.74</td>
<td>3.4±0.69</td>
<td>0.004</td>
</tr>
<tr>
<td>SWMA</td>
<td>0.49 ±0.5</td>
<td>0.29±0.45</td>
<td>0.001</td>
</tr>
</tbody>
</table>

ARD = Aortic root diameter.
LAD = Left atrial diameter.
LVEDD = Left ventricular end diastolic diameter.
LVESD = Left ventricular end systolic diameter.
SWMA = Segmental wall motion abnormalities.

**Table 4:** Frequency distribution of coronary artery ectasia involving different tritiorities in studied patients (n=90).

<table>
<thead>
<tr>
<th>Tritiority</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>LM</td>
<td>7</td>
<td>7.8</td>
</tr>
<tr>
<td>LAD</td>
<td>23</td>
<td>25.6</td>
</tr>
<tr>
<td>LCx</td>
<td>16</td>
<td>17.7</td>
</tr>
<tr>
<td>RCA</td>
<td>27</td>
<td>30</td>
</tr>
<tr>
<td>Diffuse</td>
<td>17</td>
<td>18.9</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td>100</td>
</tr>
</tbody>
</table>

LM = Left main.
LAD = Left anterior descending.
LCx = Left circumflex.
RCA = Right coronary artery.

**Table 5:** Multivariate logistic regression analysis of some variables related to coronary artery ectasia.

<table>
<thead>
<tr>
<th></th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.000</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.000</td>
</tr>
<tr>
<td>HTN</td>
<td>0.934</td>
</tr>
<tr>
<td>DM</td>
<td>0.006</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.408</td>
</tr>
<tr>
<td>Family history (1)</td>
<td>0.455</td>
</tr>
</tbody>
</table>

**Figure 3:** Echocardiographic variables between coronary artery ectasia (group I) and non ectasia (group II) groups.

**Figure 4:** Distribution of coronary artery ectasia involving different tritiorities in studied patients (n=90).
Discussion

The prevalence of CAE in the literature varies between 1.2-6% regardless of associated coronary artery stenosis [8-10].

In our study the prevalence of CAE was higher (10%), similar to the result of Sharma et al, who found an incidence as high as 10-20% in an Indian population this may be due to different demographic characteristics of the patients [11].

The prevalence of isolated CAE in our study was 3.2% which is higher than the prevalence (0.1-0.79%) found by Ceik et al [12].

Given that the mechanism that causes CAE is not clearly understood, it is important we investigate the risk factors in these patients which could influence the appearance of this condition. In our series, after correction for other variables, male sex, age and diabetes mellitus were the only variables independently associated with CAE.

Patients with CAE are predominantly men and in our study they represent 81.1% of all cases. Also, patients with CAE were predominately smoker (65.5%).

Sudhir et al [13] found a higher prevalence of CAE in patients with a family history of high blood cholesterol. In our study percentage of hyperlipidemia (47.7%) and hypertension (60%) were high, but similar to those of patients with ischemic heart disease and without CE, which is consistent with other findings [14].

Pinar et al [15] reported minimal prevalence of diabetes among patients with CE. The percentage was especially low among those with CE but without lesions (3%). It was also low among patients with CE and coronary artery stenosis (28%). In both cases, it was significantly lower than among patients without CE this is not easily explained.

In contrast to these data, in our study diabetes was more prevalent in CAE patients when compared to patients without CAE (42.2% Vs 37.5%) (p=0.007).

Coronary artery ectasia seems to be a distinctive form of coronary artery atherosclerosis [16], caused by the action of different risk factors based on a genetic predisposition. This would lead to initial endothelial damage activating a series of inflammatory mediators (macrophages, metalloproteins, etc) that cause degeneration of the medial layer of

Figure 5: Different angiographic views showing: (A) Ectasia of left main and proximal LAD & LCx, (B) Ectasia of RCA with stenotic lesion in the distal segment, (C) Diffuse ectasia of the RCA.
Coronary Artery Ectasia

the vessel. These structural alterations, together with the action of nitric oxide and other vasodilators, lead to a dilatation of the coronary artery: An extreme form of a positive remodeling [17,18].

Our findings can be explained by the fact that diabetic patients tend to develop a more aggressive, involved form of atherosclerosis [19].

We can probably add to these risk factors the existence of a certain genetic predisposition, as men make up more than 80% of the patients with CAE. Studies that enable us to clarify this genetic factor and explain the exact mechanisms that cause CE are needed.

Prior revascularization was significantly lower in group with CAE and this may have a variety of causes. We recognize that the population was relatively young, that most patients had only recently been diagnosed, that they had undergone coronary angiography for the first time and that CE had been diagnosed through this procedure. However, in some cases medical treatment would have been chosen as they represented with non-significant stenosis or diffuse conditions. These results are similar to the results found by Pinar et al [15].

In some previous studies, the RCA was reported to be the most commonly involved vessel, whereas others reported the LAD to be the main involved vessel [15]. In our study, RCA was the most commonly involved vessel followed by LAD, LCx, LM and diffuse ectasia in descending order.

Since the commonest cause of coronary artery ectasia is atherosclerotic process we hypothesize that the more prevalence SWMA in coronary artery ectasia is due to the double morphologic pathology. Combining ectasia and atherosclerotic narrowing of coronary artery involved.

Another possible explanation is that the ectatic segment act as a compliant distensible balloon that steel part of coronary blood flow by distension in response to the coronary perfusion pressure.

A third possible explanation is that the swirling and slow blood flow in the ectatic segment is associated with tendency to thrombus formation, distal embolizations in the coronary tree producing areas of stunned and necrotic myocardium.

Study limitations:

It is difficult to estimate the prevalence of CE in the population at large. The descriptive nature of our research, based on a series of patients referred to coronary angiography for different reasons did not enable us to establish the real prevalence of CE given that it probably exists in forms that are barely symptomatic or even asymptomatic and which therefore are not studied angiographically.

The present study also has the disadvantages of retrospective studies and we were not able to complete follow-up data adequately. Exercise testing and perfusion scans were not available for all the patients. Data on drugs received by the patients and the impact of the drugs on clinical outcomes was not available. Also, the number of patients was relatively small and a larger study is needed to reach a major conclusion.

References

Introduction

Acute coronary syndromes (ACS) are a major health problem and represent a large number of hospitalizations annually. Clinical criteria have been developed to allow the clinician to make timely decisions and to choose the best treatment based on risk stratification and a targeted approach to intervention.

The approved strategy in these cases is to alleviate ischemia and symptoms and to observe the patients using serial electrocardiograms, repeated measurements of myocardial necrosis markers (troponin and CK-MB) and to initiate appropriate therapy if the diagnosis is confirmed [1].

Vascular endothelial growth factor (VEGF) is a potent endothelial cell-specific angiogenic mitogen, which is secreted from cells exposed to hypoxia. Therefore, VEGF has been proposed as the most likely candidate in ischemia-induced collateral vessel formation, particularly in conditions such as ACS [2].

VEGF is a critical mediator of ischemia and hypoxia-induced angiogenesis. VEGF is regulated by hypoxia at the level of its steady-state mRNA due to both an increase in the transcription rate of
the VEGF gene and to an increase in the stability of its mRNA [3]. For this reason it was suggested that VEGF may have some favorable effect on cardiac remodelling after myocardial infarction.

C-reactive protein (CRP), a sensitive, non-specific marker of inflammation, is unique among the major plasma proteins because its levels appear to be unaffected by hormones and anti-inflammatory drugs. Its level in blood increases in ACS (unstable angina and acute myocardial infarction) and is associated with an adverse outcome regarding both the in-hospital and long-term prognosis [4].

Stress echocardiography is commonly used as a non-invasive imaging modality for the evaluation of ischaemic heart disease. In patients with acute myocardial infarction, it has been used to identify residual viable tissue and predict improvement of function over time [5].

The aim of this work is to determine the level of VEGF & CRP in patients with acute coronary syndrome and to study the impact of these two markers on predicting the prognosis in those patients by using dobutamine stress echocardiography.

**Patients and Methods**

This study included 70 subjects, (30) normal subjects as control group, and (40) patients presented by ACS (18 patients with ST elevation myocardial infarction (STEMI) and 22 patients with Non STEMI).

Exclusion criteria includes patients who were subjected to coronary artery bypass graft or percutaneous transluminal coronary angioplasty [6], patients treated from acute myeloid leukemia and myelodysplastic syndrome [6], patients who were suffering from acute infectious disease [7] and bronchial asthma [8], diabetic patients [8], postmenopausal females maintained on hormone therapy [9], patient maintained on statin for long time [10], patients who were subjected to renal transplantation or has chronic renal diseases [11], and all patient suffering from malignancies and autoimmune diseases [12].

**Methods:**

The subjects of control group were apparently healthy people who were matched for age and sex to the study group. They were selected on the basis of clinical examination, resting ECG and echocardiography, serum levels of VEGF and C-reactive protein were also measured for those subjects.

Diagnosis of patients with acute coronary syndrome was based on full history taking, clinical examination, resting ECG, cardiac enzymes and echocardiography.

1- **Full history taking:** With special consideration to coronary risk factors assessment as regards to age, sex, smoking, dyslipidemia and hypertension. Detailed analysis of the current chest pain was done as regards: the onset of chest pain, its character and duration and the referring areas.

2- **Clinical examination:** Pulse, blood pressure were measured and patients who were hemodynamically unstable were identified. Also, heart and chest were auscultated to identify the presence of any murmur or crackles.

3- **ECG:** Electrocardiograms were recorded immediately, patients with acute myocardial infarction were diagnosed on the basis of presence of elevated ST segment, i.e. new ST segment elevation at J point with the cut-off points >0.2 mv in V₁ through V₃ and >0.1 mv in other leads. Patients without ST-segment elevation, i.e ST-segment depression or T wave abnormalities, were identified and were followed up by serial ECG and cardiac enzymes [13].

4- Patients who were diagnosed as cases of ACS were admitted to coronary care unit, serial cardiac enzymes (CPK, CK-MB and Troponin) were done to diagnose myocardial infarction. The patient received the recommended medical treatment according to diagnosis. Thrombolytic therapy was given when indicated and also if there were no contraindications.

5- All patients were followed up for in hospital mortality, morbidity and occurrence of complications throughout their hospital stay as: occurrence of reinfarction in which recurrent chest pain occurred associated with ST segment elevation and re-evaluation of CKMB, presence of heart failure in which basal rales were heard over the lung bases covering more than 50% of the lung field, or if gallop rhythm was heard on the apex or death.

6- **The following investigations were performed for all patients enrolled in this study:**

A- Blood sugar, total cholesterol level, HDL cholesterol, LDL cholesterol and triglycerides.
B- VEGF-165 levels were assayed by ELISA technique using commercial kit "Accucyte: Human VEGF-165" provided by Cytimmune Sciences Inc College Park, Maryland, 20740 USA, and we followed the protocols recommended by the manufacturer. Blood samples were taken during the first day, and on the 7th day after the onset of the acute attack. The collected samples were left for 1 hour at temp. 37ºC and then serum stored at –20ºC till time of assay. The reference value of normal population for VEGF is recorded as 0.78 ng/ml or less and the range of detection was 0.78 ng/ml to 200 ng/ml.

C- CRP levels were assayed by ELISA technique using the commercial kit "Active C-reactive protein ELISA, DSL-10-42100" provided by Diagnostic Systems Laboratories Inc, Webster Texas USA, and the protocols recommended by the manufacturer was followed. The DSL-10-42100 active CRP ELISA is an enzymatically amplified "two-step" sandwich-type immunoassay. The reference range of the assay is 0.025-1.6 mg/dL.

D- Dobutamine stress echocardiography:
Individuals of patient group who passed the period of admission with no complication were subjected to dobutamine stress echocardiography to evaluate viability and contractility of ischemic myocardium. Dobutmaine was administered intravenously by an infusion pump, starting at a rate of 5 µg/kg/min and increasing every 3 min to 10, 20, 30 up to a maximum of 40 µg/kg/min under continuous electrocardiographic and echocardiographic monitoring. Blood pressure was measured at baseline and at the end of each stage [14]. Echocardiographic end points that considered as criteria for test positivity were defined as follows: a) new abnormality of wall motion or myocardial thickening in a region with normal resting function (i.e. normokinesia becoming hypokinesia, akinesia or dyskinesia), b) worsening of rest dyssynergy (i.e hypokinesia becoming akinesia or dyskinesia) [15]. Also improvement in the wall motion was recoded i.e. hypokinesia may be changed to normokinesia. Other end-points required termination of the test were the following: peak dobutamine doses with achievement of 85% of target heart rate, severe angina and intolerable symptoms, hypertension (systolic blood pressure >220 mmHg, diastolic blood pressure >120 mmHg), hypotension (relative or absolute <30 mmHg decrease in blood pressure), and ventricular arrhythmias (ventricular tachycardia, frequent polymorphous premature ventricular beats) [16]. Two dimensional echocardiographic images were recorded at baseline, at the end of low and peak dobutamine dose and during recovery (four- stage protocol), using an ESA-OTE ultrasound machine equipped with stress protocol software and quad-screen display format. The studies were compared off line in a cine-loop mode, side by side. Segmental wall motion was assessed using the 16 segment model (the American Society of Echocardiography recommendation), each segment was semi-quantitatively graded as follows: 1= normal (>40 percent thickening with systole), 2= hypokinetic (10 to 30 percent thickening), 3=severe hypokinesis to akinesis (<10 percent thickening)), 4=dyskinesis; and 5=aneurysm. Wall motion score index calculated as follow:

\[
WMSI = (\text{Sum of assigned number}/\text{number of scored segments}).
\]

A normally contracting LV has a WMSI of 1, and the index increases as wall motion abnormalities become more severe [17].

After patients discharge, they were followed up for 6 months and any complications or recurrent attacks of acute coronary syndrome were recorded. After 6 months dobutamine stress echoes were repeated for patients who passed with no serious complication and wall motion score indices were recalculated. The results of the two stress echoes of each patient (stress echo after the attack, and after 6 month) were compared, allowing the patient group to be subdivided into subgroups of improved and non improved patients groups. The initial levels and the 7th day levels of VEGF and CRP were determined and compared in the patients subgroups.

Statistical analysis:
Statistical analyses were carried out with the use of SPSS software version 12 (SPSS Inc, Chicago, IL). The data were collected as mean ± standard deviation; student t-test was utilized for comparing quantitative values, chi-square test and fisher exact test for qualitative values. p-value considered significant if <0.05, highly significant if <0.01, and non significant if >0.05.

Results
This study included 40 patients presented by acute coronary syndrome (18 patients with STEMI and 22 patients with Non STEMI), and 30 apparently healthy subjects as control group. Demographic data were comparable between patients & control group (Table 1).
VEGF and CRP were elevated in all patients with ACS whether STEMI or Non STEMI (2.6±1.1 ng/ml and 7.07±4.7 mg/dl) than in the control group (0.78±0.3 ng/ml and 1.03±0.49 mg/dl respectively) in the first day sample (p=0.000 for both) and also were persistently elevated after 1 week (2.8±1.1 ng/ml and 7.17±6.28 mg/dl versus 0.78±0.3 ng/ml and 1.03±0.49 mg/dl, p=0.000 and 0.002 respectively) (Table 2).

Also it was observed that VEGF levels in some patients with acute coronary syndrome were elevated in the first sample then decreased after one week and in other patients it was higher in the 2nd measurement more than the first one.

Table (3) shows the resting and the peak echo score indices both after the attack (1.6±0.3 versus 1.5±0.2, p=0.023) and after 6 months follow-up (1.7±0.2 versus 1.6±0.4, p=0.08).

**Improved versus non-improved patient subgroup:**

According to the differences between echo score indices, the patients group were subdivided into 22 improved patients and 18 non-improved patient subgroup where the resting and peak echo score indices were significantly increased in non-improved subgroup and decreased in improved patients (Table 4, Figs. 1, 2).

VEGF was non significantly higher in non-improved subgroup on the 1st day, while it was significantly higher in improved subgroup after 7 days (Table 5, Fig. 3).

On the other hand, while CRP was significantly higher in improved subgroup on the 1st day, it became significantly higher in non-improved subgroup 7 days after the attack (Table 5, Fig. 4). So the study showed that patients who improved, had higher levels of VEGF and lower levels of CRP after 1 week.

In the follow-up period 5 patients developed heart failure. There were no significant differences of VEGF in patients with heart failure and control group, but there were a significant differences in CRP between patients with heart failure and control group denoting that absence of a compensatory increase in VEGF levels might have an impact on the prognosis and may affect the power of contractility up to the level of clinical presentation of heart failure (Table 6).
Table 5: Comparison of VEGF and CRP levels on the 1st day and 7 days after the attack between improved and non-improved patient subgroups.

<table>
<thead>
<tr>
<th></th>
<th>Improved Mean ± S.D.</th>
<th>Non-improved Mean ± S.D.</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF at the 1st day</td>
<td>2.4 ± 1.0</td>
<td>2.8 ± 1.3</td>
<td>1.125</td>
<td>0.268</td>
</tr>
<tr>
<td>VEGF after 1 week</td>
<td>3.6 ± 0.7</td>
<td>2.0 ± 0.9</td>
<td>5.953</td>
<td>0.000*</td>
</tr>
<tr>
<td>CRP at the 1st day</td>
<td>9.2 ± 5.8</td>
<td>5.27 ± 2.26</td>
<td>-2.71</td>
<td>0.01*</td>
</tr>
<tr>
<td>CRP after 1 week</td>
<td>5.05 ± 3.14</td>
<td>9.74 ± 7.85</td>
<td>2.57</td>
<td>0.014*</td>
</tr>
</tbody>
</table>

Table 6: Comparison of VEGF and CRP levels between patients with heart failure and control group.

<table>
<thead>
<tr>
<th></th>
<th>Control group Mean ± S.D.</th>
<th>Patients group with heart failure (N=5) Mean ± S.D.</th>
<th>t</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF1 ng/ml</td>
<td>0.78 ± .2884</td>
<td>1.0600 ± .5814</td>
<td>-.736</td>
<td>0.467</td>
</tr>
<tr>
<td>VEGF2 ng/ml</td>
<td>0.78 ± .2884</td>
<td>.9800 ± .4025</td>
<td>-.272</td>
<td>.787</td>
</tr>
<tr>
<td>CRP1 mg/dL</td>
<td>1.03 ± .49</td>
<td>4.16 ± 2.42</td>
<td>-6.769</td>
<td>.000</td>
</tr>
<tr>
<td>CRP2 mg/dL</td>
<td>1.03 ± .49</td>
<td>7.49 ± 4.91</td>
<td>-7.553</td>
<td>.000</td>
</tr>
</tbody>
</table>

1st day sample, 2nd day sample.

Figure 1: Comparison of echo score indices (resting and peak) after the attack and after 6 months in improved subgroup.

Figure 2: Comparison of echo score indices after the attack and after 6 months in non-improved subgroup.

Figure 3: Comparison of VEGF and CRP on the 1st day and after 1 week in improved patients.
In the present study we evaluated the circulating levels of VEGF and CRP in patients with acute coronary syndrome to determine the impact of these two markers on predicting the prognosis in such patients. This study included 40 patients presented by ACS, compared to 30 apparently healthy subjects as control group.

After admission, blood samples were taken in the first day and in the 7th day and VEGF and CRP level were measured.

After patient stabilization, low dose dobutamine stress echo was done to evaluate the myocardial contractility and viability and it was repeated after 6 months for all patients of the study group.

According to the differences between echo score indices, the patients group were subdivided into 22 improved patients and 18 non-improved patient subgroup.

**Value of CRP in acute coronary syndrome:**

The commercial availability of routine assays for CRP has enabled a flood of studies demonstrating a powerful relationship between increased CRP production even within the range previously considered to be normal and the atherothrombotic events. Circulating CRP values correlate closely with other markers of inflammation. However, CRP itself is particularly interesting with respect to cardiovascular biology and pathology, because not only does it bind selectively to LDL but it is actually deposited in the majority of such plaques and it has a range of pro-inflammatory properties that could potentially contribute to the pathogenesis, progression and complications of atheroma [18].

CRP levels were significantly higher after 1 week in non-improved patients subgroup. However in improved patients CRP values were lowered after 1 week than its values during the 1st day.

In the present study the values of CRP were significantly higher in patient group (STEMI and Non-STEMI) than in control group either during the 1st day of the attack and after 7 days.

These results were in concordance with the study of Mohamed, et al (2005) who assessed the association between CRP levels and morbidity and mortality in patients admitted with acute MI and its role in risk stratification of those patients early during in hospital period to identify patients at higher risk. They found that the serum levels of CRP significantly correlated with the occurrence of in hospital major adverse cardiac events [19].

The present study differed from the previous study in measuring CRP level on admission and after 1 week. Also we attempted to evaluate the myocardial contractility during rest and after dobutamine infusion to evaluate myocardial viability.

Another study conducted by Mahmoud, et al (2003) aimed to evaluate levels of CRP in patients with STEMI compared to control subjects and related its level to the extension of acute MI, the response to thrombolytic therapy, left ventricular ejection fraction and post- infarction cardiovascular complication [20].

As in our study they showed that CRP levels on admission were significantly higher in patients than controls. Also, CRP levels were positively

**Discussion**

In the present study we evaluated the circulating levels of VEGF and CRP in patients with acute coronary syndrome to determine the impact of these two markers on predicting the prognosis in such patients. This study included 40 patients presented by ACS, compared to 30 apparently healthy subjects as control group.

After admission, blood samples were taken in the first day and in the 7th day and VEGF and CRP level were measured.

After patient stabilization, low dose dobutamine stress echo was done to evaluate the myocardial contractility and viability and it was repeated after 6 months for all patients of the study group.

According to the differences between echo score indices, the patients group were subdivided

![Figure 4: Comparison of VEGF and CRP on the 1st day and 1 week after the attack in non-improved subgroup.](image-url)
correlated with extent of acute myocardial infarction based on ECG finding and cardiac enzymes, age of patients and history of pre-infarction angina. Predischarge follow-up ejection fraction was inversely correlated with CRP level. So the study concluded that CRP has a strong association with Q-wave AMI supporting the inflammatory basis of acute coronary syndrome.

While the previous study concluded that CRP levels on admission is an independent predictor of reperfusion failure, the present study showed that elevated CRP is related directly to the cardiac response and the underlying atherosclerotic process, and its prognostic value may be broader than the effect on thrombolysis or reperfusion failure as shown by evaluation of myocardial salvage by stress echocardiography.

CRP was also studied for its value in short-term risk stratification in patients with ACS, it was found that serum CRP concentrations predict in hospital deleterious events namely pump failure than mortality. Therefore the additive role played by CRP in emergency room help to identify those liable to reinfarction, pump failure, different forms of arrhythmias or recurrent chest pain that help to identify risky patients who are in need for intensive coronary care monitoring [21]. Therefore by adding these results to our findings, one may conclude that CRP maybe an important tool in short and long term follow-up and long term prognostic evaluation in patients with ACS.

### Value of VEGF in acute coronary syndrome:

In the present study the VEGF levels were significantly higher in patient group (STEMI and Non-STEMI) than in control group either during the 1st day of the attack or after 7 days.

Also it was observed that the VEGF levels were significantly higher in improved patients subgroup either with STEMI or with non STEMI after 1 week, while it were lower in the non improved subgroup.

Coronary angiogenesis, the de novo formation of capillaries and post capillary vessels, and collateral growth, the enlargement of and perhaps increase in numbers of arterial- arterial collateral connections, are chronic coronary adaptations of myocardial ischemia that restore the coronary flow and can prevent or minimize ischemic myocardial injury. Among many growth factors, VEGF, a potent angiogenic factor, has been associated with coronary angiogenesis and collateral growth. In one study, they evaluated the causal role of VEGF in coronary collateral growth during repetitive myocardial ischaemia by systemic inhibition of VEGF via administration of neutralizing antibody against VEGF (Anti-VEGF).

Repetitive ischemia (RI) was introduced by manual inflation of the occluders for coronary arteries of rats which divided into 2 groups. Rats without anti-VEGF (control group) and rats with intraperitoneal anti-VEGF administrations. X-ray micro CT analysis revealed 3-fold decrease in the number of arterial-arterial anastomoses per heart after RI which was prevented by treatment with anti-VEGF. Also, in rats without anti-VEGF, the growth of collateral circulation was functional after the RI protocol as complete coronary occlusion did not induce any untoward effect on hemodynamics or arrhythmias. In the anti-VEGF group, coronary occlusion at the end of the protocol induced many arrhythmias and deterioration of function. In concordance with the present study, the previous study concluded that expression of VEGF is critical to the growth of coronary collaterals although the previous study was done on rats while the present one was done on humans, and also the previous study used anti-VEGF to evaluate the effect of VEGF while the present study measured levels of VEGF and the effect of its different levels on the myocardium [22].

Also, Sang et al (2000) studied ventricular biopsy of patients undergoing coronary bypass surgery. The specimens were examined by light microscopy for evidence of ischemia, evolving infarction, or a normal histologic appearance by a cardiac pathologist. The specimens were also analyzed with the reverse-transcriptase polymerase chain reaction for hypoxia inducible factor alpha (HIFα1) and VEGF messenger RNA expression and by immunohistochemical analysis for the location of the HIF-1α and VEGF protein. The goal of the study was to examine specimens of humans heart tissue affected by various degrees of ischaemic insult and to correlate the physiologic and pathological state of the heart with the temporal and spatial expression of (HIF-1α) and VEGF [23]. They found that, to survive, during periods of stress and ischemia the human heart has developed mechanisms to adapt to change in its environment. One of these mechanisms is the ability to promote growth of new blood vessels into ischaemic areas,
Vascular Endothelial Growth Factor & C-Reactive

thus, limiting the regions of impairment and ultimately preserving myocardial function. In agreement with the present study their results suggested that HIF-1α and VEGF is considered to be an early molecular markers of myocardial ischaemia or infarction as VEGF immunoreactivity was seen in biopsy specimens with evidence of acute ischaemia.

In present study we did not only measure the values of VEGF after ischaemic insults but also we determined its effects on the prognosis of myocardial contractility which was positively correlated with its levels.

On the other hand Chung et al (2003), showed that plasma VEGF levels in the acute MI group were the same as healthy control while significantly higher VEGF levels were found in the chronic MI patients compared to acute MI patients and healthy controls [24].

The present study differs with this opinion in the fact that VEGF could be considered as a biochemical marker of acute coronary insult and also it may be considered as a marker of angiogenesis.

In another study authors attempted to study the levels of VEGF in patients who underwent successful reperfusion therapy by streptokinase for AMI, and by coronary angioplasty (with or without stenting) in patients with unstable angina. Blood samples were obtained from all patients with ACS at initial diagnosis and 20-30 min after successful reperfusion therapy and from all control subjects. They found that serum concentrations of VEGF in all patients were markedly increased before reperfusion compared to those in healthy control subjects and returned almost completely to the normal control range within 20-30 min after reperfusion. Although the results of the present study agree with the results of previous one in the fact that VEGF is markedly elevated in cases of ACS, the previous study reported that VEGF levels returned to normal after interventional therapy, but in the present study the level of VEGF was not affected by different medications. This difference may be due to fact that VEGF was measured at different intervals in the two studies. Also patients treated by PCI were excluded from our study [25].

Patients with ACS were reported to show progressive increase in the level of VEGF from the acute phase reaching its peak at 6 weeks. Therefore VEGF levels may reflect the progressive stages of angiogenetic activity in ischaemic-necrotic myocardium, and the raised VEGF level in the peripheral blood may have pathophysiological relevance to the ischaemic-induced angiogenesis in the myocardium [26]. Although there was no direct evidence in the previous study that increased plasma levels of the measured indices actually reflects the angiogenetic activity in the ischaemic myocardium, in our study the myocardial contractility and its response to dobutamine infusion were evaluated, consequently, VEGF indices in the present study actually can reflect the angiogenetic activity of VEGF in the ischaemic myocardium.

In concordance with the present study, Subodh et al (2004), studied the effect of myocardial ischaemia on endothelial progenitor cells (EPCs) biology in the form of differentiation or mobilization. EPCs were isolated from the peripheral venous blood of healthy male volunteers, cells were cultured in endothelial cell in absence or presence of CRP and or VEGF. EPCs differentiation, survival and function were assayed. They proved that CRP at high concentration directly inhibits differentiation, survival and function of EPC, this occurs along with decreased levels of VEGF [27]. They concluded that systemic inflammation in addition to recognized growth factor could play a role in the peripheral mobilization of EPCs in patient with anginal syndromes. In agreement of this study, our study showed that the levels of VEGF were inversely proportional to levels of CRP in acute ischaemic heart disease and this relationship extended to be reflected on cardiac performance and myocardial contractility.

However, some patients are not suitable candidates for revascularization, including those with diffuse coronary artery disease, microcirculatory impairment or repetitive CABG failure. There is therefore a need to develop alternative treatment strategies for such patients.

Therapeutic angiogenesis and administration of an angiogenic stimulus to promote the growth of collateral blood vessels to provide adequate tissue perfusion is a promising approach for reducing myocardial ischaemia [28]. Initial studies administering basic fibroblastic growth factor (bFGF) as intravascular angiogenetic protein growth factor were however unsuccessful. Although modest benefits were obtained with multiple intracoronary or intravascular administration of VEGF-165, attempts at direct injection of FGF protein into the myocardium of patients during CABG provided some proof of concept with evidence of collateral blood
vessel formation. Gene therapy offers an alternative approach for the delivery of angiogenic proteins allowing more sustained production of the chosen therapeutic protein from a single administration. An adenoviral construct containing the human FGF-5 gene has been successfully tested in ameroid pig model of myocardial ischaemia with significantly improved myocardial blood flow and wall thickening observed and no evidence of hepatic or myocardial toxicity. The AGENT (Angiogenic Gene Therapy) trials were planned to test the clinical efficacy and safety of Ad5FGF-4 in patients. AGENT and AGENT2 were clinical trials assessing safety and efficacy, and have been completed with positive results.

The AGENT study was the first randomized double blind placebo controlled trial of gene therapy in therapeutic coronary angiogenesis to be conducted, and was designed to assess the safety and anti-ischaemic effects by Ad5FGF-4 in patients with stable exertional angina [29].

A total of 79 patients with chronic stable angina were enrolled and randomized to receive either Ad5FGF-4 or placebo. Treatment was administrated via intracoronary infusions through special catheters into each major coronary artery. Efficacy was assessed by measuring the increase in exercise treadmill testing time with assessment at 4 and 12 weeks post-treatment. The results from AGENT were very promising, showing both tolerability and some evidence of efficacy. However, no direct assessment of myocardial perfusion was performed, an issue that would be addressed in subsequent AGENT II trial [28].

The second trial in the AGENT program, AGENT2 was a randomized, double blind, placebo controlled trial in patients with unstable angina CCS class II or III who remain symptomatic despite receiving medication. The primary objective of this study was to determine whether intracoronary administration of Ad5FBF-4 could improve myocardial perfusions compared with placebo. The primary end point in this study was to change in stress-related reversible perfusion defect size (RPDs) as it was assessed by single positron emission computed tomography (SPECT). As with the AGENT trial, the safety of treatment was a paramount concern and an extensive serious safety results showed that the treatment was well tolerated. Also, administration of Ad5FBF-4 resulted in a significant improvement in stress related reversible perfusion defect size (RPDs) relative to baseline 8 weeks in spite of the change in RPDs between Ad5FBF-4 and placebo was not significant [28].

In VIVA trial patients with stable exertional angina, unsuitable for standard revascularization, were randomized to receive placebo, low- dose recombinant human (rh) VEGF or high dose rh VEGF by intracoronary infusion on day 0 followed by intravenous infusion at day 3, 6 and 9. Exercise treadmill test, angina class and quality of life assessments were performed at baseline, day 60 and day 120. Myocardial perfusion imaging were performed at baseline and day 60. At day 60, the changes in exercise treadmill time from baseline were not different between groups. By day 120, placebo treated patients demonstrated no benefit in all 3 measures, with no significant difference compared with low dose rh VEGF. In contrast, high dose rh VEGF resulted in significant improvement in angina class at day 120, as well as favorable trends for exercise treadmill time and quality of life. This may suggest a dose-dependent effect of recombinant VEGF. Concern exists about pathological angiogenesis, such as accelerated growth of malignant tumors, retinopathy, or progression of atherosclerosis with the use of angiogenetic growth factor. Results of this trial indicate excellent short-term safety with rh VEGF [165]. No patients treated with rh VEGF developed cancer or ophthalmological abnormalities [30].

There was no evidence for progression of atherosclerosis by angiography and no deaths or myocardial infarctions in patients treated with rh VEGF according to the previous study. Further assurances of safety will require a larger number of patients treated with longer-term follow-up but the results of this study were encouraging as well as identifying the ideal target population.

Lastly, the present study was a trial to plot partially a biochemical scenario curve of what happens in ACS, what are mediators with and what are mediators against improved outcomes, hoping in future studies for more elucidation aiming to improve quality of life for our patients.

Therefore by using dobutamine stress echo it was found that the higher the values of CRP, the more worse the outcome and the worse the prognosis. On the other hand the higher the levels of VEGF, the better the outcome and the better the prognosis, and that the lower the value of vascular endothelial growth factor, the more worse the prognosis is.
So, this study showed that the measurements of CRP and VEGF have a predictive value in acute coronary syndrome (whether it was ST elevation myocardial infarction or non ST elevation myocardial infarction).

**Conclusion**

The present study showed that VEGF and CRP were significantly higher in patients with ACS than in apparently healthy population, also VEGF and CRP have prognostic value in patients with acute coronary syndrome as it was found that, the higher the value of VEGF and the lower the value of CRP especially after 7 days of the attack, the better the prognosis. VEGF may be upregulated and may play some roles to reduce the damage of ischaemic myocardium by increasing the angiogenetic activity and by potentiating the collateral circulation which was reflected on myocardial performance.

**References**


Laboratory Assessment of Pattern of Platelet Morphology and Function in Patients with Acute Coronary Syndrome

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**Background:** Large platelets are more thrombogenic and thus put the patients at a higher risk status. Mean platelet volume (MPV) is a determinant of platelet functionality and increased MPV is associated with increased risk of myocardial infarction, stroke and transient ischaemic attacks.

**Aim of Work:** Is to evaluate some laboratory parameters of platelet morphology and function in patients with acute coronary syndrome (ACS).

**Subjects and Methods:** They were 38 males and 12 females. These 50 patients with ACS (test group) were subclassified into: Subgroup A (AMI subgroup): Included 34 patients with AMI. They were 28 males with mean age of 55.43 (±10.97) years and 6 females with mean age of 55.67 (±5.5) years. Subgroup B (Unstable Angina subgroup): Included 16 patients with unstable angina. They were 10 males with mean age of 53.1 (±8.39) and 6 females with mean age of 50.17 (±4.54) years. Another group (control group) consisted of 10 healthy individuals, with mean age of 28.67 (±3.64) and 1 female with age of 29 years was also included in the study. All subjects were subjected to thorough history, complete examination, electrocardiography, plain X-ray chest and echocardiography. Also, routine laboratory tests, c-reactive protein, cardiac enzyme were done. Complete blood picture was done for study of platelet count, MPV, platelet distribution width (PDW). Blood film was done for assessment of presence of abnormal platelet morphologies (e.g. microplatelets, giant platelets and aggregate clumps). Photo-optical method for platelet aggregometry done for assessment of maximal aggregation ratio for adenosine diphosphate [MAR (ADP)].

**Results:** Platelet count shows no significant difference between studied groups (p>0.05), MPV and PDW shows significant difference when test group (subgroup A and B) compared with control group (p<0.05) but both variables show no statistically significant difference, when subgroup A compared with subgroup B (p>0.05). MAR (ADP) show significant difference when test group compared to control group (p<0.05). There also significant presence of aggregates clumps in subgroup A (acute MI) when compared to both subgroup B (unstable angina) and control group (p<0.05).

**Conclusion:** Platelet function and morphology showed changes that can be considered as a reflection of the complex structure of the pathogenesis of ACS. Since platelet morphology changes can be assessed more easily, they may be used as a simple and feasible diagnostic method for evaluation of pathogenesis and complications of ACS.

**Key Words:** Platelet morphology & function – Acute coronary syndrome – MPV.

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**Introduction**

Platelets are small discoid anucleate cells 2 to 3μm in diameter. In human they circulate at a concentration of 250,000±100,000 cells/μl of blood. The primary function of platelets is to prevent hemorrhage resulting from defects in blood vessel walls by forming an aggregate at the site of injury. In addition to primary hemostasis, they participate in reactions of blood coagulation, inflammation and wound healing [1].

Much of what is known about platelet function relates to participation of platelets in hemostasis and therefore, the pathophysiologial processes of bleeding disorders due to platelet dysfunction are reasonably well understood. However, the greatest importance of platelets in human disease is in their role in the pathogenesis of atherosclerosis and thrombosis [2].
Acute coronary syndromes (ACS) are the consequence of a build up of pathological events that culminate in myocardial ischemia, myocardial infarction (MI) and death [3]. The immediate precipitating cause is intravascular thrombus formation. The thrombus can be totally or severely obstructive, or be the source of distant embolization of thrombotic material plugging the microcirculation. The inter-myocardial platelet aggregates are found in association with non-occlusive thrombi at pathology in approximately half of the patients with unstable angina dying suddenly [4].

Platelets play a key role in such circumstances. Not only do they react to stimuli from blood and the diseased vessel wall, there is compelling evidence that altered platelet function itself may be pathologically implanted [5].

Functional abnormalities described in platelets from patients with coronary artery disease include increased spontaneous aggregation [6] and increased secretion of beta thromboglobulin, fibrinopeptide A and platelet factor 4 [6,7].

Large platelets are more thrombogenic and thus put the patients at a higher risk status. Mean platelet volume (MPV) is a determinant of platelet functionality and increased MPV is associated with increased risk of myocardial infarction, stroke and transient ischaemic attacks [8].

**Aim of work:**

Is to evaluate some laboratory parameters of platelet morphology and function in patients with acute coronary syndrome.

**Subjects and Methods**

This study comprised 50 patients with acute coronary syndrome admitted to the Coronary Care Unit at Mansoura Emergency Hospital, Mansoura University, in the period between Sept. 2007 and April 2008. They were 38 males and 12 females.

**These 50 patients with ACS (test group) were subclassified into:**

Subgroup A (AMI subgroup): Included 34 patients with AMI. They were 28 males with mean age of 55.43 (±10.97) years and 6 females with mean age of 55.67 (±5.5) years.

Subgroup B (Unstable angina subgroup): Included 16 patients with unstable angina. They were 10 males with mean age of 53.1 (±8.39) and 6 females with mean age of 50.17 (±4.54) years.

Another group (control group) consisted of 10 healthy individuals, with mean age of 28.67 (±3.64) and 1 female with age of 29 years was also included in the study.

**Inclusion criteria:**

The inclusion criteria for this study were adopted according to:

1- Clinical criteria: It include prolonged chest pain (>10min.), anginal pain at rest within 24 hours of randomization, new onset (de novo), severe (Class III of the Canadian Cardiovascular Society Classification) angina, or recent destabilization of previously stable angina with at least CCS III angina characteristics (crescendo angina) [9].

2- ECG criteria (ST deviation criteria): A new ST segment depression of at least 0.1mv or more and/or temporary or persistent T-wave inversion of ≥0.1mv below baseline in at least two contiguous leads [10].

3- Elevated serum cardiac markers (CM and CPK-MB): In patients with AMI.

**Exclusion criteria:**

Patients were excluded from the study if they had:

- Primary myocardial disease.
- Valvular heart disease.
- Advanced renal insufficiency.
- Decompensated hepatic functions.
- Patients with bleeding tendency.
- Patients on oral anticoagulants or antiplatelets.
- Patients with recent or history of cerebral strokes.
- Coronary artery by-pass grafting (CABG) or percutaneous transluminal coronary angiography (PTCA).
- Secondary angina with an identified precipitating factor (e.g., severe anaemia, thyrotoxicosis, heart failure and tachyarrhythmia).
- Pregnancy or lactation.

**Methods:**

All subjects were subjected to the following:

A- Thorough history taking.
B- Clinical examination: General and cardiac.
C- Electrocardiogram (ECG).
D- Plain X-ray chest and heart (posterior and anterior view).
E- Echocardiography.
F- Laboratory investigations:

- Routine laboratory tests: Cardiac enzymes [CK, CK-MB, CK index (=CK-MB/Total CK)] and LDH, serum creatinine, liver function test, ESR, fasting and 2 hours postprandial blood sugar and lipogram.
- C-reactive protein (CRP): Semiquantitative test was done using HUMATEX CRP.
- Complete blood picture: Complete blood picture was done using Sysmex automated hematology analyzer model K1000 (Toa medical electronics Co. Ltd., Japan) for evaluation of:
  - Hemoglobin (Normal value: male 14-18 gm%, female 12-16 gm%).
  - RBCs count (Normal value: Adult male 5.5-5.5 millions/mm³, adult female 4.5-5 millions/mm³).
  - Total leucocytic count (Normal value: 4000-11000/mm³).
  - Platelet count (Normal value 150,000-400,000/mm³).
  - Mean platelet volume (Normal value 7.4-10.4 fl).
  - Platelet distribution width.

- Blood film was prepared from anti-coagulated blood (using EDTA) by the wedge method [12]. The film was then stained with Giemsa stain [13]. The blood film was first scanned at medium power (x20) to confirm reasonably even distribution of leukocytes and check for abnormally large or immature cells in the side and feathered edges of the film. The feathered edge was examined for platelet clumps. The optimal portion of the film was then examined at high power (100x, oil immersion) to systematically assess the size, shape and to determine presence of abnormal platelet morphologies (e.g. microplatelets, giant platelets and aggregate clumps).
- Platelet function assay [14]: Platelet function study was carried on using Photo-optical (turbidometric) method of platelet aggregometry utilizing the chrono-log aggregometer (chrono-log, Havertown, Pa) for assessment of maximum aggregation ratio for adenosine diphosphate [MAR (ADP)].

**Statistical methods for data analysis:**

Data were analyzed with the SPSS (Statistical Package for Social Science) for Windows 10.0.5 software modules (SPSS Inc.). The qualitative data were presented in the form of number and percentage. Chi-square and Chi-square with Yates correction was used as a test of significance for quantitative data. The quantitative data were presented in the form of mean and standard deviation. Comparison between quantitative data were assessed with the non parametric test. Significance was considered when p value less than 0.05, highly significance was considered when p value less than 0.01 and extremely significance when p value less than 0.001.

**Results**

Demographic and risk factors characteristics of studied groups were described in Tables (1,2). Platelet count shows no significant difference between studied groups (p>0.05), MPV and PDW shows significant difference when test group (subgroup A and B) compared with control group (p<0.05) but both variables show no statistically significant difference, when subgroup A compared with subgroup B (p>0.05). MAR (ADP) show significant difference when test group compared to control group (p<0.05) (Table 3).

Table (4) demonstrates significant presence of aggregates clumps in subgroup A (acute MI) when compared to both subgroup B (unstable angina) and control group (p<0.05).

Table (5) shows significant increase in MPV in complicated MI group when compared with non complicated MI group (p=0.046).

As shown in Tables (6,7) there were no significant differences in all platelet related variables in both subgroups (A and B) when comparing diabetic with non diabetic (p>0.05).

There were a significant positive correlation between MAR (ADP) and CK, CRP and EF (p=0.0001). There was also significant positive correlation between PDW and CRP (p=0.044). Also there were a positive correlation between aggregate clumps and CK and CK-MB (p=0.035, 0.048, respectively).
Table 1: Demographic data of study group.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Male No.</th>
<th>Male Mean Age</th>
<th>Female No.</th>
<th>Female Mean Age</th>
<th>Total No.</th>
<th>Total Mean Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable Angina</td>
<td>10</td>
<td>53.1±8.39</td>
<td>6</td>
<td>50.1±4.54</td>
<td>16</td>
<td>52.7±7.16</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>28</td>
<td>55.4±10.97</td>
<td>6</td>
<td>55.6±5.5</td>
<td>34</td>
<td>55.4±10.15</td>
</tr>
<tr>
<td>Control</td>
<td>9</td>
<td>28.6±3.64</td>
<td>1</td>
<td>29</td>
<td>10</td>
<td>28.7±3.43</td>
</tr>
<tr>
<td>Total</td>
<td>47</td>
<td>49.8±13.99</td>
<td>13</td>
<td>51.0±8.53</td>
<td>60</td>
<td>50.0±12.95</td>
</tr>
</tbody>
</table>

Table 2: Risk factors among study group.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Hypertensive</th>
<th>Diabetic</th>
<th>Smoker</th>
<th>Dyslipidemeric</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable Angina</td>
<td>13</td>
<td>7</td>
<td>9</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>21</td>
<td>17</td>
<td>20</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td>24</td>
<td>29</td>
<td>32</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Comparative analysis of some platelet related variable between studied groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unstable Angina Mean ± SD</th>
<th>Myocardial Infarction Mean ± SD</th>
<th>Control Mean ± SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet Count</td>
<td>223.3±63.3</td>
<td>239.2±73.4</td>
<td>252.7±42.2</td>
<td>p1 = 0.097</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p2 = 0.368</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p3 = 0.333</td>
</tr>
<tr>
<td>MPV</td>
<td>10.04±0.78</td>
<td>10.29±1.37</td>
<td>9.07±0.48</td>
<td>p1 = 0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p2 = 0.008</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p3 = 0.512</td>
</tr>
<tr>
<td>PDW</td>
<td>12.93±1.60</td>
<td>13.01±2.33</td>
<td>11.29±0.78</td>
<td>p1 = 0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p2 = 0.007</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p3 = 0.942</td>
</tr>
<tr>
<td>MAR (ADP)</td>
<td>99.56±3.85</td>
<td>103.12±4.13</td>
<td>94.7±4.47</td>
<td>p1 = 0.010</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p2 = 0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p3 = 0.005</td>
</tr>
</tbody>
</table>

Table 4: Comparative analysis of some platelet morphological related variables between studied groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unstable angina (n=16)</th>
<th>Myocardial infarction (n=34)</th>
<th>Control (n=10)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggregates clumps</td>
<td>5 (31.25%)</td>
<td>21 (61.76%)</td>
<td>2 (20%)</td>
<td>p1 = 0.537</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p2 = 0.022</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p3 = 0.046</td>
</tr>
<tr>
<td>Giant platelets</td>
<td>7 (43.75%)</td>
<td>16 (47.06%)</td>
<td>3 (30%)</td>
<td>p1 = 0.492</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p2 = 0.344</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p3 = 0.828</td>
</tr>
<tr>
<td>Micro platelets</td>
<td>6 (37.5%)</td>
<td>13 (38.24%)</td>
<td>2 (20%)</td>
<td>p1 = 0.356</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p2 = 0.29</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p3 = 0.961</td>
</tr>
</tbody>
</table>

Table 5: Comparative analysis of some platelet related variable between complicated and non complicated cases of myocardial infarction.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Complicated (n=14) Mean ± SD</th>
<th>Non complicated (n=20) Mean ± SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet Count</td>
<td>255.4±72.1</td>
<td>227.9±73.9</td>
<td>0.323</td>
</tr>
<tr>
<td>MPV</td>
<td>10.4±0.99</td>
<td>9.76±1.17</td>
<td>0.046</td>
</tr>
<tr>
<td>PDW</td>
<td>13.8±2.12</td>
<td>12.45±2.35</td>
<td>0.052</td>
</tr>
<tr>
<td>MAR (ADP)</td>
<td>104.0±3.33</td>
<td>102.5±4.58</td>
<td>0.377</td>
</tr>
<tr>
<td>Giant Platelets</td>
<td>6 (42.86%)</td>
<td>10 (50%)</td>
<td>0.686</td>
</tr>
<tr>
<td>Micro Platelets</td>
<td>7 (50%)</td>
<td>6 (30%)</td>
<td>0.245</td>
</tr>
<tr>
<td>Aggregates Clumps</td>
<td>10 (71.43%)</td>
<td>11 (55%)</td>
<td>0.339</td>
</tr>
</tbody>
</table>

Table 6: Comparative analysis of some platelet related variable between diabetic and non diabetic in MI subgroup.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Diabetic (n=17) Mean ± SD</th>
<th>Non diabetic (n=17) Mean ± SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet Count</td>
<td>236.9±48.9</td>
<td>241.5±93.3</td>
<td>0.973</td>
</tr>
<tr>
<td>MPV</td>
<td>9.8±1.1</td>
<td>10.32±1.2</td>
<td>0.128</td>
</tr>
<tr>
<td>PDW</td>
<td>12.4±2.2</td>
<td>13.62±2.4</td>
<td>0.259</td>
</tr>
<tr>
<td>MAR (ADP)</td>
<td>103.0±4.1</td>
<td>103.2±4.2</td>
<td>0.610</td>
</tr>
<tr>
<td>Aggregates clumps</td>
<td>11 (64.71%)</td>
<td>10 (58.82%)</td>
<td>0.728</td>
</tr>
<tr>
<td>Giant platelets</td>
<td>9 (52.94%)</td>
<td>7 (41.18%)</td>
<td>0.498</td>
</tr>
<tr>
<td>Micro platelets</td>
<td>7 (41.18%)</td>
<td>6 (35.24%)</td>
<td>0.728</td>
</tr>
</tbody>
</table>

Table 7: Comparative analysis of some platelet related variable between diabetic and non diabetic in UA subgroup.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Diabetic (n=7) Mean ± SD</th>
<th>Non diabetic (n=9) Mean ± SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet Count</td>
<td>191.3±51.3</td>
<td>248.2±62.9</td>
<td>0.114</td>
</tr>
<tr>
<td>MPV</td>
<td>10.4±0.6</td>
<td>9.8±0.8</td>
<td>0.114</td>
</tr>
<tr>
<td>PDW</td>
<td>13.5±1.6</td>
<td>12.5±1.5</td>
<td>0.252</td>
</tr>
<tr>
<td>MAR (ADP)</td>
<td>99.4±3.1</td>
<td>99.7±4.5</td>
<td>0.918</td>
</tr>
<tr>
<td>Aggregates clumps</td>
<td>3 (42.86%)</td>
<td>2 (22.22%)</td>
<td>0.392</td>
</tr>
<tr>
<td>Giant platelets</td>
<td>4 (57.14%)</td>
<td>3 (33.33%)</td>
<td>0.356</td>
</tr>
<tr>
<td>Micro platelets</td>
<td>2 (28.57%)</td>
<td>4 (44.44%)</td>
<td>0.529</td>
</tr>
</tbody>
</table>

MPW = Mean Platelet Volume.
PDW = Platelet Distribution Width.
MAR (ADP) = Maximum Aggregation Ratio for ADP.
The putative role of platelets in the pathogenesis and clinical manifestations of acute coronary syndromes goes beyond their obvious part in the formation of intracoronary thrombus. The diurnal variation in incidence of myocardial infarction corresponds with a similar variation in the degree of platelet aggregability, suggesting an association with platelet aggregability and the triggering of myocardial infarction [15,16].

Structural characteristics of platelets have also been linked with increased susceptibility to clinically apparent coronary artery disease [17,18].

Platelet production is governed by various agents. Thrombopoietin has been shown to be a major agent controlling platelet numbers and changes in platelet production from megakaryocytes is probably modulated by a series of cytokines (IL-3, IL-6, IL-11) [19,20,21].

Pizzulli et al [22] have demonstrated that in stable angina platelet count was unchanged compared to patients with normal coronary arteries but that the size was increased. However, in the patients with unstable angina, the platelet count was decreased and even larger increase in size had been observed.

In the present study, there was a highly significant increase in platelet volume in the subgroup with unstable angina (p<0.001, Table 3) and the subgroup with AMI (p<0.001, Table 3) when compared to control group, but a non significant increase in the subgroup with AMI when compared to the subgroup with unstable angina (p>0.05, Table 3). Various studies found the same findings [22-25] while Halbmoyer et al [26] reported no effect.

The reduction in platelet count and increased platelet volume in patients with unstable angina and AMI reflects that either process may be associated with or preceded by a systemic increase in platelet destruction rate that is not completely

Table 8: Correlation between some platelet related variable and some lab and echo parameters.

<table>
<thead>
<tr>
<th></th>
<th>CK</th>
<th>CK-MB</th>
<th>CRP</th>
<th>EF</th>
<th>LV T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets Count</td>
<td>r</td>
<td>.030</td>
<td>.144</td>
<td>.145</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>.823</td>
<td>.418</td>
<td>.270</td>
<td>.987</td>
</tr>
<tr>
<td>MPV</td>
<td>r</td>
<td>.173</td>
<td>-.067</td>
<td>.196</td>
<td>-.182</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>.186</td>
<td>.706</td>
<td>.132</td>
<td>.172</td>
</tr>
<tr>
<td>PDW</td>
<td>r</td>
<td>.200</td>
<td>-.081</td>
<td>.261</td>
<td>-.204</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>.125</td>
<td>.651</td>
<td>.044</td>
<td>.124</td>
</tr>
<tr>
<td>MAR (ADP)</td>
<td>r</td>
<td>.495</td>
<td>-.035</td>
<td>.483</td>
<td>-.486</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>.000</td>
<td>.846</td>
<td>.000</td>
<td>.000</td>
</tr>
<tr>
<td>Giant Platelets</td>
<td>r</td>
<td>.006</td>
<td>.183</td>
<td>.115</td>
<td>-.111</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>.967</td>
<td>.299</td>
<td>.383</td>
<td>.408</td>
</tr>
<tr>
<td>Micro Platelets</td>
<td>r</td>
<td>.152</td>
<td>.009</td>
<td>.090</td>
<td>-.048</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>.247</td>
<td>.958</td>
<td>.494</td>
<td>.722</td>
</tr>
<tr>
<td>Aggregates Clumps</td>
<td>r</td>
<td>.273</td>
<td>-.342</td>
<td>.191</td>
<td>-.085</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>.035</td>
<td>.048</td>
<td>.143</td>
<td>.528</td>
</tr>
</tbody>
</table>

**Discussion**

The putative role of platelets in the pathogenesis of acute coronary syndromes goes beyond their obvious part in the formation of intracoronary thrombus. The diurnal variation in incidence of myocardial infarction corresponds with a similar variation in the degree of platelet aggregability, suggesting an association with platelet aggregability and the triggering of myocardial infarction [15,16].

Structural characteristics of platelets have also been linked with increased susceptibility to clinically apparent coronary artery disease [17,18].

Platelet production is governed by various agents. Thrombopoietin has been shown to be a major agent controlling platelet numbers and changes in platelet production from megakaryocytes is probably modulated by a series of cytokines (IL-3, IL-6, IL-11) [19,20,21].

Pizzulli et al [22] have demonstrated that in stable angina platelet count was unchanged compared to patients with normal coronary arteries but that the size was increased. However, in the patients with unstable angina, the platelet count was decreased and even larger increase in size had been observed.

In our study, the non significant correlation in platelet count in the subgroup with unstable angina or subgroup with AMI when compared to control group was in accordance to what was mentioned by Pizzulli et al [22] who demonstrated no significant change in platelet count between patients with normal coronary artery angiogram and those with atherosclerotic CAD.

In the present study, there was a highly significant increase in platelet volume in the subgroup with unstable angina (p<0.001, Table 3) and the subgroup with AMI (p<0.001, Table 3) when compared to control group, but a non significant increase in the subgroup with AMI when compared to the subgroup with unstable angina (p>0.05, Table 3). Various studies found the same findings [22-25] while Halbmoyer et al [26] reported no effect.

The reduction in platelet count and increased platelet volume in patients with unstable angina and AMI reflects that either process may be associated with or preceded by a systemic increase in platelet destruction rate that is not completely
compensated for by an increase in platelet production rate, resulting in release of large platelet from the bone marrow [22].

The platelet distribution width is a measure of platelet function reflecting the un-equality of platelet size in relation to MPV and is correlated with platelet count and MPV [27]. Our results revealed a significant increase in PDW when either the subgroups with unstable angina or subgroup with AMI were compared to control (p=0.002 and p=0.007, Table 3). However, a non significant increase was noticed when both subgroup of unstable angina and subgroup with AMI were compared (p=0.942, Table 3).

Such finding is a logic expectation since PDW correlated with MPV which showed the same changes mentioned previously (Table 3).

An increased mean platelet volume (MPV) in patients with acute coronary syndromes (ACS) has been previously reported by Martin et al [24] to be an independent predictor of recurrent myocardial infarction and cardiac death.

The increase of MPV in ACS patients can be attributable to the presence of reticulated platelets (RP), in fact, more recently, increased levels of RP have been reported in patients presenting arterial thrombosis including cerebrovascular disease and ACS [28,29].

Mean platelet volume is known to be higher in patients with unstable versus stable angina [22] and is a strong independent predictor of impaired reperfusion and six-month mortality in patients with STEMI treated with primary PCI [30]. Moreover, increased MPV in patients presenting myocardial infarction has been associated with restenosis, larger infarcts and increased development of left ventricular failure [31].

Comparative analysis of maximum aggregation ratio in the subgroup with unstable or AMI versus control group revealed a highly significant increase (p<0.01 and p<0.0001, Table 3).

A similar observation was present when the subgroup with unstable angina was compared with subgroup with AMI (p<0.005, Table 3).

The increased aggregation in the test group reflects the role played by thrombogencity in the development of AMI; which is considered an expected finding.

Cesari et al [32] demonstrate a significant positive correlation between platelet aggregation and MPV.

A highly significant increase was noticed in aggregates clumps in patients with AMI (p<0.05, Table 4), but no significant difference in subgroup with unstable angina when compared with control group (p>0.05).

From the previous findings, one can conclude that follow-up of patients with unstable angina for the presence of aggregates clumps can be of considerable help denoting that progression of ACS from unstable angina to the development of AMI.

However, comparative analysis for the presence of giant platelet test group versus control revealed non significant difference (p>0.05, Table 4).

The presence of giant and micro-platelets reflects a rapid production of platelets from their precursor i.e. the megakaryocytes of the bone marrow. The increased number of either giant or micro platelets can be considered as a measure of their consumption in the process of thrombus formation during the pathogenesis of ACS. Such result can be explained by what was mentioned by Altes et al [33] and Behrens [34] who reported that, platelet size is a difficult parameter to accurately quantitate and use diagnostically because of their wide physiologic variation in normal subjects and their susceptibility to time dependent swelling in vitro.

Comparative analysis for morphological and function platelet parameters showed significant increase in platelet volume and PDW in the subgroup with complicated AMI versus the subgroup without complications (p<0.05, Table 5).

These findings may be considered as parameters reflecting the prognosis in patients with AMI. This is logic expectation since large platelets have higher thrombotic potential [35], express higher levels of procoagulating surface proteins such as P-selectin [36] and glycoprotein IIIa [37].

Platelet aggregation is induced by a variety of stimuli including ADP, thrombin, thromboxan A2, collagen and epinephrine [38].

From the previous findings, one also can conclude that a change in both platelet function parameters and morphological one can occur in patients with ACS. Changes in morphology pattern
can be supported by what was mentioned by Ware and Coller [38] who stated that a pseudo-formation due to outward projections of the microfilaments resulting from contraction of the microfilament system within the platelets. The difference between our results and that described by Ware and Coller [38] is that our morphological changes are seen by light microscope which is an easier and rapid technique than the electron microscope used by latter authors.

The behavior of platelet function in diabetic patients was illustrated in Tables (6,7) in the present work.

Either platelet morphology parameters or function showed no significant changes when diabetics with either unstable angina or myocardial infarction were compared to non diabetic patients with unstable angina or AMI (p>0.05, Tables 6,7).

Platelets from diabetic subjects exhibit enhanced adhesiveness and hyper coagulation in response to both strong (e.g. thrombin, thromboxan A$_2$) and weak (e.g. adenosine diphosphate, epinephrine, collagen) agonists [39,40]. Platelet hypersensitivity is more evident in diabetic with vascular complications. However, it is also observed in newly diagnosed diabetic patients, suggesting that altered platelet function may be a consequence of metabolic changes secondary to diabetic state [39,41].

Our contradictory results can presumably be explained by the small number of our diabetic patients. A next large number trial can disclose the reported behavior of platelets in diabetic patients.

Zuberi et al [8] demonstrate that MPV was significantly increased in the impaired fasting glucose (FG) group, as compared to non-DM group and it increased further when comparing the DM to IFG groups.

In an attempt to disclose a relationship between platelet morphology and function parameters and some laboratory and echocardiography parameters, correlation coefficient was done (Table 8).

There was significant correlation between CK-MB and the platelet aggregates ($r$=0.342, $p$=0.048, Table 8).

Similarly, significant correlation was present between either C-reactive protein and ejection fraction (EF) and maximum aggregation ratio ($r$=0.483, $p<0.0001$ and $r$=0.486, $p<0.0001$, Table 8).

Finally, we can conclude that both platelet function and morphology showed changes that can be considered as a reflection of the complex structure of the pathogenesis of ACS. Since platelet morphology changes can be assessed more easily, they may be used as a simple and feasible diagnostic method for evaluation of pathogenesis and complications of ACS.

References


Myocardial Performance Index after Surgical Correction of Ventricular Septal Defects

YASSER BAGHDADY, MD*; YASSER HUSSEIN, MD**; WALED AMMAR, MD*

Myocardial performance index (MPI) has been described as a noninvasive Doppler measurement of ventricular function.

The Aim of this Study: Was to assess myocardial performance index following surgical correction of congenital ventricular septal defects and to evaluate its impact on postoperative recovery.

Methods: This is a prospective study involving 30 children (16 girls and 14 boys) operated on for simple ventricular septal defect (VSD), (Group I), mean age: 24.5±2.29 months. The control group (Group II) consisted of 30 healthy children (mean age: 32.2±5.2). Oral consent from the parents of the children was obtained.

Results: We found that both the right and left ventricular (RV & LV) MPI correlated significantly with the ejection fraction (EF) \( r=-0.49; p=0.006; r=-0.51; p=0.004 \), respectively. The LV EF and the LV FS was negatively correlated, while the left and right ventricular MPI was positively correlated with the: LVEDD \( p=0.000 \), the VSD size \( p=0.000 \) and the post-operative course of the patients in terms of the duration of ventilation \( p=0.000 \), the duration of use of inotropics \( p=0.000 \) and the duration of staying in the ICU \( p=0.000 \). By linear regression, the factors that correlated with the post-operative course of VSD surgery, was the RV MPI pre surgery, MPI 2 days after surgery and the ejection fraction \( p=0.000 \).

Conclusion: MPI is a useful index for a measurement of the left and right ventricular function. It correlates significantly with the ejection fraction, fractional shortening, VSD size and the left ventricular size. It also significantly predicts the outcome of surgery to the VSD.

Key Words: Myocardial performance index – Ventricular septal defect.
therapeutic decisions in the postoperative period. An evaluation of both systolic and diastolic performance of either right or left ventricle is mandatory. The majority of children treated surgically present less or more pronounced symptoms of heart failure [10]. The form and severity of cardiac defect, injury caused by surgical trauma itself and by employment of cardiopulmonary bypass as well as dynamic changes of the hemodynamic conditions following surgical repair contribute to the postoperative changes of myocardial function [11].

The use of an extra-corporeal circulation system results in a systemic as well as local inflammatory response [12]. It has been suggested that the severity of the inflammatory processes and associated risk of heart failure development in the postoperative period correlate with previous myocardial remodeling [13]. Haemodynamic changes related to the cardiac defect induce mechanisms that enable sufficient cardiac performance under the circumstances of the pathologic loading [14]. Subsequently, the myocardium undergoes remodeling [15]. In the remodeled myocardium, in addition to changes detected at either organ or tissue level, there are molecular changes that lead to increased cellular vulnerability to oxidative stress [16]. Such stress is produced by ischemia, followed by reperfusion during the cardiopulmonary bypass [17].

**Aim of the work:**
To assess myocardial performance index following surgical correction of congenital ventricular septal defects and to evaluate its impact on postoperative recovery.

**Methods**

**Studied groups:**
This prospective study involved 30 children (16 girls and 14 boys) operated on for simple ventricular septal defect (VSD), (Group I). The mean age of the studied children was 24.5 (±2.29) months and they were recruited over one year (January 2008-December 2008) from the Pediatric and Cardiology Departments of the Faculty of Medicine children, Cairo University. An oral consent was obtained from the parents of the Patients. Patients with VSD as part of more complex congenital defects were excluded from the study.

The control group (Group II) consisted of 30 healthy children, referred for echocardiographic examination due to the presence of any cardiac murmur, history of chest pain or an abnormal ECG who had normal echocardiographic findings. An oral consent was obtained from the parents of the children for the use of their echocardiographic data.

**Echocardiographic examination:**
Complete transthoracic echocardiography including M-mode, two-dimensional and Doppler (pulsed-wave, continuous-wave and color) measurements was performed to all enrolled patients at rest using Sonos 5500 ultrasound system (HP Hewlett Packard), with a 5MHz transducer for children.

Left ventricular (LV) end-systolic, end-diastolic and left atrial dimension were measured in the parasternal long-axis and short axis views. Ejection fraction and fractional shortening of the left ventricle were estimated according to the guidelines of the American Society of Echocardiography. The global systolic function was considered abnormal if the ejection fraction was less than 55% and the fractional shortening was below 30% [18,19].

Ventricular septal defects were identified in different windows, parasternal, subcostal and four chamber views where their location and size were identified. Shunt volume (restrictive or unrestrictive) was detected indirectly by measuring the dimension of left atrium and left ventricular end diastolic dimension [20].

The mitral and tricuspid inflow velocities were recorded from the apical-4-chamber view with the pulsed-wave Doppler sample volume positioned at the tips of the mitral or tricuspid leaflets during diastole, respectively. The left ventricular outflow velocity pattern was recorded from the apical long-axis view with Doppler sample volume positioned just below the aortic valve and the right ventricular outflow velocity pattern was recorded from the parasternal short axis view with Doppler sample volume positioned just below the pulmonary valve. An electrocardiogram was simultaneously recorded with a Doppler echocardiogram in all subjects.

The interval ‘a’ from cessation to onset atrioventricular valve inflow is equal to the sum of isovolumetric contraction time (ICT), ejection time and isovolumetric relaxation time (IRT). Ejection time ‘b’ is derived from the duration of ventricular outflow Doppler velocity profile. The sum of ICT and IRT was obtained by subtracting ‘b’ from ‘a’. The MPI was calculated as: \((a - b) / b\), Fig. (1), [21,22].
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The MPI was evaluated on the 2nd day, 7th day after surgery and on follow-up visit one month after surgery. The MPI was calculated as previously described separately for LV and RV.

**Postoperative course:**

We also analyzed the potential association between the size and severity of VSD defect, myocardial performance and postoperative course.

VSD severity was defined based on the pressure gradient between RV and LV across the ventricular septum calculated prior to surgery and the size of VSD was determined in mm.

The postoperative course was defined based on assisted ventilation time, inotropic support time and intensive care unit stay time. These parameters were correlated with MPI value evaluated on the 2nd day after surgery.

**Statistical method:**

Numerical data was expressed as a mean ± standard deviation. Comparison of means for changes in variables was performed using the Paired Student’s *t*-test, while the non-Paired Student’s *t*-test was used for numeric comparison between two different groups. ANOVA (analysis of variance) was used to compare between more than two numeric groups. Correlations were performed using the Pearson bivariate correlation. Non-numeric data was compared using Chi-square test, when two groups were compared. ANCOVA (analysis of co-variance) was used when more than 2 groups were compared. A *p* value of <0.05 was considered significant in our statistical analysis.

**Results**

**Healthy children:**

The LV and RV dimensions, shortening fraction, PAP, LV MPI and RV MPI values in the healthy children, (Group II), are outlined in (Table 1) and their results were found to be within the normal ranges.

As regards the contractile indices we found that the ejection and fractional shortening were significantly correlated (*r*=0.98; *p*=0.000); also there was a significant negative correlation between the ejection fraction and fractional shortening and the RV MPI (*r*=-0.49; *p*=0.006) and the LV MPI (*r*=-0.51; *p*=0.004).

**Children with VSD:**

The LV and RV dimensions, shortening fraction, RV MPI, LV MPI and VSD size in mm in (Group I) are outlined in (Table 2).

**Statistical method:**

Numerical data was expressed as a mean ± standard deviation. Comparison of means for changes in variables was performed using the Paired Student’s *t*-test, while the non-Paired Student’s *t*-test was used for numeric comparison between two different groups. ANOVA (analysis of variance) was used to compare between more than two numeric groups. Correlations were performed using the Pearson bivariate correlation. Non-numeric data was compared using Chi-square test, when two groups were compared. ANCOVA (analysis of co-variance) was used when more than 2 groups were compared. A *p* value of <0.05 was considered significant in our statistical analysis.

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**Children with VSD:**

The LV and RV dimensions, shortening fraction, RV MPI, LV MPI and VSD size in mm in (Group I) are outlined in (Table 2).

**Table 1:** General characteristics of the control group.

<table>
<thead>
<tr>
<th>Number 30</th>
<th>Age m</th>
<th>RV MPI</th>
<th>LV MPI</th>
<th>LV EDD</th>
<th>FS %</th>
<th>RV mm</th>
<th>PAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>20-40</td>
<td>0.31-0.32</td>
<td>0.32-0.34</td>
<td>2.9-3.1</td>
<td>28-38</td>
<td>1.15-1.3</td>
<td>21-29</td>
</tr>
<tr>
<td>Mean</td>
<td>32.16</td>
<td>0.315</td>
<td>0.332</td>
<td>3.013</td>
<td>32.16</td>
<td>1.220</td>
<td>25.66</td>
</tr>
<tr>
<td>Std. Deviation</td>
<td>5.31</td>
<td>0.005</td>
<td>0.005</td>
<td>0.007</td>
<td>2.001</td>
<td>0.237</td>
<td>1.935</td>
</tr>
</tbody>
</table>

**Table 2:** General characteristics of the patient group.

<table>
<thead>
<tr>
<th>Number 30</th>
<th>Age m</th>
<th>LV EDD</th>
<th>FS %</th>
<th>RV mm</th>
<th>RV MPI</th>
<th>LV MPI</th>
<th>VSD mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>22-28</td>
<td>3.1-3.7</td>
<td>25-31</td>
<td>1.3-1.8</td>
<td>0.32-0.45</td>
<td>0.32-0.44</td>
<td>6-10</td>
</tr>
<tr>
<td>Mean</td>
<td>24.56</td>
<td>3.346</td>
<td>27.26</td>
<td>1.513</td>
<td>0.41</td>
<td>0.40</td>
<td>8.13</td>
</tr>
<tr>
<td>Std. Deviation</td>
<td>2.299</td>
<td>0.1547</td>
<td>1.760</td>
<td>0.1357</td>
<td>0.02</td>
<td>0.03</td>
<td>0.937</td>
</tr>
</tbody>
</table>
Myocardial Performance Index after Surgical Correction of Ventricular Septal Defects

**Preoperative study:**

Patients with ventricular septal defect had higher RVMPI, (0.41±0.02 Vs. 0.315±0.005) and LVMPI (0.40±0.03 Vs. 0.332±0.005) than healthy control group with p value = (<0.0001) for both indices.

As regards the contractile indices there was a significant negative correlation between the ejection fraction and fractional shortening in the preoperative echocardiogram and the preoperative left and right ventricular MPI (p=0.004 and 0.006, respectively).

The left and right ventricular MPI was positively correlated with the: LVEDD (p<0.0001), the VSD size (p<0.0001).

**Postoperative study:**

The results of sequential LV and RV MPI measurements in children operated on for VSD are listed in Table (3). In children operated on for VSD, on the 2nd day after surgery a significant elevation of both RV MPI and LV MPI was observed (Fig. 2).

Values of RV MPI and LV MPI were significantly higher in the patient group than in the control group especially on the 2nd and 7th postoperative days (p=0.000). This difference disappeared at 1 month (p=0.3) [NS] between control and 1 month post-operative, both LV and RV MPI).

The regression of the LV and RV MPI significantly decreased over the one month period (ANOVA p=0.000).

**Table 3:** MPI values (both RV and LV) over the 1 month post-operative follow-up.

<table>
<thead>
<tr>
<th>Number</th>
<th>RV MPI d2</th>
<th>RV MPI d7</th>
<th>RV MPI 1m</th>
<th>LV MPI d2</th>
<th>LV MPI d7</th>
<th>LV MPI 1m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>0.42-0.51</td>
<td>0.37-0.40</td>
<td>0.31-0.32</td>
<td>0.45-0.58</td>
<td>0.36-0.41</td>
<td>0.32-0.34</td>
</tr>
<tr>
<td>Mean</td>
<td>0.467</td>
<td>0.388</td>
<td>0.316</td>
<td>0.491</td>
<td>0.374</td>
<td>0.332</td>
</tr>
<tr>
<td>Std. Deviation</td>
<td>0.020</td>
<td>0.009</td>
<td>0.004</td>
<td>0.0364</td>
<td>0.138</td>
<td>0.005</td>
</tr>
</tbody>
</table>

**Correlations with VSD severity:**

The LV EF and the LV FS was negatively correlated, while the left and right ventricular MPI was positively correlated with the: LVEDD (p=0.000), the VSD size (p=0.000) Figs. (3-6).

**Correlations with postoperative course:**

The LV EF and the LV FS was negatively correlated, while the left and right ventricular MPI was positively correlated with the post-operative course of the patients in terms of the duration of ventilation (p=0.000), the duration of use of inotropes (p=0.000) and the duration of staying in the ICU (p=0.000).
By linear regression, the factors that correlated with the post-operative course of VSD, in terms of ICU admission, the duration of inotropics and the duration of ventilation was the RV MPI pre surgery, MPI 2 days after surgery and the ejection fraction Fig. (7).

**Figure 3:** Shows the significant negative correlation between the ejection fraction and RV MPI.

**Figure 4:** Significant negative correlation between the ejection fraction and VSD size.

**Figure 5:** Significant positive correlation between the VSD size and RV MPI.

**Figure 6:** The highly significant correlation between the LV MPI and the VSD size.

**Figure 7:** Linear regression analysis showing a significant correlation \((p=0.000)\) between RV MPI 2 days after surgery and the post-operative course of surgery to VSDs.
Myocardial Performance Index after Surgical Correction of Ventricular Septal Defects

Discussion

A myocardial performance index (MPI) has been described as a noninvasive Doppler measurement of ventricular function [4,6,8,23,24]. The MPI is a ratio between the sum of isovolumic time intervals, namely, isovolumic contraction time (ICT) and isovolumic relaxation time (IRT) and ejection time. These intervals can be easily obtained by routine Doppler techniques during a standard echocardiographic examination with excellent inter- and intraobserver reproducibility [25-28].

Because this index is a ratio of time intervals, it is not limited by the geometric shape of the ventricle and has been shown to be independent of heart rate [2,8]. The MPI has been shown to correlate well with other invasive and noninvasive measures of left ventricular function in adults [10]. In addition; studies in pediatric and adult patients have demonstrated that this index can quantitatively assess right ventricular (RV) dysfunction [27,28].

In this study we found that all contractile indices, ejection fraction, fractional shortening and both the right and left ventricular MPI are significantly correlated with the severity of the ventricular septal defect, in terms of size of the VSD, the left ventricular dimensions and can give a good indication on the post-operative recovery of the patients after surgical closure. Thus, these indices give us a good indication about the dysfunction, in the right and left ventricles, that result from the VSD shunt.

By linear regression we also found that the RV MPI (preoperative and immediately after surgery) and the ejection fraction are the factors that most significantly affect the post-operative course of surgery for VSD. This is an important finding, since estimation of RV function by traditional methods is hampered by its geometric shape. Thus, using this method early identification of RV dysfunction can be made.

The duration of post operative ICU stays place a considerable burden on the resources of the institution. Nonetheless, despite the magnitude of the problem of long stay in children after cardiac surgery, a detailed assessment of the specific factors that predict and necessitate prolonged intensive care stay after surgery for heart disease in children is lacking.

This study indicates that RV and LV MPI following closure of ventricular septal defects impacts upon recovery time. It follows, therefore, that perioperative assessment of MPI correlate with recovery time and that consideration of this measurement in conjunction with the intended operative procedure before scheduling operations may facilitate bed turnover. When ICU bed availability is an issue, children with complex chronic medical conditions including those with abnormal MPI should be electively scheduled for surgery in a series rather than parallel. In the setting of congestive heart failure, Allen et al., found that rightsided MPI was correlated with measures of LV diastolic dysfunction and may be linked to high LA pressures and reduced LV compliance, characteristic of patients with more restrictive filling patterns and elevated RV MPI was indicative of worsening prognosis in CHF patients, independent of diastolic stage [32].

In another series including children with congenital heart disease, Ishii et al., found that there was no significant difference in RV MPI between children with atrial septal defect and healthy children but there was a significant difference in RV MPI between patients who had had a Senning operation (0.58±0.09) and healthy children (p<0.01), concluding that, the MPI is a feasible approach to use when assessing global RV function in children with congenital heart disease [33]. In more complex cases Yu-Qi et al., evaluated MPI in children with single ventricle and was found to be impaired compared to normal children and may worsen with age. MPI in their series provided an accurate method for assessing ventricular function in children with single ventricles before and after total cavopulmonary connection [34].

Cardiac output is a commonly used parameter in the postoperative period. However, preload, afterload, myocardial contractility and heart rate all affect this index; thus its value in the assessment of functional status of the myocardium is very limited. Theoretically MPI meets the criteria of a method capable to adequately evaluate myocardial performance. In the examined group of healthy children, the small deviation of the results and particularly narrow range of MPI value confidence interval and the high level of consistency with data found in the literature confirm that the control group adequately reflected population data [33].

In the case of almost equal pressures in both cardiac ventricles, the RV is exposed to a significant pressure overload that induces hypertrophy and
remodelling of the myocardium [35]. Such a ventricle becomes particularly vulnerable to injuries related to the cardiopulmonary bypass. It leads to RV dysfunction disclosed by increased RVMPI. Postoperative course (catecholamine administration time, intubation time as well as ICU stay) correlated significantly with the index value calculated on the 2nd day following surgery.

This study documented the high usefulness of MPI measurements for the assessment of ventricular function, especially that of RV, which, if decreased, often leads to serious clinical problems in the postoperative period.

Limitations:
The lack of surgical data, intraoperatively, was a limitation of the study and in itself could have affected the post-operative recovery.

Conclusion

MPI is a useful index for a measurement of the left and right ventricular function; it correlates significantly with the ejection fraction, fractional shortening, VSD size and the left ventricular size.

The right and left ventricular MPI values are significantly elevated immediately post-closure of the VSD and over a one month period it normalizes to be comparable with the values of the control group. The RV preoperative MPI and the immediate post-operative MPI also significantly correlates with the post-operative course of the surgery and is strongly correlated with the duration of ICU stay, the duration of ventilation and the duration of inotropic use.

Recommendations:

Preoperative MPI for the right and left ventricle correlate significantly with VSD severity and could help in patient selection for VSD repair.

The use of right and left ventricular myocardial performance index for assessment of ventricular function especially those of right ventricle could predict the postoperative recovery course after surgical repair of VSD and may facilitate bed turnover.

References


Myocardial Performance Index after Surgical Correction of Ventricular Septal Defects


Heart failure (HF) with preserved systolic function (HF-PSF) is a common form of HF that is difficult to diagnose and has a poor prognosis. HF-PSF has a complex pathophysiology, with several precipitating/causative factors, including hypertension, left ventricular hypertrophy (LVH), myocardial infarction (MI) and supraventricular arrhythmias. It typically occurs in elderly patients with several co-morbidities that contribute to the symptoms and deterioration of the disease.

Diagnosis of subtle left ventricular systolic dysfunction using conventional echocardiographic parameters (EF, FS) is of limited value.

So, this study was conducted to evaluate left ventricular atrioventricular plane displacement in this aspect. It included 30 patients known to have diastolic failure and 20 persons as a control group. All were subjected to thorough history taking, general and local examination routine laboratory investigations, 12-leads resting E.C.G. and echocardiographic examination including M-mode, 2-D and Doppler with estimation of atrioventricular plane displacement (AVPD). AVPD was significantly lower in patients group (9.5±0.6) than control group (15.1±1.9). Patients group was divided into group A (AVPD ≤10mm) and group B (AVPD ≥10mm). Doppler study revealed that early diastolic E waves, E/A ratio were significantly lower in group A and group B when compared with control group and group A and versus group B.

Late diastolic A waves were significantly lower in group A than control group and group A than group B but difference between group B and control group does not reach level of significance.

Isolvolmic relaxation time (IVRT) was significantly higher in group A and group B when compared with control group and in group B than group A.

Conclusion: The present study revealed that in early stage of HF-PSF, actually systolic dysfunction starts to develop but a sensitive too 1 is needed to assess. AVPD assessment is a reliable, simple and non-invasive method for evaluation of LV systolic function especially in patients with diastolic HF.

Key Words: Ventricular systolic atrioventricular plane – Diastolic heart failure.
highlight the need for further research and clinical trials examining this condition [1].

Diastolic heart failure is the paradoxical condition where the patient has the symptoms and signs of heart failure with preserved left ventricular ejection fraction and diastolic dysfunction [2].

Many studies have investigated the morbidity and mortality in patients with diastolic heart failure.

By the Framingham meta-analysis the annual mortality varies from 1.3 to 17.5%. This wide variability depends on several factors including, the modality used to classify this kind of HF, age and follow-up duration.

Also, Philbin et al, 2000 [3] found that the mortality was lower in patients with EF ≥50% than in those with EF ≤39%. The Framingham offspring cohort informed that the rate of death after 5 years is 68% in patients with HF and normal EF in comparison with 82% of systolic HF, with mortality, however, four times greater than that presented by healthy subjects.

So, there is a need for a method to predict systolic dysfunction aiming at earlier diagnosis and earlier management in order to decrease mortality of this kind of heart failure in patients with diastolic dysfunction.

This needed method has to be non invasive, easy to use, safe, inexpensive and has no influence on the patient hemodynamics.

Echocardiography has fulfilled these preconditions and atiroventricular plane displacement may represent this needed tool for predicting diastolic dysfunction.

Aim of the work:

Studying the value of left ventricular systolic atrioventricular plane displacement in the prediction of systolic dysfunction in patients with diastolic heart failure.

Patients and Methods

The present work included 39 patients with preserved LV systolic function and impaired LV diastolic function as assessed by conventional Echo-Doppler measurements.

Another 20 healthy normal subjects matched for age and sex were included in the study as a control group.

Patients were classified according to AV plane displacement into two groups:

• Group I: With atrioventricular plane displacement <10mm.
• Group II: With atrioventricular plane displacement ≥10mm.

Basic characteristics:

• Group I: (Atrioventricular plane displacement <10mm).
  ° 7 males and 5 females.
  ° Age ranged from 44 to 58 years with a mean age of 52.2±4.0 years.
• Group II: (Atrioventricular plane displacement ≥10mm).
  ° 10 Males and 8 females.
  ° Age ranged from 50 to 62 years with a mean age of 59.9±7.7 years.

Control group:

Included 20 persons with age and sex matched normal control:

° 12 Males and 8 Females.
° Age ranged from 45 to 60 years with a mean age of 53.9±8.1 years.

Diagnostic criteria for diastolic heart failure [4]:

1) Signs or symptoms of congestive heart failure:

Exertional dyspnea, orthopnea, gallop sounds, lung crepitations.

Normal or mildly reduced left ventricular systolic function:

LVEF ≥45%.

Slow isovolumic left ventricular relaxation:

• IVRT >92ms in patients <30 yr.
• IVRT >100ms in patients 30-50 yr.
• IVRT >150ms in patients >50 yr.

And/or slow early left ventricular filling:

In patients <50 year:

E/A <1.0 and DT >220.

In patients >50 year:

E/A >0.5 and DT >280ms.
All patients included in the study were subjected to:

Full history taking, complete general and local examination of the heart, chest and abdomen. 12 leads resting ECG, Routine laboratory investigations including: Fasting and 2 hours post-prandial blood sugar level, urea, creatinine, SGPT, SGOT, PT, Cholesterol, Triglycerides, HDL, LDL and uric acid and Echocardiographic examination including. M-mod, Two-Dimensional Echocardiography, Conventional Doppler Echocardiography.

Echocardiographic procedures:

Echocardiographic examination was performed in each subject while lying in the left lateral decubitus position. All studies were performed according to the recommendations of the American Society of Echocardiography using conventional views and measurements [5].

Left ventricular dimensions and function were assessed using two dimension guided M-mode echocardiography with calculation of end systolic dimension (ESD), end diastolic dimension (EDD), fractional shortening (FS) and ejection fraction (EF).

Doppler echocardiography:

Transmitral flow velocities were recorded using pulsed-wave Doppler technique from the apical four-chamber view with the sample volume placed at the tip of the mitral valve and the following measurements were assessed:

- Mean early transmitral velocity E (cm/s).
- Mean late transmitral velocity A (cm/s).
- Ratio of early to late transmitral velocities E/A.
- Mean deceleration time of E wave (msec).

In five-chamber view, the sample volume placed between aortic and mitral valve and Isovolumic relaxation time (IVRT) (in msec) was obtained [16].

Measurement of systolic atrioventricular plane displacement:

This was calculated using two dimensionally guided M-mode echocardiography in the two and four chamber views. The regional displacement (in millimeters) was the distance covered by the atrioventricular plane between the position most remote from the apex (corresponding to the onset of contraction) and the position closest to the apex (corresponding to the end of contraction including any post ejection shortening) that is the full extent of the displacement. This was measured in the septal, lateral, posterior and anterior regions and was calculated from an average of four measurements. The mean of the systolic atrioventricular plane displacement in the four regions was then calculated [7-9].

Statistical analysis:

Statistical analysis was done by suing SPSS statistical package for social science program version 10, 1999. The data were parametric by using kolmogrov smirned test. The quantitative data were presented in the form of mean and standard deviation. Student t test was used as a test of significance for two groups.

Results

According to the results of atrioventricular plane displacement the patients with diastolic heart failure (studied group) were divided into two groups:

- Group A: With atrioventricular plane displacement <10mm.
- Group B: With atrioventricular plane displacement ≥10mm.

Table (2) shows that 12 patients (40%) with normal left ventricular systolic function as determined by conventional methods (FS% and EF%) were found to have abnormal systolic AV plane displacement <10mm (Group A) and 18 patients (60%) had atrioventricular plane displacement ≥10mm (Group B).

Table 1: Left atrioventricular plane displacement (AVPD).

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Patients</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVPD (mm)</td>
<td>15.1±1.9</td>
<td>9.5±0.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 2:

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A &lt;10 mm</td>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>Group B ≥ 10 mm</td>
<td>18</td>
<td>60</td>
</tr>
</tbody>
</table>

Total 30 100
### Table 3:

<table>
<thead>
<tr>
<th></th>
<th>Control (20)</th>
<th>Group A (12)</th>
<th>Group B (18)</th>
<th>Control versus A</th>
<th>Control versus B</th>
<th>A versus B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>53.9±8.1</td>
<td>52.2±4.0</td>
<td>59.9±7.7</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12 (60%)</td>
<td>7 (58.3%)</td>
<td>10 (55.6%)</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>Female</td>
<td>8 (40%)</td>
<td>5 (41.4%)</td>
<td>8 (44.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST-T wave chases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zero%</td>
<td>4 (33.3%)</td>
<td>5 (27.8%)</td>
<td></td>
<td><em>p&lt;0.05</em></td>
<td><em>p&lt;0.05</em></td>
<td>N.S.</td>
</tr>
<tr>
<td>Hypertension number &amp;%</td>
<td>0%</td>
<td>7 (58%)</td>
<td>12 (66%)</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>N.S.</td>
</tr>
<tr>
<td>Diabetes mellitus number &amp;%</td>
<td>0%</td>
<td>8 (66%)</td>
<td>13 (72%)</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>N.S.</td>
</tr>
<tr>
<td>IHD</td>
<td>0%</td>
<td>5 (41.6%)</td>
<td>8 (44.4%)</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**Systolic indices:**

<table>
<thead>
<tr>
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<th>Control (20)</th>
<th>Group A (12)</th>
<th>Group B (18)</th>
<th>Control versus A</th>
<th>Control versus B</th>
<th>A versus B</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDD (cm)</td>
<td>4.67±0.6</td>
<td>6.6±0.89</td>
<td>5.5±0.42</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ESD (cm)</td>
<td>2.94±0.29</td>
<td>4.72±0.5</td>
<td>3.7±0.55</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>EF</td>
<td>65.1±4.5</td>
<td>48.9±2.84</td>
<td>51.1±0.39</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FS</td>
<td>36.1±2.61</td>
<td>29.6±2.01</td>
<td>31±1.9</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**Doppler indices**

**Mitral flow indices:**

<table>
<thead>
<tr>
<th></th>
<th>Control (20)</th>
<th>Group A (12)</th>
<th>Group B (18)</th>
<th>Control versus A</th>
<th>Control versus B</th>
<th>A versus B</th>
</tr>
</thead>
<tbody>
<tr>
<td>E (cm/s)</td>
<td>83.1±6.9</td>
<td>44.4±1.9</td>
<td>49.6±2.9</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>A (cm/s)</td>
<td>77.1±10.5</td>
<td>57.1±6.2</td>
<td>75.2±8.7</td>
<td>&lt;0.01</td>
<td>N.S.</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>E/A</td>
<td>1.07±0.01</td>
<td>0.78±0.04</td>
<td>0.67±0.0</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Deceler time (ms)</td>
<td>211±18</td>
<td>228.5±7</td>
<td>158±17.9</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>IVRT</td>
<td>111±14</td>
<td>122.1±4</td>
<td>148.9±13.1</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**Figure 1:** A=Atrial velocity (m/s), DT=Deceleration time of E velocity (ms), E=Early diastolic velocity (cm/s), IVRT=Isovolumic relaxation time (ms) (Robert, 2005).
Diastolic heart failure or heart failure with preserved systolic function (HF-PSF) is difficult to diagnose and is known to have poor prognosis, complex pathophysiology and difficult management [10].

Echocardiography has a great value in the assessment of left ventricular function with providing a chance for early diagnosis, early management and estimation of long-term prognosis. In this respect left ventricular ejection fraction (LVEF) is one of most important parameters. However, LVEF is not sensitive in defining early ventricular changes in normal ageing, early coronary artery disease and in conditions in which ventricular morphology is significantly altered as ischaemic cardiomyopathy [11].

So, recently great efforts have been made to search for alternative and non-invasive parameters. AVPD is now considered an important component of overall ventricular function especially it represents the subendocardial layers of myocardium that is very sensitive to ischemia [12].

This study was conducted in order to evaluate value of LV AVPD displacement in assessment of systolic function in patients with HF-PSF. The study has included 30 patients with diastolic heart failure as a test group, healthy and 20 age and sex matched persons as a control group. The patients group was divided according to LV AVPD into two group: Group A with AVPD <10mm and group B with AVPD >10mm (Table 2).

In our study, assessment of LV systolic function by recording LVEDD, LVESD, LVEF and LVFS revealed significant difference between group A and group B being more affected in group A (Table 3).

**Assessment of LV systolic Function using AV plane displacement:**

The principal finding of this study is that a substantial proportion of patients with suspected heart failure and apparently preserved systolic function, as assessed by conventional measures, may have an unrecognized reduction in left ventricular contractility. Depending on which measure of systolic function and what “upper limit of normal” is considered.

Results of the current study show that in patients with diastolic heart failure the mean AV plane displacement was 9.5±0.6mm and in the control group was 15.1±1.9mm. The AV plane displacement was significantly lower in patients with diastolic heart failure than the normal controls (p<0.001). In the present work twelve patients (40%) with normal left ventricular systolic function as determined by conventional methods (FS percentage and EF%) were found to have abnormal systolic AV plane displacement (<10mm). These results indicated that patients with isolated diastolic heart failure had concomitant systolic dysfunction in spite of the fact that systolic function appears
normal when assessed by the conventional methods (FS% and EF%).

These findings raise the possibility that many patients thought to have "diastolic dysfunction" may in fact, have systolic dysfunction undetected by the measurements usually made when patients with suspected heart failure undergo routine echocardiography assessment.

Systolic AV plane displacement is quite different from left ventricular ejection fraction. Whereas the latter assess mainly contraction of circumferentially orientated fibers, systolic AV plane displacement is related more to contraction of longitudinal fibers [13,14].

Systolic AV plane displacement assess global left ventricular function as it is measured in four separate regions of the left ventricle (septal, lateral, posterior and anterior) and consequently, describes total shortening along the left ventricular long axis [7,15].

Reduced AVPD is reported by many studies to be a powerful predictor of poor prognosis especially if its value less than 10mm [8,16-18].

So, these results may be triggering for starting the use of AVPD in assessment of LV global systolic function especially in patients with diastolic heart failure or more accurately HF-PSF.

Cheuk-Man et al, 2002 [19] postulated that in the early course of cardiac diseases in which diastolic dysfunction was evident by Doppler echocardiography, systolic dysfunction starts to develop. As diastolic dysfunction progressed to clinical heart failure (i.e., DHF), systolic function is further jeopardized. Eventually, the disease progressed to a full-borne picture in which both systolic and diastolic dysfunctions are clinically evident.

In addition, Aly et al, 2007 [18] found that diastolic dysfunction invariably coexists in patients with SHF. Because systole and diastole are closely coupled in the cardiac cycle, it is possible that functional abnormalities of intracellular calcium handling and the interaction of myofilaments resulting in diastolic abnormalities also affect systolic function.

However a larger study is needed to support these results especially with incorporation of tissue Doppler imaging as a part of echocardiographic examination.

References


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Value of Transpulmonary Venous Flow Pattern and Mitral Flow Pattern in the Evaluation of Left Ventricular Diastolic Function in Hypertensive Patients

MAHMOUD MA YOSSOF, MD; HAMAZA KABIL, MD*; ASHRAF OMAR, MD; AYMAN ABD EL-SAMAD, MD; MAGED ZAGHLOL AMER, MD

Until recently, evaluation of diastolic function by Doppler echocardiography has been limited to measurement of transmitral velocities. Blood flow from the pulmonary circulation into the left ventricle, however, also involves pulmonary venous flow, left atrial contraction and relaxation as well as flow across the mitral valve. By examining pulmonary vein velocities in conjunction with mitral velocities, a more complete assessment can be made of the filling characteristics of the left side of the heart.

Abnormal left ventricular diastolic function is the earliest functional change in hypertension. Pulmonary congestion may result form left ventricular diastolic dysfunction even without any deterioration of systolic function.

In order to evaluate the usefulness of transmitral flow velocity patterns in conjunction with pulmonary venous flow pattern in the assessment of left ventricular diastolic function in patients with hypertension, the present study included 25 hypertensive patients as a test group and 20 apparently healthy subjects as a control group. For all, history taking, clinical examination, routine laboratory investigations and Doppler echocardiography with characterization of transmitral and pulmonary venous flow patterns were done. The results of the present study shows that left ventricular hypertrophy as evident by interventricular septal thickness, posterior wall thickness and left ventricular mass was more in patients group than control group.

Left ventricular diastolic dysfunction as evident by increase "A" wave, decrease "E" wave and decrease E/A ratio was more also in the patients group.

Regarding pulmonary venous flow, there is non significant difference in "S" wave between the two groups but "D" wave is significantly higher and S/D ratio is significantly lower in patients group than control group.

The use of pulmonary venous flow patterns shows a higher sensitivity and specificity then the use of transmitral flow pattern in the evaluation of left ventricular diastolic function.

Thus the use of pulmonary venous flow pattern with transmitral flow pattern in the evaluation of left ventricular diastolic function may add more sensitivity and specificity.

Key Words: Transpulmonary venous pattern and mitral flow.

Introduction

Hypertension represent an important health problem being common, asymptomatic, often leads to lethal complications if untreated. Also, more than half of heart attacks and two-thirds of strokes, occur in hypertensive patients [1]. Hypertension is responsible for left ventricular hypertrophy which is a major cardiovascular risk factor [2].

Although in this early form of left ventricular hypertrophy systolic pump function as measured by ejection fraction is not impaired, diastolic filling of the left ventricle is compromised by the process of left ventricular hypertrophy. Due to increase in diastolic stiffness and impaired relaxation, end-diastolic pressure and in turn pulmonary venous pressure increase. This may explains why patients...
with arterial hypertension have a pathological increase in pulmonary artery pressure under exercise despite a normal systolic pump function [3].

Current non invasive methods based on the detection of change in the ventricular physiological mechanisms not only provide the best chance for early cardiovascular diagnosis and intervention, but also the estimation of long-term prognosis. In this respect, the value of echocardiography in the assessment of LV dysfunction is evident especially in the quantification of LV systolic and diastolic function as being reliable indicators of mortality [4].

Doppler echocardiography is one of the most useful clinical tools for the evaluation of diastolic function. Mitral inflow and pulmonary venous flow are used not only for the assessment of diastolic function but also for prediction of prognosis [5].

The pattern of mitral flow may be affected by several factors e.g. location of Doppler sample volume [6], aging [7] and presence of "pseudonormalization" pattern which may influence the recording [8].

These deficiencies in the transmitral flow analysis have led to the need to assess the left ventricular function by another method which is also noninvasive and might be complementary to the transmitral flow analysis, as pulmonary venous flow pattern.

Since the left atrium serves as a reservoir during ventricular systole and as a conduit during early diastole, Doppler interrogation of pulmonary venous flow may help in assessment of left ventricular diastolic function [9].

**Aim of the work:**

The aim of the present study is to evaluate left ventricular diastolic function in hypertensive patients and also, to correlate Doppler pulmonary venous flow with mitral flow velocities and other parameters of left ventricular diastolic function in these patients.

**Patients and Methods**

The present study included 25 hypertensive as a test group (age range 38-68 with mean ± standard deviation 56±6.1 and 20 subjects with matched age and sex as a control group (age range 37-66 with mean ± standard deviation 55±9.9. Patients with atrial fibrillation or valvular heart disease or cardiomyopathy were excluded from this study. Patients and subjects included in the present work were subjected to thorough history taking, careful clinical examination, routine laboratory investigations and echo-Doppler examination.

**Echo-cardiographic examination include:**

A- M-mode and two dimensional evaluation of cardiac chambers in a standard manner from the parasternal views [10] with determination of left atrium size, left ventricular end diastolic dimension, end systolic dimension, ejection fraction, fractional shortening, posterior wall and interventricular septal thickness with calculation of left ventricular mass. It was calculated according to the following equation [11]:

\[
\text{L.V. mass (in grams)} = 1.04 \times (\text{posterior wall thickness} + \text{septal thickness} + \text{left ventricular end-diastolic diameter})^3 - \left(\text{left ventricular end-diastolic diameter}\right)^3 \times 0.8 \pm 0.6.
\]

*NB* Normal value: Females = 66-150, Males = 96-200 grams.

B- Doppler examination including continuous wave and pulsed wave Doppler with recording of mitral flow velocity pattern and pulmonary venous flow velocity pattern:

1- **Mitral flow velocity pattern:**

It was obtained in the apical four-chambers view with the sample volume carefully placed between the tips of the mitral valve leaflets and recording maximal flow. The following parameters were recorded and measured:

- E wave maximal velocity (normal range 48-76cm/sec).
- A wave maximal velocity (normal range 45-73cm/sec).
- E/A ratio (normal range 1-1.4).

2- **Pulmonary venous flow velocity pattern:**

It was obtained in the apical four-chamber view. Left atrial filling from the pulmonary vein is characterized by red signal along the interatrial septum in the upper part of the left atrium in the colour Doppler mode.

The orifice of the right pulmonary vein is imaged at the bottom of the flame like red signals and the pulsed Doppler sample volume was set just at the orifice of the right pulmonary vein and the waves were recorded.
The following parameters were measured:

- S wave maximal velocity (normal range 53-71 cm/sec).
- D wave maximal velocity (normal range 27-47 cm/sec).
- S/D ratio (normal range 1.1-1.8).

The normal pulmonary vein flow pattern consists of biphase forward flow, systolic and diastolic, as well as an atrial reversal flow.

**Systolic forward flow:**

During left ventricular contraction, the annulus moves downwards toward the apex causing an increase in the left atrial volume. Thus increase in the left volume results in a drop in left atrial pressure with a subsequent increase in from the pulmonary veins into the left atrium.

There is a linear correlation between cardiac output and the velocity of systolic forward flow.

**Diastolic forward flow:**

The diastolic forward flow in the pulmonary veins reflects the transmitral filling pattern. After mitral valve opening, the left atrial pressure is reduced and flow from the pulmonary vein passes through the left atrium into the left ventricle because the left atrium acts as an open conduit.

Both the peak diastolic velocity and deceleration time of the pulmonary vein are similar to the E velocity and deceleration time of the mitral flow. Therefore, the pulmonary vein diastolic flow is dependent on the same factors that influence the mitral valve E velocity and deceleration time; these include left atrial pressure, left ventricular relaxation and iscoelastic forces of the myocardium.

**Atrial reversal:**

Atrial contraction results in forward flow across the mitral valve and retrograde flow into the pulmonary veins.

Transmitral flow Doppler tracing

- Restrictive pattern of diastolic dysfunction.
- Exaggeration of the ratio bet E/A (↑ = ↓).

Pulmonary venous flow tracing

- Reversed E/A ratio.
- Prolonged deceleration time.
**Value of Transpulmonary Venous Flow Pattern & Mitral Flow Pattern**

**Statistical analysis:**

Statistical analysis was done by suing SPSS statistical package for social science program version 10, 1999. The data were parametric by using kolmogrov smirned test. The quantitive data were presented in the form of mean and standard deviation. Student $t$ test was used as a test of significance for two groups.

**Results**

The results shown Tables (1-3).

### Table 1: Some clinical data.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients group (25)</th>
<th>Control group (20)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>56±6.1</td>
<td>55±9.4</td>
<td>N.S.</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18 (72%)</td>
<td>13 (65%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Female</td>
<td>7 (28%)</td>
<td>7 (35%)</td>
<td></td>
</tr>
<tr>
<td>Systolic Blood pressure</td>
<td>160±8.7</td>
<td>120±5.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>(range 150-190)</td>
<td>(range 110-125)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic Blood pressure</td>
<td>105±8.3</td>
<td>80±6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>(range 95-130)</td>
<td>(range 70-85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>88.9±5.3</td>
<td>72±5.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>(69-92)</td>
<td>(65-86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of hypertension</td>
<td>9.2±3.9</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>(5-20)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2: Some echo-Doppler data.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients group (25)</th>
<th>Control group (20)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVESD (mm)</td>
<td>34.1±10.6 (26-53)</td>
<td>31.3±8.1 (23-41)</td>
<td>N.S.</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>51±8.7 (43-69)</td>
<td>46.1±7 (39-56)</td>
<td>N.S.</td>
</tr>
<tr>
<td>E.F.</td>
<td>55±2.1 (50-61)</td>
<td>62.2±6.2 (54-72)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>IVS thickness (mm)</td>
<td>16.7±2.1 (13-18)</td>
<td>9.8±0.3 (8-11)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>P.W. thickness (mm)</td>
<td>12.3±1.2 (10-15)</td>
<td>8.8±0.7 (8-11)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LVM (gm)</td>
<td>188±22</td>
<td>118±16</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**Mitral flow:**

- E-wave: $64.1±9.8$ (49-74) vs. $76.1±14.9$ (44-89) <0.01
- A-wave: $76.2±15.8$ (42-90) vs. $59.1±11.9$ (45-74) <0.01
- E/A ratio: $0.84±0.12$ vs. $1.28±0.21$ <0.01

**Pulmonary venous flow:**

- S cm/sec: $61.1±7.8$ vs. $59.7±8.1$ N.S.
- D cm/sec: $63.8±9.9$ vs. $40.1±10.8$ <0.01
- S/D ratio: $0.95±0.12$ vs. $1.48±0.05$ <0.01

### Table 3: Sensitivity and specificity of pulmonary venous flow pattern and mitral flow via detection of E/A ratio.

<table>
<thead>
<tr>
<th></th>
<th>Mitral</th>
<th>Pulmonary venous</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positive</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>True negative</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>False positive</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>False negative</td>
<td>9</td>
<td>11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary venous flow</td>
<td>0.86</td>
<td>0.69</td>
</tr>
<tr>
<td>Mitral flow</td>
<td>0.67</td>
<td>0.60</td>
</tr>
</tbody>
</table>
Discussion

Systemic hypertension has been known to be an important contributor in the enhanced incidence of cardiac morbidity and mortality [12]. The earliest functional cardiac changes in hypertension are in left ventricular diastolic function and relaxation abnormalities frequently precedes systolic dysfunction in hypertensive patients [13].

Sever diastolic dysfunction with abnormal filling pattern even in presence of normal systolic pump may cause pulmonary congestion and dyspnoea especially with exercise [3].

For better evaluation of left ventricular diastolic function, Doppler recording of mitral flow velocity pattern may be combined with recording or pulmonary venous flow pattern.

The present study was conducted to assess left ventricular diastolic function in hypertensive patients via recording of pulmonary venous flow pattern and mitral flow velocity pattern. 25 hypertensive patients (as a test group) and 20 apparently healthy subjects (as a control group) were included in the study.

Regarding clinical data, on comparing patients group versus control group there is no significant difference in age or sex but there is significant difference in systolic blood pressure, diastolic blood pressure and heart rate (Table 1). Study of echocardiographic data of both groups revealed significant increase of interventricular septal thickness, left ventricular posterior wall thickness and left ventricular mass in patients group than control group.

Significant increase of "A" wave but significant decrease of "E" wave and E/A ratio were found in patients group than control group (Table 2).

The results are in agreement with many studies [14,15]. Thus essential hypertension is accompanied by diastolic dysfunction of left ventricle which may be explained by increase stiffness, abnormal compliance with increase resistance to diastolic filling and so, decrease the rate of rapid filling. This is evident in our study by increase of IVS thickness, LVPW thickness and left ventricular mass and by abnormalities of mitral flow velocity pattern. Lee et al, 2006 [16], mention that alterations in left ventricular diastolic function may reduce the height of the E wave and increase the height of the A wave. The hemodynamic abnormalities responsible for this pattern usually are reduced left ventricular relaxation and slower fall in left ventricular pressure. This situation occurs with left ventricular hypertrophy, myocardial ischemia or even normal aging.

In order to make near complete assessment of the filling characteristics of the left side of the heart, recording of pulmonary venous flow velocity pattern was done. There is no significant difference between patients group and control group as regards "S" wave but "D" wave is significantly higher in patients group than control group. Also S/D ratio is significantly lower in patients than control group (Table 2).

Regarding sensitivity and specificity, the use of pulmonary venous flow pattern in the valuation of left ventricular diastolic function show specificity 69% and sensitivity 86% while the use of mitral flow pattern (E/A ratio) show specificity 60% and sensitivity 67% (Table 3).

Masuyama et al [10] 2005 concluded that Doppler evaluation of pulmonary venous velocity pattern may be more feasible and accurate in the assessment of left ventricular diastolic function.

Also, Nishimura et al, 2001 [17]; concluded that examination of the pulmonary venous velocities provides additional information regarding diastolic function. This information cannot be obtained from the mitral flow velocities alone.

Kuecherer et al, 2003 [18]; found that pulsed Doppler echocardiography of pulmonary venous flow may provide a useful clinical tool to reliably diagnose elevated pulmonary capillary wedge pressure as a result of impaired systolic function, diastolic dysfunction, or both.

Thus the present study has used patterns of mitral flow velocity and pulmonary venous flow in assessment of left ventricular diastolic function in hypertensive patients. This give a more accurate, near complete assessment. However, assessment of pulmonary venous flow pattern may be time consuming and difficult than recording transmitral flow velocity pattern.

There is need for a large scale study with use of tissue Doppler to confirm the results obtained from the present work.
Value of Transpulmonary Venous Flow Pattern & Mitral Flow Pattern

References


Safety and Cardiac Chronotropic Responsiveness to the Early Injection of Atropine During Dobutamine Stress Echocardiography in Hypertensive Patients

INAS IBRAHIM EWEDA, MD

Objective: Dobutamine-atropine stress echocardiography (DASE) is an established method for evaluating patients who have coronary artery disease (CAD). The aim of the study was to evaluate the effects of early administration of atropine during dobutamine stress echocardiography at 20µg/Kg/min EA-DSE, as compared to its conventional use at 40µg/Kg/min in hypertensive patients.

Methods: Sixty hypertensive patients were referred to the dobutamine stress echocardiogram, for detection of CAD, administration of atropine was randomized into two groups: group I at 20µg/Kg/min and group II at 40µg/Kg/min (EA-DSE and DASE) respectively. Diagnostic accuracy for detecting CAD (>50% stenosis) was assessed by coronary angiography ≤ 3 months of stress testing. We investigated the efficacy and diagnostic accuracy of EA-DSE versus those of DASE in hypertensive patients.

Results: The mean test time was 15.3±1.6 minutes in EA-DSE, 29.3±1.8 minutes in DASE (p<0.0001). EA-DSE resulted in diminished incidence of premature ventricular contractions, supraventricular tachycardia, atrial fibrillation, ventricular tachycardia, bradycardia and hypertensive response compared with DASE. Sensitivities, specificites and test accuracies did not differ between the EA-DSE and DASE.

Conclusion: EA-DSE is a safe and effective alternative to DASE and had a similar accuracy for detection of CAD.

Key Words: Dobutamine atropine stress echocardiography – Coronary artery disease.
mechanisms, including the extent of reduction in systemic vascular resistance, the magnitude of increase in cardiac output and the possible occurrence of intracavitary obstruction or stimulation of vagal reflexes [16,17,18]. The diagnosis of coronary artery disease using high doses of dobutamine infusion is based on the induction of myocardial ischemia by increasing myocardial oxygen demand through positive inotropic and chronotropic effects [19].

Recent modifications in the dobutamine stress echocardiography protocols include earlier injection of atropine in patients with poor chronotropic response to dobutamine [20-23]. This strategy has been shown to be safe and effective in reducing the test duration, maintain similar diagnostic accuracy for detecting angiographically significant CAD to that with the conventional protocol [22]. This strategy has been shown to be safe and effective in reducing the test duration, maintain similar diagnostic accuracy for detecting angiographically significant CAD to that with the conventional protocol [22].

The aim of this study is to determine the safety and efficacy of the early injection of atropine during dobutamine stress echocardiography in hypertensive patients with known or suspected CAD, as compared with the conventional protocol.

Methods

Patient population:
The study population comprised 60 patients with limited exercise capacity referred to our imaging laboratory for evaluation of myocardial ischemia by DSE. Hypertension, as diagnosed by the referring physician, was present in all patients. DSE was not performed in cases of severe heart failure, significant valvular heart disease, severe hypertension (blood pressure ≥180/110 mm Hg), hypotension (blood pressure <90/60 mm Hg), or unstable chest pain. Patients were divided into two groups, group one, who received atropine at dobutamine concentration 20µg/Kg/min and group two who received atropine as the conventional protocol at dobutamine concentration 40µg/Kg/min.

Dobutamine stress test:
Dobutamine was infused through an antecubital vein starting at a dose of 5 µg/kg per minute followed by 10 µg/kg per minute (3-minute stages), increasing by 10 µg/kg per minute every 3 minutes to a maximum of 40 µg/kg per minute. Atropine sulphate was initiated at a dose of 0.25 up to 0.5 mg and increased until a maximum dose of 2 mg in patients not achieving 85% of age-predicted maximal heart rate and dobutamine infusion was continued. Atropine injection was given at 20µg/Kg/min in group I (EA-DSE) and at 40µg/Kg/min group II (DASE). Cuff blood pressure was measured at rest, every 3 minutes during stress and at maximal stress. The test was interrupted if any of the following appeared during the test: severe chest pain, ST segment depression greater than 2 mm, significant ventricular or supraventricular arrhythmia, hypertension (blood pressure ≥240/120 mm Hg), systolic pressure fall greater than 40 mm Hg, or any intolerable side effect regarded as being caused by dobutamine. Metoprolol (1 to 5 mg) was available and used intravenously to reverse the effects of dobutamine if they did not revert spontaneously and quickly. The test was considered feasible if the patient could achieve 85% of the maximal heart rate predicted for age and/or when an ischemic end point (angina, ST segment depression, new or worsened wall motion abnormalities) was reached. All patients gave verbal informed consent to undergo the study.

Stress echocardiography:
Echocardiographic images were acquired when patients were at rest and during stress and recovery. The echocardiograms were digitized on optical disk and displayed side by side in quad-screen format (Vivid V, Vivid VII) to facilitate the comparison of rest and stress images. The left ventricular wall was divided into 16 segments and scored with a four-point scale (1=normal, 2=hypokinesis, 3=akinesis, 4=dyskinesis). Ischemia was defined as new or worsening wall motion abnormalities. As we have previously concluded, ischemia was not considered when akinetic segments at rest became dyskinetic during stress without improvement at a low dose of dobutamine (5 to 10 µg/kg per minute) [23-24].

Coronary angiography:
Coronary angiography was performed within 3 months from dobutamine atropine stress echocardiography. Significant coronary artery disease was defined as a stenosis diameter greater than or equal to 50% in one or more major epicardial artery.

Statistical analysis:
Data are presented as mean±SD. The X² test was used to compare differences between proportions. Student’s t test was used for analysis of
continuous data. The difference in risk was expressed as odds ratio (OR) with the corresponding 95% confidence interval (CI). Differences were considered significant if the null hypothesis could be rejected at the .05 probability level. Sensitivity, specificity and accuracy of dobutamine atropine stress echocardiography for the diagnosis of significant coronary artery disease were derived according to standard definitions.

Results

No death or myocardial infarction occurred during or shortly after the test. Peak systolic and diastolic blood pressure were significantly lower in the EA-DSE group than the DASE group. Also, there was a significant reduction in the complications of the test and the test duration as shown in the following tables.

Table 1: Clinical characteristics of the patients of group I (EA-DSE) and group II (DASE).

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Group I (EA-DSE)</th>
<th>Group II (DASE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55.7±2.9</td>
<td>64.2±3.3</td>
</tr>
<tr>
<td>Male</td>
<td>18 (60%)</td>
<td>54±3.2</td>
</tr>
<tr>
<td>Smoking</td>
<td>18 (60%)</td>
<td>44±1.7</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>20 (67%)</td>
<td>19 (63%)</td>
</tr>
<tr>
<td>DM</td>
<td>12 (40%)</td>
<td>11 (37%)</td>
</tr>
<tr>
<td>MI</td>
<td>5 (17%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>CABG</td>
<td>2 (7%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>PTCA</td>
<td>2 (7%)</td>
<td>5 (17%)*</td>
</tr>
<tr>
<td>Blockers</td>
<td>10 (33%)</td>
<td>11 (37%)</td>
</tr>
<tr>
<td>Ca-Ch blocker</td>
<td>5 (17%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>10 (33%)</td>
<td>14 (47%)*</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>6 (20%)</td>
<td>5 (17%)</td>
</tr>
<tr>
<td>Rest EF (%)</td>
<td>64.2±3.3</td>
<td>63.9±6.1</td>
</tr>
</tbody>
</table>

*p<0.05 between groups. Data are mean±SD or numbers (percentages).

Table 2: Hemodynamic data of group I (EA-DSE) and group II (DASE).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I (EA-DSE)</th>
<th>Group II (DASE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest heart rate (beat/min)</td>
<td>74.3±5.6</td>
<td>74.9±6</td>
</tr>
<tr>
<td>Rest systolic blood pressure (mmHg)</td>
<td>124.1±10.9</td>
<td>123.3±11.5</td>
</tr>
<tr>
<td>Rest diastolic blood pressure (mmHg)</td>
<td>78.6±8.1</td>
<td>76.7±8.3</td>
</tr>
<tr>
<td>Rest rate-pressure product (mmHg/min)</td>
<td>9230.9±1195.4</td>
<td>9267.9±1347.9</td>
</tr>
<tr>
<td>Peak heart rate (beat/min)</td>
<td>147.9±15.3</td>
<td>137.4±7.1*</td>
</tr>
<tr>
<td>Peak systolic blood pressure (mmHg)</td>
<td>148.2±8.7</td>
<td>161.7±11.1*</td>
</tr>
<tr>
<td>Peak diastolic blood pressure (mmHg)</td>
<td>91.4±4.5</td>
<td>100.4±8.6*</td>
</tr>
<tr>
<td>Peak rate-pressure product (mmHg/min)</td>
<td>23327.5±1687.1</td>
<td>21906.4±1319.7*</td>
</tr>
<tr>
<td>Test time (minutes)</td>
<td>15.3±1.6</td>
<td>29.3±1.8*</td>
</tr>
</tbody>
</table>

*p<0.05 between groups. Data are mean±SD.

Heart rate, blood pressure and rate-pressure product for the 2 protocols are listed in Table (2). Patients who underwent EA-DSE achieved significant increases in heart rate, peak heart rate and rate pressure product at peak stress than did patients who underwent DASE.

Table 3: Adverse effects observed during the test in group I (EA-DSE) and group II (DASE).

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Group I (EA-DSE)</th>
<th>Group II (DASE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature ventricular contraction</td>
<td>6 (20%)</td>
<td>10 (33%)*</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>0 (0%)</td>
<td>3 (10%)*</td>
</tr>
<tr>
<td>Non sustained ventricular tachycardia</td>
<td>0 (0%)</td>
<td>3 (10%)*</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0 (0%)</td>
<td>4 (13%)*</td>
</tr>
<tr>
<td>Symptomatic bradycardia</td>
<td>1 (3%)</td>
<td>6 (20%)*</td>
</tr>
<tr>
<td>Chest pain</td>
<td>3 (10%)</td>
<td>10 (33%)*</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (7%)</td>
<td>11 (37%)*</td>
</tr>
<tr>
<td>Symptomatic hypotension</td>
<td>2 (7%)</td>
<td>7 (23%)*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0 (0%)</td>
<td>5 (17%)*</td>
</tr>
</tbody>
</table>

*p<0.05 between groups. Data are numbers (percentages).

The adverse effects were significantly lower in group I EA-DSE, hypertensive response to stress did not occur in any of the patients of the EA-DSE, neither did any serious arrhythmias as ventricular tachycardia or supraventricular tachycardia.
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Test time was 15.3±1.6 minutes in group I EA-DSE and 29.3±1.8 minutes in group II DASE \( p<0.0001 \).

Table 4: Diagnostic parameters of group I EA-DSE and group II DASE for the detection of coronary artery disease.

<table>
<thead>
<tr>
<th>Diagnostic parameters</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity LAD</td>
<td>95.8% (23/24)</td>
<td>96.4% (27/28)</td>
</tr>
<tr>
<td>Sensitivity LCX</td>
<td>95% (20/21)</td>
<td>94.7% (18/19)</td>
</tr>
<tr>
<td>Sensitivity RCA</td>
<td>95% (19/20)</td>
<td>95% (20/21)</td>
</tr>
<tr>
<td>Specificity LAD</td>
<td>83.3% (5/6)</td>
<td>100% (2/2)</td>
</tr>
<tr>
<td>Specificity LCX</td>
<td>88.9% (8/9)</td>
<td>90.9% (10/11)</td>
</tr>
<tr>
<td>Specificity RCA</td>
<td>80% (8/10)</td>
<td>88.9% (8/9)</td>
</tr>
<tr>
<td>Accuracy LAD</td>
<td>93.3% (28/30)</td>
<td>96.7% (29/30)</td>
</tr>
<tr>
<td>Accuracy LCX</td>
<td>93.3% (28/30)</td>
<td>93.3% (28/30)</td>
</tr>
<tr>
<td>Accuracy RCA</td>
<td>90% (27/30)</td>
<td>93.3% (28/30)</td>
</tr>
</tbody>
</table>

\* \( p<0.05 \) between groups.  
Data are numbers (percentages).

Figure 2: Comparison between group I EA-DSE and group II DASE as regards adverse effects at peak stress.

Figure 3: Comparison between group I EA-DSE and group II DASE as regards test time.

Figure 4: Diagnostic parameters of group I EA-DSE and group II DASE for the detection of coronary artery disease

Discussion

Hypertension is a risk factor frequently encountered in patients referred for noninvasive diagnosis or functional evaluation of CAD [2-25]. Exercise electrocardiography and myocardial perfusion scintigraphy may have limitations in the diagnosis of coronary artery disease in these patients [2]. Alternatively, DSE is being increasingly used, particularly in patients with limited exercise capacity [9-26]. This study demonstrates that DASE is a feasible and safe method for evaluation of coronary artery disease in hypertensive patients with suspected myocardial ischemia and limited exercise capacity. No myocardial infarction or death occurred during the test.

In the present study, a comparison between EA-DSE and DASE was performed. EA-DSE required smaller doses of dobutamine and resulted in lower rates of adverse effects compared with DASE in hypertensive patients similar to those reported previously [4-27-28]. Conventional administration of atropine at peak doses may lead to rapid increase in heart rate and rate-pressure product only in the latest phase of stress testing. With this strategy, atropine may reach its maximal blood activity only after the test has been terminated. This study confirmed that the early administration of atropine resulted in a shorter duration of dobutamine infusion and less adverse effects than did DASE. The diagnostic accuracy of the 2 protocols for detecting significant CAD was in accordance with previously reported results [10-29]. EA-DSE resulted in early
chronotropic stimulation, which may balance the inotropic stimulation provided by dobutamine. This effect is associated with a shorter duration of dobutamine infusion, might explain the decreased rate of minor adverse effects observed with EA-DSE.

The number of patients who had hypertensive response was significantly larger for DASE than for EA-DSE as our patients were all hypertensive so they were more prone for occurrence of hypertension with higher dose of dobutamine. Dobutamine stress-induced hypotension has been shown in 5% to 37% of patients [10-30]. Possible mechanisms related to hypotension during dobutamine stress echocardiography include an inadequate increase in cardiac output to compensate for an expected decrease in systemic vascular resistance or a disproportionate decrease in systemic vascular resistance [17]. This late effect may occur due to an excessive sensitivity of the peripheral circulation to Beta 2 receptor density or to a neurally mediated mechanism. In these circumstances, vigorous myocardial contraction stimulates intramyocardial mechanoreceptors, resulting in sympathetic withdrawal and enhanced parasympathetic activity (Bezold-Jarisch reflex) [17].

Therefore, early administration of atropine may prevent this effect, resulting in a lower incidence of bradycardia & hypotension. Another important point to be considered is the decreased incidence of arrhythmias observed in EA-DSE. The incidence of premature ventricular complexes and supraventricular or ventricular tachycardia in patients underwent DASE was similar to that of previous reports [31,32,33]. The shorter exposure to an adrenergic drug that occurs in the protocol for EA-DSE may explain the lower incidence of premature ventricular complexes and supraventricular or ventricular tachycardia.

In conclusion, early injection of atropine is a safe and effective strategy during dobutamine stress echocardiography and this protocol has a diagnostic accuracy for detecting CAD that is similar to that observed for the conventional protocol.

References
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Inferior Vena Cava Index, A New Approach for Monitoring Patients in Acute Decompensated Congestive Heart Failure

HATEM EL-ATROUSH, MD

Acute exacerbation of chronic heart failure represents an important health problem and economic burden in recent medicine. Despite increasing interest in noninvasive tools for diagnosis and monitoring therapy in patients with decompensated heart failure, its reliability is still debatable. The aim of this study is to investigate the validity of inferior vena cava (IVC) dynamics as a noninvasive diagnostic and monitoring tool in patients with acute exacerbation of heart failure. Fourty patients with decompensated heart failure 21 males and 19 females with mean age 55±13 years were included. All were in NYHA class and Killip class III-IV and had the clinical criteria of acute decompensated heart failure. All patients were admitted to ICU and subjected to echocardiographic study on admission, on days 5 and 10 of medical treatment. Echocardiographic examination included parameters of left ventricular dimensions and functions, IVC dynamics which include, measurements of IVC diameter at end expiration (Dmax), at end inspiration (Dmin), collapse index (IVCci) and IVC to aorta index (IVC/Ao). IVCci was calculated as Dmax minus Dmin divided by Dmax and multiplied by 100 and expressed as percentage. The IVC/Ao index was calculated by dividing the maximum IVC diameter recorded during regular respiration and divided by the aorta diameter. A control group of ten volunteers 5 males and 5 females were included in the study and the same echocardiographic left ventricular measurements and IVC dynamics were recorded to establish a normal reference range for IVC dynamics.

Significant improvement in clinical and left ventricular functions were observed. Significant increase in IVCci was recorded from 12±4% on admission to 26±8% and 42±9% (p<0.001) on day 5 and 10 respectively. The IVC/Ao index decreased significantly from 0.66±0.1 on admission to 0.58±0.1 and 0.54±0.1 (p<0.001) on day 5 and 10 respectively. Significant correlations were found between the changes in left ventricular functions and IVC dynamics.

**Conclusion:** Estimation of IVC dynamics seems to be a reliable and reproducible noninvasive diagnostic and hemodynamic monitoring tool in management of patients with acute decompensated heart failure.

**Key Words:** Inferior vena cava dynamics – Congestive heart failure – Echocardiography – Noninvasive – Hemodynamic monitoring.
pressures and decreased tissue perfusion, which in turn produce the fundamental symptoms of heart failure, including swelling, dyspnea, fatigue and a decrease in exercise capacity. Elevated venous pressures lead to left and/or right atrial hypertension, which results in edema or dyspnea, while increased peripheral resistance and reduced cardiac output lead to fatigue and reduced exercise capacity. To alleviate symptoms and improve patient well-being, pharmacologic intervention for decompensated heart failure is targeted at underlying hemodynamic alterations [3].

Classical signs and symptoms of venous congestion such as pulmonary and peripheral edema are often primary diagnostic factors in hospital admittance and acute implementation of diuretic treatment, which is clearly appropriate. Quantitative evaluation of hemodynamic indices and the adequacy of tissue perfusion should play a primary role in the decision to initiate additional therapies (e.g., intravenous vasodilators, natriuretic peptides, or inotropic agents) and to determine patient disposition upon hospitalization. Reliance on physical examination skills such as jugular venous distention or pulmonary rales is straightforward but relatively insensitive and the ability to accurately judge patients’ clinical or hemodynamic status from history and from physical examination is inadequate. Studies evaluating the ability of clinicians to accurately assess preload based on an examination of the jugular venous pressure indicate that clinicians are only correct about 50% of the time when relying upon clinical judgment. These shortcomings in clinical assessment relegate treatment decisions to poorly guided empiricism [4,5].

When targeting hemodynamics for treatment of symptomatic heart failure, the primary physiological determinants of cardiac performance are most easily modulated by pharmacological and mechanical interventions; these are preload, afterload, heart rate and contractility. Most therapies to date have focused on modulating either preload or afterload to unload the heart, improve cardiac performance and alleviate both congestive and low-output symptoms associated with heart failure. There is evidence that a tailored, hemodynamic approach to treatment has an important impact on outcome. Steimle et al. reported successful outcomes utilizing tailored therapy for heart failure inpatient management in patients with advanced disease. Specific hemodynamic goals included reductions in wedge pressure, systemic vascular resistance and right atrial pressure while maintaining arterial blood pressure [6].

An accurate assessment of the preload, afterload and contractility is a significant challenge during every clinical examination. In all cases of heart failure, the therapy and its effectiveness depend on their accurate evaluation. There are many useful noninvasive methods for monitoring patients with decompensated congestive heart failure such as clinical examination, biochemical markers, bioimpedance and Doppler Echocardiography. However, all of these methods are burdened with some limitations when used in clinical practice. The advantages of ultrasound imaging are commonly known and ultrasound units are present in every emergency department (ED) where fast imaging technique is indispensable [7].

Therefore, in this study we concentrate on the usefulness of the sonographic assessment of IVC dynamics in patients with decompensated heart failure treated with aggressive medical treatment in ICU. Simultaneously, we are aware of some limitations of this method, such as problems with equipment, necessity of comparing results with body surface area (BSA), measurement of IVC diameter during maximal inspiration and expiration (needing cooperation of the patient) and lack of reference values for IVC diameter. For these reasons, we introduce a new sonographic parameter, the "IVC/aorta diameter Index (IVC/Ao)" an innovation that is convenient, fast, easy to perform, and effective non invasive monitoring for patients in decompensated congestive heart failure in the ICU.

Material and Methods

Control group:
Ten volunteers (five men and five woman) aged between 19 and 67 years, were enrolled into the study. All hemodynamic, Doppler echocardiographic and IVC dynamic measurements were recorded together with blood pressure, weight and height. The collapse index of the IVC (IVCci) was derived as the ratio of the difference between Dmax and Dmin to the Dmax and expressed as a percentage value. The IVC diameter was measured again during a regular breathing cycle (D reg) and the maximum value was recorded. The ratio of the D reg to the aorta diameter (IVC/Ao) was also calculated for all volunteers. Table (1) shows aorta and IVC dynamics characteristics of the control group.
Patients:
This study includes 40 patients, 21 males and 19 females, with age range from 18 to 70 years. All were admitted to critical care department suffering from acute decompensation of congestive heart failure due to dilated cardiomyopathy. The diagnosis was based on full medical history, physical examination, Doppler echocardiography, electrocardiography, full laboratory evaluation and plain chest x-ray. None of them was on mechanical ventilation, had chronic atrial fibrillation, pulmonary embolism, diabetes mellitus, end stage renal disease nor severe anemia. Table (2) shows patients characteristics in this study.

Table 1: Control group characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: female/male (n)</td>
<td>5/5</td>
</tr>
<tr>
<td>Age (years)</td>
<td>43±16</td>
</tr>
<tr>
<td>Body surface area (m2)</td>
<td>1.9±0.2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>73±26</td>
</tr>
<tr>
<td>SAP (mmHg)</td>
<td>119±8</td>
</tr>
<tr>
<td>DAP (mmHg)</td>
<td>75±7</td>
</tr>
<tr>
<td>IVC ci (%)</td>
<td>69±6</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>71±6</td>
</tr>
<tr>
<td>IVC/Ao</td>
<td>0.44±0.08</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation except where indicated. n=10 (SAP: Systolic arterial pressure; DAP: Diastolic arterial pressure; IVC ci: Inferior vena cava collapse index; LVEF: Left ventricular ejection fraction; IVC/Ao: Inferior vena cava maximum diameter during regular respiration/aorta diameter index).

Study design:
The duration of the study was 10 days for each patient. On admission, all patients were subjected to full history taking, physical examination and complete electrocardiographic, radiographic, laboratory and Doppler echocardiographic examinations. Echocardiographic examinations were performed by the same operator using transthoracic ultrasound device (ATL, HDI 5000) equipped with a phased array transducer of 2.5 MHz. Conventional echocardiography, including M-mode, two-dimensional (2D) and pulsed and color Doppler measurements was performed.

The left ventricular ejection fraction (LVEF) was measured using the biplane Simpson’s method from the apical two-chamber and four-chamber views [8].

Inferior vena cava (IVC) study was done by 2D echocardiography in the longitudinal view in supine position with a 3.5 to 5 MHz convex probe at 2 centimeter below its entrance into the right atrium. Inferior vena cava diameter (IVCD) was measured at end-expiration to obtain the maximum IVC diameter (Dmax) and at end-inspiration to obtain the minimum IVC diameter (Dmin). The collapse index of the IVC (IVC ci) was derived as the ratio of the difference between Dmax and Dmin to the Dmax and expressed as a percentage value (Fig. 1). The IVC diameter was measured again during a regular breathing cycle (D reg) and the maximum value was recorded. The ratio of the D reg to the aorta diameter (IVC/Ao) was also calculated for all patients. All patients received aggressive medical treatment including diuretics, vasodilators and inotropic support and all measurements were repeated and recorded on the fifth and tenth day of treatment. Patients who did not complete the 10 days duration of the study were excluded.

Table 2: Patients characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: female/male (n)</td>
<td>19/21</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55±13</td>
</tr>
<tr>
<td>Body surface area (m2)</td>
<td>1.9±0.16</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>107±9</td>
</tr>
<tr>
<td>SAP (mmHg)</td>
<td>123±16</td>
</tr>
<tr>
<td>DAP (mmHg)</td>
<td>85±16</td>
</tr>
<tr>
<td>IVC ci (%)</td>
<td>12±4</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>19±6</td>
</tr>
<tr>
<td>IVC/Ao</td>
<td>0.66±0.11</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation except where indicated. n=40 (SAP: Systolic arterial pressure; DAP: Diastolic arterial pressure; IVC ci: Inferior vena cava collapse index; LVEF: Left ventricular ejection fraction; IVC/Ao: Inferior vena cava maximum diameter during regular respiration/aorta diameter index).

Figure 1: Example of echographic recording of respiratory changes in inferior vena cava diameter.
Statistical analysis:

Continuous variables are presented as mean ± SD while categorical variables were expressed as frequency. Baseline continuous variables were compared using the student t test and categorical variables were compared using Chi-square analysis. For testing the strength of an already existing relationship between continuous normally distributed variables, Pearson Coefficient correlation was used. A \( p \)-value <0.05 was considered significant.

Results

The IVC/Ao indices were obtained using the following formula: maximum IVC diameter recorded during regular breathing divided by the aorta diameter. The IVCci was obtained by dividing the IVC diameter during maximal inspiration by the minimum IVC diameter recorded during end expiration.

Comparing the IVCci and IVC/Ao indices between the control group and the patients group we found a statistically significant difference (69%±6 and 0.44±0.08) Vs (12%±4 and 0.66±0.11) respectively (\( p < 0.001 \)). Significant improvement in clinical and Doppler echocardiographic measurements were observed during the duration of the study (10 days). The IVCci increased from (12±4) on admission to (26±8) and (42±9) on day 5 and day 10 respectively (\( p < 0.001 \)). IVC/Ao index showed significant correlation with echocardiographic data concerning left ventricular functions and significant correlation with IVCci. The IVC/Ao index decreased significantly from (0.66±0.1) to (0.58±0.1) and (0.54±0.1) on day 5 and day 10 respectively (\( p < 0.001 \)) (Table 3) (Fig. 2).

Table 3: Patients hemodynamic and IVC dynamics data on admission, on day 5 and on day 10.

<table>
<thead>
<tr>
<th>N=40</th>
<th>On admission</th>
<th>On day 5</th>
<th>On day 10</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVCci (%)</td>
<td>12±4</td>
<td>26±8</td>
<td>42±9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IVC/Ao</td>
<td>0.66±0.1</td>
<td>0.58±0.1</td>
<td>0.54±0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>19±3.6</td>
<td>25±5</td>
<td>31±5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CI, L/min/m²</td>
<td>1.5±0.2</td>
<td>1.8±0.3</td>
<td>2±0.3</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

(CI: Cardiac index; LVEF: Left ventricular ejection fraction; IVC/Ao: Inferior vena cava to aortic index; IVCci: Inferior vena cava collapse index). Values are mean ± standard deviation.

Discussion

The main aim of this study was to investigate the reliability and the validity of indices derived from echocardiographic IVC study in estimation and monitoring of left ventricular function during treatment of patients with acute exacerbation of congestive heart failure. In this study we evaluated two important IVC indices, the first is the IVC collapse index (IVCcI) which require measurement of IVC diameter at end inspiration and end expiration and the second index is the IVC/Ao which require the measurement of the maximum IVC diameter during normal respiration divided by the aorta diameter. The second index from the practical point of view should be easy to perform, quick, precise and repetitive particularly in critically ill patients.

The observed IVCci values were consistent with values previously published for controls and for patients with various forms of cardiac disease. Vourvouri et al in 2003 confirmed that the change in IVC dynamics can be used in screening for LV dysfunction and reported that the sensitivity of a IVCci less than 50% to detect LV dysfunction with LVEF less than 40% approached 96% [9]. There are many studies reporting that the diminished respiratory variation in IVC diameter in patients with congestive heart failure reflects exhaustion of the IVC capacitance due to markedly increased right heart filling pressure and volume overload [10] and it was reported that the dilated IVC without...
decreased inspiratory collapse is a marker of poor survival independent of the history of heart failure or the ventricular function [11].

In our study strong and significant correlation was found between echo determined parameters of LV function on day 5 and day 10 and parameters of IVC dynamics. The strongest correlation was between the changes in IVCci and CI on day 5 and 10 of treatment ($r=0.78$ and 0.69 respectively). These results coincide with the results obtained by Hollerbach S. et al in 2001, who studied the validity of IVC dynamics as a clinical tool to assist in monitoring of therapy in patients with CHF. In their study, IVC diameter decreased continuously and significantly ($p<0.003$) from day 1 to day 10 of diuretic therapy. Also, at the beginning of therapy the IVCci was significantly lesser in patients than in controls. However, after 10 days of therapy this index reached similar values to those observed in controls. They concluded that ultrasonic measurements of IVC diameters and inspiratory movements are a quantifiable and reliable approach to assess the hypervolemia associated with CHF. Sasaki T et al in 2001, in a study over 373 patients admitted due to acute exacerbation of chronic HF, found that IVC dimensions were not correlated with the etiology of HF, NYHA class and severity of pulmonary congestion (Killip class) but were correlated with EF% ($r=0.76$, $p<0.0001$) [13].

The IVC/Ao index was first introduced into clinical practice for evaluating pediatric emergency patients and was very helpful in diagnosing dehydration as well as overhydration status in emergency patients [14]. In our study strong and significant correlation were found between the changes in IVC/Ao index and CI on day 5 and 10 ($r=0.68$ and 0.72 respectively) and significantly correlate with other parameters of left ventricular functions.

Comparing IVC diameter with aorta diameter can be a promising method of estimating body water status and left ventricular functions without the necessity of looking for reference values for each age group or calculating per BSA, which saves the time needed for setting a final diagnosis. The IVC/Ao index seems to play a very important role in diagnosing dehydration as well as overhydration status in emergency patients and an accurate and rapid evaluation of left ventricular functions in patients with congestive heart failure. The simplicity of the examination technique with quite constant measurement points can eliminate the examiner dependence. According to our observations, the IVC/Ao index seems to be more adequate and correlates more precisely with clinical course than does other IVC measurements. Our results are very promising, indicating the necessity of further studies to prove the usefulness of the IVC/Ao index in clinical practice.

**Conclusions**

From the results of our study we can conclude that IVC dynamics are valid and reliable as a simple, noninvasive hemodynamic tool in diagnosis and monitoring therapy for acute exacerbation of CHF. IVC dynamics can replace echocardiographic parameters of LV function at bedside evaluation for monitoring therapy of acute exacerbation of CHF. In our opinion, the IVC/Ao index assessment should be introduced in every situation where body fluid status and left ventricular functions affects further treatment and prognosis.

**References**

8. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, St John Sutton M, Stewart WJ: Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005; 18: 1440-1463.


Introduction

The long-predicted endocrine function of the heart has been proven by the discovery of atrial natriuretic peptide (atrial natriuretic factor; A-type natriuretic peptide; ANP) 20 years ago. This subsequently led to the description of a whole family of structurally similar but genetically distinct peptides, the natriuretic peptide family, which contributes to cardiovascular homeostasis. These looped peptides promote natriuresis and diuresis, act as vasodilators and exert antimitogenic effects on cardiovascular tissues. The aim of this study was to assess the role of brain natriuretic peptide (BNP) on the in-patients with congestive heart failure and its relation to the patient outcome.

Objective: The long-predicted endocrine function of the heart has been proven by the discovery of atrial natriuretic peptide (atrial natriuretic factor, A-type natriuretic peptide; ANP) 20 years ago. This subsequently led to the description of a whole family of structurally similar but genetically distinct peptides, the natriuretic peptide family, which contributes to cardiovascular homeostasis. These looped peptides promote natriuresis and diuresis, act as vasodilators and exert antimitogenic effects on cardiovascular tissues. The aim of this study was to assess the role of brain natriuretic peptide (BNP) on the in-patients with congestive heart failure and its relation to the patient outcome.

Design: Randomized prospective controlled study.

Setting: Department of Critical Care Medicine, Cairo University.

Patient: A total of 40 patients, 26 males (65%) and 14 females (35%) with mean age of 37.1±13.2 years complaining of symptoms of congestive heart failure all patients were subjected to full history taking, complete general examination, complete local examination, laboratory profile including: CBC, Liver function tests, Kidney function tests, ECG, Echocardiography and laboratory BNP measurements.

Interventions: None.

Measurements and Results: There was a statistically significant difference between serum BNP level in the groups involved in the study, the mean BNP level was 8.4ng/ml, 2.3ng/ml, 0.2ng/ml in group I, II and III, respectively. p value between group I and group II was 0.001. BNP level was found to have positive correlation to both LVESD and LVEDD in all groups (r=0.77, p=0.000) and LVEDD (r=0.81, p=0.000). Serum level of BNP was found to be inversely proportional to both ejection fraction (EF%) and fraction shortening (FS%) (negative correlation) (r=-0.73, p=0.000) and (r=-0.77, p=0.000) respectively.

Conclusion: This study proved that BNP level was a useful predictor of decompensated CHF outcome this could be explained by the fact that BNP is a purely ventricular hormone. There was a direct relationship between ventricular wall stress and secretion of BNP.

Key Words: Heart failure – Brain natriuretic peptide.
ANP and its N-terminal prohormone fragments in myocardial infarction as well as in chronic heart failure patients. Natriuretic peptides represent an important class of molecules in patients with congestive symptoms. As such, natriuretic peptide measurements can assist in the evaluation of patients with heart failure or to exclude this as a cause in patients with dyspnea. Increasing the levels of natriuretic peptides may offer an important therapeutic advance in patients with heart failure [1].

**Aim of the work:**

The aim of this study was to assess the role of brain natriuretic peptide (BNP) on the in-patients with congestive heart failure and its relation to the patient outcome.

**Patients and Methods**

This study was performed on 40 patients 26 males (65%) and 14 females (35%) with mean age of 37.1±13.2 years complaining of symptoms of congestive heart failure, they were admitted to the Critical Care Department in Kasr-El-Aini Hospital. Twenty healthy volunteers were taken as control group.

**Inclusion criteria:**

**Criteria for inclusion included:**

- New onset CHF confirmed by at least one cardiologist using standard Framingham criteria.
- Exacerbation of previously documented CHF.
- All patients had to be at least NYHA class III to be included.
- The initial BNP level should be drawn with 24 hours of admission and within 24 hours of discharge or death.

**Exclusion criteria:**

1- Impaired kidney function or renal failure.
2- Ascitis.
3- Liver cell failure.

**All patients were subjected to:**

1- Full history taking including present history of the disease (duration of illness, presence of symptoms as Dyspnea, cough and expectoration and past history of ischemic heart diseases.
2- Complete general examination for manifestations of congestive heart failure.

3- Complete local examination: To detect left ventricular systolic dysfunction.
4- Laboratory:
   a- Complete blood picture.
   b- Liver function tests.
   c- Kidney function.
5- Standard 12 leads electrocardiography (ECG).
6- 2-D and M-mode echocardiography.
7- Laboratory BNP measurement:

   This was done by the use of competitive enzyme immunoassay kit (Pensula laboratories INC) which is designed to detect the specific peptide indicated on the enclosed data sheet. The kit is designed for the measurement of Human plasma without the use of an extraction procedure enabling the generation of duplicate six or ten point standard curves and the analysis of up to 41 samples in duplicate.

**Results**

This study was conducted on 40 patients and 20 healthy controls they were classified into the following groups:

- Group I: 20 patients with acute heart failure.
- Group II: 20 patients with compensated heart disease.
- Group III: 20 healthy volunteers, matched for age and sex to patient, taken as control group.

**Table 1: Demographic data.**

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Male</td>
</tr>
<tr>
<td>Group I</td>
<td>20</td>
<td>45.2±15</td>
<td>13</td>
</tr>
<tr>
<td>Group II</td>
<td>20</td>
<td>48.3±12.1</td>
<td>13</td>
</tr>
<tr>
<td>Group III</td>
<td>20</td>
<td>41.6±6.2</td>
<td>10</td>
</tr>
</tbody>
</table>

**Classification of cases according to the etiology of heart failure:**

They were divided into 3 groups ischemic dilated cardiomyopathy: 25 patients (62.5%), Rheumatic heart disease: 10 patients (25%), idiopathic dilated cardiomyopathy: 5 patients (12.5%).

**Results of BNP in the studied groups on admission and discharge:**

**Estimation of serum BNP level in different studied groups:**

There was statistically significant difference between serum BNP level in the groups involved
in the study, the mean BNP level in group I is 8.4 ng/ml while in group II it is 2.3 ng/ml, in group III it is 0.2 ng/ml. \( p \) value between group I and group II is 0.001 \( p \) value between group I and group III is 0.001.

Figure 1: According to the echocardiographic data, the patients with heart failure (HF) were divided into: Group A including twelve patients (30%) with systolic HF, group B including 12 patients (30%) with diastolic HF and group C including 15 patients (40%) with combined HF (Fig. 2).

Figure 2: Distribution of the studied cases according to the type of heart failure.

Table 2: BNP level in group I on admission and discharge.

<table>
<thead>
<tr>
<th></th>
<th>Admission</th>
<th>Discharge</th>
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<tbody>
<tr>
<td>Maximum</td>
<td>20</td>
<td>19.6</td>
</tr>
<tr>
<td>Minimum</td>
<td>1.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Mean</td>
<td>8.4</td>
<td>6.4</td>
</tr>
<tr>
<td>SD</td>
<td>5.8</td>
<td>6.0</td>
</tr>
<tr>
<td>Median</td>
<td>6.4</td>
<td>2.8</td>
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</table>

Figure 3: BNP level in group I on admission and discharge.

Table 3: BNP level in group II.

<table>
<thead>
<tr>
<th>BNP level</th>
<th></th>
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<tbody>
<tr>
<td>Maximum</td>
<td>2.98</td>
<td>2.98</td>
</tr>
<tr>
<td>Minimum</td>
<td>1.29</td>
<td>1.29</td>
</tr>
<tr>
<td>Mean</td>
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<td>2.3</td>
</tr>
<tr>
<td>SD</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Median</td>
<td>2.3</td>
<td>2.3</td>
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</tbody>
</table>

Table 4: BNP level in the control group.

<table>
<thead>
<tr>
<th>BNP level</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum</td>
<td>0.67</td>
<td>0.67</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Mean</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>SD</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Median</td>
<td>0.2</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Table 5: Mean BNP level in the studied group.

<table>
<thead>
<tr>
<th>Mean BNP level</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8.4</td>
<td>2.3</td>
<td>0.2</td>
</tr>
</tbody>
</table>

\( p \) value between group I & III = 0.001.

\( p \) value between group I & II = 0.0001.
**Correlation between BNP level and NYHA class:**

In group I: There was significant statistical correlation between BNP level and NYHA class *p* value: 0.001.

In group II: BNP level is also directly proportional to the NYHA class but with no significant value, *p* value: 0.021.

**Table 6:** Serum level of BNP in relation to different functional classes in both group I & II.

<table>
<thead>
<tr>
<th>BNP (ng/ml)</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>FC II</td>
<td>2.8</td>
<td>1.9</td>
<td>2.3</td>
</tr>
<tr>
<td>FC III</td>
<td>10</td>
<td>1.5</td>
<td>7.1</td>
</tr>
<tr>
<td>FC IV</td>
<td>20</td>
<td>1.8</td>
<td>10.2</td>
</tr>
</tbody>
</table>

**Figure 5:** Mean BNP level in the different NYHA classes.

**Correlation between BNP level and echocardiographic findings:**

BNP level was found to have positive correlation to both LVEDD and LVESD in all groups (serum BNP level is directly proportional to both LVESD (*r*=-0.77, *p*=0.000) and LVEDD (*r*=-0.81, *p*=0.000)).

Serum level of BNP was found to be inversely proportional to both ejection fraction (EF%) and fraction shortening (FS%) (negative correlation) (*r*=-0.73, *p*=0.000) and (*r*=-0.77, *p*=0.000) respectively.

**Figure 6:** Correlation of serum level of BNP to LVESD.

**Figure 7:** Correlation of serum level of BNP to LVEDD.

**Figure 8:** Correlation of serum level of BNP to ejection fraction.

**Figure 9:** Correlation of serum level of BNP to fraction shortening.
**Discussion**

The vasodilator neurohormonal peptide family may be better candidates for neurohormonal profiling in CHF [2]. In particular, BNP has drawn recent interest in its ability to match the decompensated state of circulatory congestion [3,4].

BNP level was measured in the three studied groups there was statistical significant difference between the three studied groups, it was higher in group I than group 2 (8400pg/ml [8.4ng/ml] Vs 2300pg/ml [2.3ng/ml]) and in both group, it was significantly higher than in control group (200pg/ml). In agreement with our results Maiser et al, found that the mean of BNP was statistically significantly different between the HF groups and the control group (p<0.001) [5,6].

In the current study, the mean BNP level showed a statistically significant difference (p<0.001) between the different functional classes patients who were admitted with NYHA III or IV, the mean BNP level was 8400pg/ml while the mean BNP level in patients admitted with NYHA class I or II was 2300pg/ml, these results were also confirmed by Jourdan et al, who reported that BNP level increased through NYHA classes from I to IV with statistical significant difference between the different classes (p>0.001) [7]. Thus BNP level could guide the clinical estimation of the functional classification, however no cutoff level was established to differentiate between the different functional classes neither in this study nor in the study reported by Villacorta J et al [8].

In the present study, BNP level showed a positive significant correlation with LVESD, LVEDD in all heart failure patients (r=0.77, 0.81 & p<0.01) in group I and group 2 respectively. These results were in accordance with Groenning et al, who conducted that BNP was the strongest independent marker for LVEDD (r=0.71, p<0.0001) and LVESD (r=0.75, p<0.001) [9,10]. BNP release increase with the stretch of left ventricle and volume overload which is in accordance to Saul & Shatzer [11].

In the current study, BNP level was inversely correlated with EF in the congestive heart failure patients (r=-0.73 & p<0.01).

Grooning et al, also found that BNP was the strongest independent marker for EF (r=-0.75 & p<0.0001) and was a powerful indicator for left ventricular dimensions and systolic function in patients with heart failure. It discriminates well between healthy subjects and subjects with impaired left ventricular systolic functions or increased left ventricular dimensions. These results were also in accordance with, Morrison LK, who stated that BNP correlated negatively with LVEF [12].

Although extensive guidelines have been published on the outpatient management of patients with CHF or asymptomatic LV dysfunction (ACC/AHA, task force report, 1995) few guidelines address appropriate management during the period of inpatient hospitalization (the phase of care that contributes highly to morbidity and cost). In this study we examined outcomes of patients admitted for decompensated CHF using BNP elvel drown throughout hospitalization, patients whose discharge BNP level fell below 8ng/ml (8000pg/ml) with treatment in the hospital had a reasonable likelihood of leaving the hospital in good condition and not being readmitted within the following month. A final BNP level <5ng/ml (5000pg/ml) had a strong negative predictive value for re-admission.

Four patients in our study died and their level of BNP didn't decrease markedly, while 5 patients with BNP level ranged between 6.8ng/ml and 19ng/ml were readmitted within 2 weeks of discharge.

These results were going with the study done by Cheng et al, who stated that patients discharge BNP level fell below 1, 220pg/ml with treatment in the hospital had a reasonable outcome and not being readmitted within the following 30 days, there final BNP level <430pg/ml had a strong negative value for readmission.

This study proved that BNP level was a useful predictor of decompensated CHF outcome this may be explained by the origin of BNP level which is purly ventricular hormone. There was a direct relationship between ventricular wall stress and secretion of BNP [13]. B-type natriuretic peptide responded to changes in LV filling pressure Cheung et al, suggested that BNP level reflects long term interavascular volume status rather than momentary volume. Our data agreed those with Tsutamoto et al, whose data suggest that BNP was the emergency hormone that responds immediately to ventricular overload [14,15].
Conclusion

Our results suggest that Brain natriuretic peptide level may be even more useful as prognostic indicator as well as diagnostic marker. In healthy subjects, as a screening tools for heart disease, BNP measurements in the general population, such as an elderly population, can reflect cardiac disease status such as congestive heart failure and ischaemic heart disease, this was also stated by Wallen et al [16].

References

Prognostic Value of Beta1-Adrenerceptor Gene Polymorphism in Patients with Congestive Heart Failure

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Background: Activation of the sympathetic nervous system is part of the pathophysiological adaptation of the circulatory system in heart failure which help to maintain cardiac performance over a short term by increasing the contractility and heart rate. The continuously increased adrenergic drive present in the failing human heart delivers adverse biological signals to the cardiac myocyte via β1- and likely β2 and α-adrenergic receptors. This is the fundamental basis for the use of the antiadrenergic agents in the treatment of chronic heart failure. The β-adrenergic family members (β1, β2 and β3) are highly polymorphic. Studies of genetic polymorphisms have shown two polymorphisms of the β1-adrenoceptor gene. The present work aims at assessing the prevalence of the different genotypes of β1-adrenoceptor gene polymorphism at position 389 and to relate such finding to the natural coarse and ultimate outcome in heart failure patients.

Methods: Various hemodynamic variables (heart rate and blood pressure) and echocardiographic parameters (assessing systolic and diastolic functions) were measured at regular intervals during the follow-up period of 775±75 days in one hundred patients diagnosed clinically and non-invasively as having heart failure, (NYHA class II to IV), secondary to different causes, including ischemic cardiomyopathy (64%), hypertension (6%), myocarditis (5%), peripartum cardiomyopathy (8%) and idiopathic cardiomyopathy (17%). Males were 65% while females were 35% with their age ranged from 27 to 74 years old (mean 55.6±10.3 years). All patients and control subjects were subjected to genetic analysis for genotyping their β1-adrenoceptor gene polymorphism at position 389.

Results: The prevalence of different genotypes of β1-adrenoceptor gene were nearly identical between the control and heart failure subjects. Control and patients with the Arg389Arg genotype (homozygous-wild type) were 53.4% and 59% respectively, and those with Arg389Gly genotype (heterozygote) were 46.6% and 41% respectively. Neither control nor patients groups demonstrated Gly389Gly genotype (homozygous mutant). With long-term metoprolol therapy in addition to the conventional therapy, heart failure patients with Arg389Gly genotype showed the highest improvement in ejection fraction (34±4 Vs 40±4 with highly significant p value) and the highest incidence of improvement of diastolic function [24 of 26 patients (92.3%)]. Moreover, they were associated with lowest number of cardiovascular re-hospitalization with a relative risk = 0.15 and p value = 0.017. Also, they demonstrated highest survival incidence, as non of them died during the follow-up period. On the other hand, number of cardiovascular re-hospitalization and survival were highest and lowest respectively in heart failure patients with Arg389Arg genotype (wild type) who did not received β-blocker, metoprolol.

Conclusion: Individuals with heart failure harboring the Arg389Gly genotype of the β1-adrenoceptor gene was associated with the maximal improvement in both systolic and diastolic functions and a decreased morbidity and mortality risk. These data suggest that the β1-adrenoceptor Arg389Gly variant might be associated with altered receptor function, resulting in myocardial protection in patients with heart failure.

Key Words: Polymorphism (genetics) – Adrenergic receptors – Heart failure – Cardiomyopathy – Mortality – Beta-blocker – Metoprolol.

Introduction

Despite recent advances, chronic heart failure is a difficult condition to manage in clinical practice and mortality remains high. The medical treatment of chronic heart failure has undergone a remarkable transition in the past 15 years. The approach has changed from a short term hemodynamic / pharmacological paradigm to a more long-term, reparative strategy that aims to favorably alter the biological properties of the failing heart [1].

The failing human heart is adrenergically activated, which help to maintain cardiac performance over a short term by increasing contractility and heart rate. In contrast, in the resting state, there is no adrenergic support of normally functioning
human left ventricles. The continuously increased adrenergic drive present in the failing human heart delivers adverse biological signals to the cardiac myocyte via $\beta_1$- and likely $\beta_2$- and $\alpha$-adrenergic receptors. This is the fundamental basis for the use of antiadrenergic agents in the treatment of chronic heart failure [2-4].

For a number of cardiovascular diseases, it has been proposed that both the susceptibility to disease and the interindividual variability in response to treatment relates in part to genetic polymorphisms, particularly those polymorphisms for neurotransmitter and drug receptors. The most intensively studied family of receptors are the G-protein-coupled receptors, of which the $\beta$-adrenergic receptor is the prototype [5].

The $\beta$-adrenergic receptor family members ($\beta_1$, $\beta_2$ and $\beta_3$) are highly polymorphic. In patients with congestive heart failure, polymorphism of both $\beta_1$- and $\beta_2$-adrenoceptors have been linked with disease expression. N-terminal polymorphisms of the $\beta_1$-adrenoceptor have been associated with an increased risk of developing idiopathic dilated cardiomyopathy. However, the most attention has been focused on single-nucleotide polymorphisms of the $\beta_2$-adrenergic receptor [6].

The gene coding the $\beta_1$-adrenergic receptor has been cloned and sequenced. Two new polymorphisms in the $\beta_1$-adrenergic receptor have been discovered in humans: At position 49, serine is substituted for glycine and at position 389, glycine is substituted for argenine. The mutation in the N-terminal part of the receptor was first reported by Borjesson et al, 2000 and they suggested that the Ser49Gly variant in the $\beta_1$-adrenergic receptor gene might be associated with a decreased risk of morbidity and mortality in patients with congestive heart failure and that beta-blockade treatment would be more effective in these patients [7].

The aim of the present study is to find possible genetic polymorphism in the $\beta_1$-adrenergic receptor at position 389 and to relate such findings to clinical prognosis (morbidity and mortality) and to the response to beta-blocker therapy in patients with congestive heart failure.

**Patients and Methods**

**Study population:**

The current study was conducted on a total of 100 patients with the diagnosis of heart failure of various etiology admitted to the Critical Care Medicine Department of Cairo University throughout the period from June 2001 to June 2002.

All patients met the following criteria: Symptoms and signs of heart failure for >3 months, New York Heart Association (NYHA) functional class II to IV, evidence of impaired left ventricular systolic function documented by ejection fraction % (EF%) <40% on resting transthorasic echocardiography and technically adequate Doppler echocardiographic recording.

Any patient with the following criteria was excluded from the study: Clinical deterioration during hospital course, Acute coronary syndrome or congenital heart disease, A history of previous cardiac surgery, Permanent pacemaker, Bundle branch block or any conduction defects including high grade block, Major organ failure or Malignancy or end stage medical conditions.

All the patients included in the study were on optimal treatment for heart failure, including angiotensin-converting enzyme inhibitors, diuretics and digitalis.

Patients were categorized according to NYHA functional class criteria according to the relation between their cardiac symptoms on admission and the amount of effort required to provoke them. Accordingly, patients were classified into: [8]

**Class I:** No limitation: Ordinary physical activity does not cause undue fatigue, dyspnea or palpitation.

**Class II:** Slight limitation of physical activity: Such patients are comfortable at rest. Ordinary physical activity results in fatigue, dyspnea or palpitation.

**Class III:** Marked limitation of physical activity: Although patients are comfortable at rest, less than ordinary activity will lead to symptoms.

**Class IV:** Inability to carry out on any physical activity without discomfort: Symptoms of CHF are present even at rest. With any physical activity, increased discomfort is experienced.

The patient group of the study were randomized to two subgroups:

**Subgroup A:** (No.=50) Included patients received optimal treatment of heart failure and did not receive $\beta$-blockers. They fulfilled all of the previously mentioned inclusion and exclusion criteria.
Subgroup B: (No.=50) Included patients received, in addition to the optimal therapy of heart failure, β blocker therapy was added. In addition to fulfillment of the previously mentioned inclusion criteria, they characterized by clinical stability for at least two weeks.

Patients were not considered for β blocker therapy if they had any of the following baseline assessment: (i) all criteria of exclusion mentioned before (ii) bradycardia with heart rate <50 beats/minute. (iii) systemic hypotension with systolic blood pressure less than 90mmHg. (iv) chronic airway limitation.

β-blockade of choice in this study was the β1-selective blocker without intrinsic sympathomimetic activity metoprolol.

After a baseline evaluation, all patients received 12.5mg daily of metoprolol for two weeks. If this dose was not tolerated, it could be temporarily reduced to 6.25mg daily and then later increased. The dose was gradually adjusted upward every two weeks, if tolerated, to a target dose of 50-200 mg daily over a period of 8-12 weeks after which therapy was maintained. During this time, the patients’ other drug therapies for heart failure were kept constant. If side effects developed that were attributed to the study drug, increments in dose were delayed or the dose could be decreased or temporarily discontinued.

Therapy with the maximal tolerated doses of the study medication, metoprolol, was maintained for up to 28.8±3.9 months after randomization, during which time background therapy with digoxin, diuretics and angiotensin converting enzyme inhibitors were continued.

Medication with metoprolol was continued until the end of the study (in June 2004). After completion of the up titration period, patients received an average dose of 72±44mg/day. Target doses were achieved in 79% of group B patients.

Control subgroup: (n=30) A random sample from the general population of individuals free from cardiovascular disorders and age-matched to the patients was used as a control. They consisted of 30 people, 19 males and 11 females. Their ages ranged between 24 to 64 years old with a mean of 52±9 years.

Methods: All patients were subjected to:

I- Full clinical examination: Full clinical examination and history with special stress on the physical signs and symptomatology pointing to heart failure was done. Patients were classified according to NYHA functional class. Non of the patients showed signs or symptoms necessitating categorizing them in grade I NYHA functional class.

Laboratory investigations included the estimation of blood sugar, the urea and creatinine level, total and direct bilirubin level, liver enzymes including serum glutamic oxalacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT), total protein and albumin.

As mentioned before patients with evidence of primary renal or hepatic impairment were excluded from the study.

II- Standard twelve lead ECG: Electrocardiographic assessment was routinely done for all patients prior to the study and during their hospital admission, aiming at identification of the cause of heart failure i.e. ischemic heart disease and identification of those having conduction abnormalities i.e. LBBB, RBBB, any degree of heart block or IVCD. Patients with conduction abnormalities were excluded from the study.

III- Echocardiographic examination: This was routinely done for all patients prior to discharge using ACUSON SEQUOIA 256 using a transducer 3.5MHz with 2D guided M-mode and pulsed Doppler facilities. All patients were examined in the partial left lateral decubitus and were angled according to necessity to obtain optimal windows for optimal views according to the recommendations of the American Society of Echocardiography [9]. Patients with non optimum windows were excluded from the study. Echocardiographic assessment included:

A- Assessment of systolic function using the following parameters:
- LVESD: Left ventricular end systolic dimension (cm).
- LVEDD: Left ventricular end diastolic dimension (cm).
- LVESV: Left ventricular end systolic volume (cm$^3$).
Prognostic Value of Beta-1-Adrenoceptor Gene Polymorphism in Patients

- LVEDV: Left ventricular end diastolic volume (cm$^3$).
- IVSd: Interventricular septum thickness during diastole (cm).
- PWTd: Posterior wall thickness during diastole (mm).
- EF: Ejection fraction = $\frac{LVEDV – LVESV}{LVEDV} \times 100$.
- FS: Fraction shortening = $\frac{LVEDD – LVESD}{LVEDD} \times 100$.
- LV mass (gm).
- LV mass index (gm/m$^2$).

$LVEDV$, $LVESV$, $FS$ and $EF$ were assessed by apical 4 chamber and apical 2 chamber views with the modified Simpson's method [10]. Images were accepted for analysis according to the guidelines proposed by Gordon et al, when at least 80% of endocardium was seen [11]. The parameters were averaged from three consecutive measurements.

Left ventricular mass ($LVM$) was calculated using the formula introduced by Deveraux et al (1977) [12].

$$LVM = \{1.04 \times [(IVSd + LVEDD + PWTd)^3 – (LVEDD)^3]\} – 13.6$$

Individual values for $LVM$ were indexed by body surface area ($LVMI$) and considered normal at <125g/m$^2$.

B- Assessment of diastolic function using the following parameters:
- E: Early peak diastolic filling velocity (cm/s).
- A: Late peak diastolic filling velocity (cm/s).
- E/A: Early (E) versus Late (A) diastolic filling wave ratio.
- DT: Deceleration time (ms).
- PVa d: Duration of Atrial flow reversal of the pulmonary vein Doppler (ms).
- IVRT: Isovolemic relaxation time (ms).

These parameters assessed from the mitral flow velocity that was obtained from a 2-dimensional apical window with a pulsed-wave technique by placing the sample volume between the tips of the mitral leaflets. All of them were calculated and averaged from 5 consecutive measurements.

Four filling patterns of mitral flow were identified: [13]

- **Normal filling pattern**: $E/A$ ratio >1, DT ranged from 140-240 msec, IVRT ranged from 70-90 msec and mitral A duration > $PVa$ duration.
- **Impaired relaxation**: $E/A$ ratio ≤ 1, DT > 240 msec, IVRT > 90 msec and mitral A duration > or < $PVa$ duration (depending on LVEDP).
- **Pseudonormal filling pattern**: $E/A$ ratio 1-1.5, DT > 160-200 msec, IVRT<90 msec, mitral A duration < $PVa$, $PVa$ velocity > 35cm/s and reversal of $E/A$ ratio (to < 1) with preload reduction (e.g. Valsalva maneuver).
- **Restrictive filling pattern**: $E/A$ ratio > 1.5, DT < 140 msec, IVRT < 70 msec, mitral A duration < $PVa$ duration and $PVa$ Velocity > 35 cm/sec.

IV- Genetic analyses:

1- Genomic DNA was extracted from 5cc peripheral blood leukocytes using the QIAamp Blood Kit (QIAGEN Inc.®).

2- Polymerase chain reactions were performed to amplify the fragment corresponding to the nucleotide position 530bp of the β1-adrenergic receptor gene, using the following oligonucleotides:
- Forward primer: CGCTCTGCTGGCTGCCCTTCTTCC.
- Reverse primer: TGGGCTTCGAGTTCACTGCTACTC.

The reaction conditions consisted of 250ng genomic DNA, 150nM of each primer, 200µM dNTPs, 2mM MgCl$_2$, 20mM Tris-HCl (pH 9), 2.5 units Taq polymerase and 10% DMSO in a final volume of 100µL.

The polymerase chain reaction was accomplished in 35 cycles (94°C for 1min, 62°C for 1min, 71°C for 1min) preceded by 2min at 94°C and followed by 7 min at 71°C.

3- The PCR product was digested with BcgI restriction enzyme incubated at 37°C for one hour. DNA fragments were separated on 2% agarose gel by electrophoresis and photographed over a UV transilluminator after staining with ethidium bromide. Two independent observers, who
were blind to the clinical characteristics of the patients, analysed the results.

4- The Arg389 allele PCR product contains a unique site for restriction by Bcg1 restriction endonuclease, thus cleavage of the 530-base pair fragment into fragments of 342 and 154-base pair confirms the presence of this allele. On the other hand, Bcg1 restriction endonuclease yielded only one band of 530-base pair in the absence of the restriction enzyme. Heterozygotes showed all three bands.

V- Patients follow-up:
All patients included in the study were followed-up regularly from the date of entry in the study until death, or completion of the study, which was June 2004. The minimal follow-up time was 24 months, the mean follow-up time for all patients in the study was 775 days. This included:

- Full clinical assessment including measurement of supine resting heart rate, blood pressure and ECG. Patients who were unable to tolerate β blockers were excluded from the study.
- Echocardiogram for assessment of both systolic and diastolic functions.
- Searching for cardiovascular morbidity, defined as re-hospitalization for heart failure exacerbation, mortality and sudden cardiac death, the mode of death was: [14]
  a- Sudden cardiac death (SCD) if it occurred within 1 hour of a change in symptoms or if it occurred during sleep or while unobserved.
  b- Progressive heart failure (mortality) if death occurred after a documented period of symptomatic or hemodynamic deterioration.
  c- Other cardiovascular death if it did not occur suddenly and was not associated with progressive heart failure.
  d- Non cardiac death.

Statistics: All data collected were subjected to full statistical analysis. Continuous variables are presented as mean ± SD. Comparison between groups were performed using unpaired Student’s t-test. Differences between proportions were assessed by a two-tailed fisher exact test. Probability values of <0.05 were considered statistically significant.

Results

I- Demographic data: One hundred patients were included in the study, with the mean age of 55.6±10.3 years, ranging from 27 to 74 years. Males were 65 (65%) while females were 35 (35%).

Many possible causes of heart failure were identified, including ischemic 64 (64%), hypertension 6 (6%), myocarditis 5 (5%), peripartum cardiomyopathy 8 (8%) and idiopathic dilated cardiomyopathy 17 (17%).

Table 1: Mean, SD and range of the baseline laboratory characteristics of the study group.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea (mg/dl)</td>
<td>45.5</td>
<td>10.5</td>
<td>21-71</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.9</td>
<td>0.2</td>
<td>0.2-1.7</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>0.99</td>
<td>0.55</td>
<td>0.4-6</td>
</tr>
<tr>
<td>SGOT (mg/dl)</td>
<td>26</td>
<td>9</td>
<td>6-53</td>
</tr>
<tr>
<td>SGPT (mg/dl)</td>
<td>19</td>
<td>7</td>
<td>4-45</td>
</tr>
<tr>
<td>Total protein (g/dl)</td>
<td>7.1</td>
<td>0.4</td>
<td>6.1-7.9</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.9</td>
<td>0.3</td>
<td>3.1-4.6</td>
</tr>
<tr>
<td>Sodium (meq/l)</td>
<td>155</td>
<td>119</td>
<td>130-156</td>
</tr>
<tr>
<td>Potassium (meq/l)</td>
<td>4.3</td>
<td>0.4</td>
<td>3.1-5.2</td>
</tr>
<tr>
<td>Blood Sugar (mg/dl)</td>
<td>110</td>
<td>9</td>
<td>88-128</td>
</tr>
</tbody>
</table>

II- Prevalence of β1-Adrenoceptor genotypes:
From the previous experimental studies [15] and clinical studies [7,16] three genotypes were obtained from genetic analysis of β1-adrenoceptor gene polymorphism at position 389:

a- Arg Arg genotype (homozygous – wild type): Where the agarose gel electrophoresis shows fragments at 342 and 154bp. (Argenin allele cleavage products).

b- Arg Gly (heterozygote): Where the agarose gel electrophoresis shows fragments at 342 and 154bp in addition to fragments at 530 (uncleaved glycine allele).

c- Gly Gly (homozygous mutant): Where the agarose gel electrophoresis shows fragments only at 530bp.

In this study, the prevalence of the three genotypes of β1-adrenoceptor gene polymorphism, in a group of normal individuals (control group) and in patient group, were identified (Table 2).

Out of thirty healthy control, 16 had the Arg389Arg genotype (wild type) (53.4%) and 14 had the Arg389Gly genotype (heterozygote) (46.6%). Non of the patients showed Gly389Gly genotype (homozygous mutant).
Table 2: Prevalence of the different genotypes of β₁-adrenoceptor gene polymorphism.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Control Group</th>
<th>Patient Group</th>
<th>Total Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No = 30</td>
<td>No = 100</td>
<td>No = 130</td>
</tr>
<tr>
<td>Arg389Arg genotype</td>
<td>16 (53.4%)</td>
<td>59 (59%)</td>
<td>75 (57.7%)</td>
</tr>
<tr>
<td>Arg389Gly genotype</td>
<td>14 (46.6%)</td>
<td>41 (41%)</td>
<td>55 (42.3%)</td>
</tr>
<tr>
<td>Gly389Gly genotype</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Table 3: Baseline characteristics of the various genotypes of β₁-adrenoceptor gene polymorphism in patient group.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Arg Arg genotype (wild type)</th>
<th>Arg Gly genotype (heterozygote)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>59</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>59.4±6.3</td>
<td>55.12±12.4</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>38 (66.1%)</td>
<td>27 (65.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>101±7</td>
<td>100±16</td>
<td>NS</td>
</tr>
<tr>
<td>BP (mmHg):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systole</td>
<td>118±13</td>
<td>113±13</td>
<td>NS</td>
</tr>
<tr>
<td>Diastole</td>
<td>72±7</td>
<td>71±6</td>
<td>NS</td>
</tr>
<tr>
<td>Mean</td>
<td>87±8</td>
<td>85±6</td>
<td>NS</td>
</tr>
<tr>
<td>Etiology (No. &amp; %):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic CM</td>
<td>44 (74.6%)</td>
<td>21 (51.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (5.1%)</td>
<td>3 (7.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>1 (1.7%)</td>
<td>4 (9.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Peripartum CM</td>
<td>1 (1.7%)</td>
<td>6 (14.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Idiopathic CM</td>
<td>50 (50%)</td>
<td>41 (41%)</td>
<td></td>
</tr>
<tr>
<td>NYHA (No. &amp; %):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>10 (16.9%)</td>
<td>12 (29.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>III</td>
<td>44 (74.6%)</td>
<td>26 (63.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>VI</td>
<td>5 (8.5%)</td>
<td>3 (7.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>ECHO parameters:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic function:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDV (cm³)</td>
<td>231±48</td>
<td>234±53</td>
<td>NS</td>
</tr>
<tr>
<td>LVESV (cm³)</td>
<td>150±37</td>
<td>154±40</td>
<td>NS</td>
</tr>
<tr>
<td>EF (%)</td>
<td>35±3</td>
<td>34±3</td>
<td>NS</td>
</tr>
<tr>
<td>LVM (gm)</td>
<td>243±54</td>
<td>244±49</td>
<td>NS</td>
</tr>
<tr>
<td>LVMI (gm/m²)</td>
<td>129±30</td>
<td>131±25</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic function:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E (cm/s)</td>
<td>0.68±0.18</td>
<td>0.75±0.22</td>
<td>NS</td>
</tr>
<tr>
<td>A (cm/s)</td>
<td>0.49±0.23</td>
<td>0.58±0.24</td>
<td>NS</td>
</tr>
<tr>
<td>E/A</td>
<td>1.65±0.84</td>
<td>1.67±0.97</td>
<td>NS</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>168±69</td>
<td>169±80</td>
<td>NS</td>
</tr>
</tbody>
</table>

There were no statistically significant differences in demographic or clinical characteristics, including age, sex, etiology of heart failure, NYHA functional class, resting heart rate, blood pressure parameters and β-blocker therapy, among the two groups.

IV- Correlative analysis of data:

A- Changes of various hemodynamic and echocardiographic parameters in relation to β-blocker therapy in different genotypes of β₁-Adrenoceptor gene polymorphism:

In contrast to patients with Arg389Arg genotype who did not receive β-blockers, patients with Arg389Arg genotype who received β-blockers showed the following statistically significant parameters: Lower heart rate (92±6 Vs 75±7) with highly significant p value, Higher EF% (34±4 Vs 39±5) with p value = 0.004, Higher left ventricular diastolic filling velocity (A) (0.45±0.17 Vs 0.57±0.18) with p value = 0.012 and Lower E/A ratio (1.8±0.74 Vs 1.3±0.5) with p value = 0.02 (Table 4).

In relation to patients with Arg389Gly genotype who did not receive β-blockers, patients with Arg389Gly genotype and received β-blocker showed the following statistically significant parameters: Lower heart rate (82±3 Vs 72±5) with highly significant p value, Higher EF% (34±4 Vs 40±4) with p value = 0.003, Lower left ventricular early peak diastolic filling velocity (E) (0.76±11 Vs 0.66±0.15) with p value = 0.024 and Higher left ventricular late peak diastolic filling velocity (A) (0.5±0.18 Vs 0.63±0.14) with p value = 0.05 (Table 4).

In patients using β-blockers, in relation to patients with Arg389Arg genotype patients with...
Arg389Gly genotype showed no statistically significant differences in the results of different hemodynamic and echocardiographic parameters (Table 4).

Table 4: Various hemodynamic and echo parameters in both genotypes in relation to β-blocker therapy.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Arg Arg genotype</th>
<th>Arg Gly genotype</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β-blocker No = 26</td>
<td>β-blocker No = 24</td>
<td>β-blocker No = 15</td>
</tr>
<tr>
<td></td>
<td>No = 35</td>
<td></td>
<td></td>
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<tr>
<td>HR (bpm):</td>
<td></td>
<td></td>
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<tr>
<td>Basic</td>
<td>101±6</td>
<td>98±7</td>
<td>100±19</td>
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<td>24 mon</td>
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<td>72±5</td>
</tr>
<tr>
<td>p value</td>
<td>0.0000</td>
<td>NS</td>
<td>0.0000</td>
</tr>
<tr>
<td>MBP (mmHg):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basic</td>
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<td>90±9</td>
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<td>24 mon</td>
<td>88±6</td>
<td>86±6</td>
<td>89±5</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Echocardiographic Parameters:</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Systolic function:</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>LVEDV (cm³):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basic</td>
<td>226±42</td>
<td>234±53</td>
<td>231±55</td>
</tr>
<tr>
<td>24 mon</td>
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<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>LVESV (cm³):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basic</td>
<td>144±32</td>
<td>154±40</td>
<td>151±42</td>
</tr>
<tr>
<td>24 mon</td>
<td>135±30</td>
<td>152±39</td>
<td>135±38</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>EF (%):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basic</td>
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<td>34±3</td>
<td>34±4</td>
</tr>
<tr>
<td>24 mon</td>
<td>39±5</td>
<td>34±4</td>
<td>40±4</td>
</tr>
<tr>
<td>p value</td>
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<td>NS</td>
<td>0.000</td>
</tr>
<tr>
<td>LVM (gm):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basic</td>
<td>256±58</td>
<td>240±49</td>
<td>252±53</td>
</tr>
<tr>
<td>24 mon</td>
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<td>222±49</td>
</tr>
<tr>
<td>p value</td>
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<td>NS</td>
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</tr>
<tr>
<td>LVMI (gm/m²):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basic</td>
<td>135±33</td>
<td>128±27</td>
<td>134±26</td>
</tr>
<tr>
<td>24 mon</td>
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<td>123±25</td>
<td>118±23</td>
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<td>p value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic function:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E (cm/s):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basic</td>
<td>0.73±0.2</td>
<td>0.65±0.15</td>
<td>0.83±0.17</td>
</tr>
<tr>
<td>24 mon</td>
<td>0.63±0.15</td>
<td>0.68±0.13</td>
<td>0.66±0.15</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>A (cm/s):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basic</td>
<td>0.52±0.25</td>
<td>0.47±0.22</td>
<td>0.54±0.24</td>
</tr>
<tr>
<td>24 mon</td>
<td>0.57±0.18</td>
<td>0.45±0.17</td>
<td>0.63±0.14</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>E/A:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basic</td>
<td>1.7±0.9</td>
<td>1.6±0.76</td>
<td>1.9±0.9</td>
</tr>
<tr>
<td>24 mon</td>
<td>1.3±0.5</td>
<td>1.8±0.74</td>
<td>1.2±0.2</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>NS</td>
<td>0.005</td>
</tr>
<tr>
<td>DF (ms):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basic</td>
<td>165±69</td>
<td>171±70</td>
<td>163±77</td>
</tr>
<tr>
<td>24 mon</td>
<td>188±48</td>
<td>162±6</td>
<td>198±36</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>NS</td>
<td>0.007</td>
</tr>
</tbody>
</table>

* = Significance between Arg Arg genotype with β-blocker and those without β-blocker.
** = Significance between Arg Gly genotype with β-blocker and those without β-blocker.
*** = Significance between Arg Arg genotype with β-blocker and Arg Gly with β-blocker.
**** = Significance between Arg Arg genotype without β-blocker and Arg Gly without β-blocker.
After long-term treatment with β-blocker, metoprolol, in addition to conventional drugs for heart failure, patients with Arg389Arg genotype showed a statistically significant lower heart rate (101±6 Vs 75±7) with highly significant p value and higher EF (36±3 Vs 39±3) with p value = 0.051 and a Lower left ventricular mass (LVM) (256±58 Vs 229±51) with p value = 0.05.

Those with Arg389Gly genotype showed a statistically significant lower heart rate (100±19 Vs 72±5) with highly significant p value, higher EF (34±4 Vs 40±4) with highly significant p value, Lower left ventricular mass (LVM) (252±53 Vs 222±49) with p value = 0.038, lower E/A ratio (1.9±0.9 Vs 1.2±0.2) with p value = 0.005 and longer DT (163±77 Vs 198±36) with p value = 0.007.

On the other hand, patients who did not receive β-blocker, neither those with Arg389Arg genotype nor those with Arg389Gly genotype showed any statistically significant changes in the different hemodynamic and echocardiographic parameters (Table 4).

Out of 24 patients with Arg389Gly genotype who used β-blocker, 22 patients (91.6%) demonstrated improvement in the left ventricular diastolic filling patterns.

Out of 17 patients with Arg389Gly who did not use β-blocker, 12 patients (70.5%) demonstrated no change in their left ventricular diastolic filling patterns and only one patient (5.9%) had a restrictive left ventricular filling pattern develop.

Out of 33 patients with Arg389Arg genotype who received β-blocker, 27 patients (81.8%) demonstrated improvement in the left ventricular diastolic filling patterns and only one patient (3%) had a restrictive left ventricular filling pattern develop.

Out of 35 patients with Arg389Arg genotype who did not use β-blocker therapy, 29 patients (82.8%) demonstrated no change in the left ventricular diastolic filling patterns and four patients (11.4%) had developed restrictive left ventricular filling pattern.

**B- Incidence of cardiovascular morbidity and mortality in different genotypes of β1-adrenoceptor gene polymorphism:**

Out of the twenty patients who were re-hospitalized due to cardiovascular causes, 16 (80%) were patients with Arg389Arg genotype with a p value >0.05 and 4 (20%) were patients with Arg389Gly genotype with a p value = 0.038.

Patients' group with Arg389Gly genotype demonstrated a statistically significant lower incidence of morbidity in relation to patients' group with Arg389Arg genotype. (p value = 0.033) (Table 5 & Fig. 1).

**Table 5: Incidence of morbidity in relation to different genotypes of β1-adrenoceptor gene.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Morbidity</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arg Arg</td>
<td>Yes (No. = 59)</td>
<td>16 (27.2%)</td>
</tr>
<tr>
<td></td>
<td>No (No = 80)</td>
<td>43 (72.8%)</td>
</tr>
</tbody>
</table>

| Significance | 0.033 | NS |

**Figure 1:** Morbidity curves expressing the risk of re-hospitalization for patients with heart failure with different genotypes of β1-adrenoceptor gene

Out of the six patients who died due to cardiovascular causes, 5 (83.3%) were patients with Arg389Arg genotype with a p value >0.05 and only one patient (16.7%) was with Arg389Gly genotype with a p value >0.05.

Patients' group with Arg389Gly genotype demonstrated a lower incidence of mortality in relation to patients' group with Arg389Arg genotype, however the difference is not statistically significant. (p value >0.05) (Table 6 & Fig. 2).
Influence of different genotypes of β<sub>1</sub>-adrenoceptor gene polymorphism on morbidity and mortality were also studied in relation to long-term treatment with β-blocker, metoprolol. The use of β-blocker was not associated with any significant effect on morbidity except for patients with Arg389Gly genotype where only one patient (5%) was re-hospitalized with a p value = 0.017.

Patients' group with Arg389Gly genotype who received β-blockers demonstrated a statistically significant lower incidence of morbidity in relation to patients' group with Arg389Arg genotype who received and those who did not receive β-blockers. (p value = 0.038 and 0.012 respectively) (Table 7 & Fig. 3).
Non of patients with Arg389Gly genotype who received long-term metoprolol therapy died. In contrast, patients with Arg389Arg genotype who did not receive metoprolol therapy demonstrated the highest incidence of mortality (4 of 6) (66.6%).

Incidence of mortality was similar in patients with Arg389Gly genotype who did not receive metoprolol therapy and those with Arg389Arg genotype who received metoprolol therapy. (one of 6) (16.7%) (Table 8 & Fig. 4).

Table 8: Incidence of mortality in relation to different genotypes of β1-adrenoceptor gene and β-blocker therapy.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Yes (No. = 6)</th>
<th>No (No. = 94)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arg Arg (No. = 59):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blocker (no=24)</td>
<td>1 (4.1%)</td>
<td>23 (95.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>No β-blocker (no=35)</td>
<td>4 (11.4%)</td>
<td>31 (88.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Arg Gly (No. = 41):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blocker (no=26)</td>
<td>0 (0%)</td>
<td>26 (100%)</td>
<td>NS</td>
</tr>
<tr>
<td>No β-blocker (no=15)</td>
<td>1 (6.6%)</td>
<td>14 (93.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Signi.</td>
<td>* NS</td>
<td>* NS</td>
<td></td>
</tr>
</tbody>
</table>

* = Significance between Arg Gly with β-blocker Arg Arg with β-blocker.
** = Significance between Arg Gly with β-blocker Arg Arg without β-blocker.

Discussion

We first delineated the genotype frequencies of the β1-adrenoceptor gene polymorphism at position 389 in a group of normal healthy individuals and in our heart failure cohort.

Out of 30 control healthy volunteers, 16 (53.4%) were Arg389Arg genotype (homozygous-wild type) and 14 (46.6%) were Arg389Gly genotype (heterozygote). Non of the control group was Gly389Gly genotype (homozygous mutant).

This result is consistent with previous report by White and coworkers (2002) [16]. They reported that out of 1076 healthy volunteers (control group), 583 (54.2%) were Arg389Arg genotype and 419 (36.9%) were Arg389Gly genotype. They reported also that 74 of the control group (6.9%) were Gly389Gly genotype.

Furthermore, we demonstrated that the frequencies of the genotypes of β1-adrenoceptor gene were nearly identical between the control subjects and the heart failure subjects. Incidence of Arg389Arg genotype in control and heart failure group were 53.4% and 59% respectively. While, the incidence of Arg389Gly genotype were 46.6% and 41% respectively. Also we demonstrated that non of the patient group had Gly389Gly genotype.

This result was supported by the observation of Lynne et al (2002) [17] who demonstrated that these three genotypes of β1-adrenoceptor gene polymorphism were not more common in patients with heart failure compared with normal controls.

Such observations suggests that β1-adrenoceptor gene polymorphisms is unlikely to be major causative factors in the development of heart failure, but can be considered to have a roles in the progression and outcome of heart failure, i.e. appears to acts as disease modifiers.

As mentioned before, non of the control and patient groups had Gly389Gly genotype (homozygous mutant). Others (White et al, 2002 and Lynne et al, 2002) [16,17] found that homozygotes with Gly389Gly genotype are markedly infrequent in both general population and heart failure patients.

These observations may suggest a possible increase in the risk of death in individuals with this genotype, however, a larger studies are needed to confirm such observations.
On studying the change in cardiac performance in relation to β1-adrenoceptor gene polymorphism, we found that heart failure patients with Arg389Gly genotype (heterozygote) demonstrated a statistically significant improvement in heart rate, systolic and diastolic functions. On the other hand, no significant changes observed in those with Arg389Arg genotype (wild type) except for heart rate.

Moreover, the result of this study show that long-term treatment (28.8±3.9 months) with β1-selective β-blocker; metoprolol, was associated with a decrease in left ventricular end-diastolic size and volume with improvement of left ventricular ejection fraction. (34±4 Vs 39±4 with highly significant p. value).

This improvement in the left ventricular ejection fraction in response to metoprolol therapy, was more pronounced in heart failure patients with Arg389Gly genotype (34±4 Vs 40±4 with highly significant p value) than those with Arg389Arg genotype (36±3 Vs 39±5 with p value = 0.051).

This beneficial effect of long-term metoprolol therapy in left ventricular ejection fraction in heart failure in this study is supported by the results of many clinical studies [18-20].

These studies have consistently shown that long-term administration of metoprolol for more than three months duration is associated with a highly significant improvement in both left ventricular systolic function and on prognosis of the heart failure patients. Left ventricular ejection fraction, one of the main prognostic factors in heart failure, has shown the most consistent improvement.

Also we found that with long-term metoprolol therapy, left ventricular mass and left ventricular mass index decreased in both genotypes. The reduction was statistically significant with left ventricular mass (254±59 Vs 224±51 with p. value = 0.045), while the reduction was not significant with left ventricular mass index (135±29 Vs 120±25 with p. value >0.05).

Moreover, the reduction in the left ventricular mass was more pronounced in heart failure patients with Arg389Gly genotype (252±53 Vs 222±49 with p. value = 0.038) than those with Arg389Arg genotype (256±58 Vs 229±54 with p. value = 0.05).

The same observation was with the reduction in the left ventricular mass index, however, the changes were not statistically significant.

These findings are supported by the observation by Packer et al (1996) [21]. They reported that, long-term metoprolol therapy in heart failure patients was associated with regression of the left ventricular dimensions, volumes and mass and a more favorable myocardial shape i.e. reversing remodeling and hence, improving the frank-starling relationship and force of contraction.

Other several effects are suggested to be involved in the improvement of left ventricular systolic function in response to long-term metoprolol therapy including, first, up-regulation of the previously down-regulated cardiac β-adrenoceptor helping in restoring maximal contractile force to β-adrenoceptor stimulation [22-23].

Second, normalization of the activity of the cardiac G, as prolonged exposure to high level of catecholamine is associated with increase in the cardiac G and so, positive inotropic effect of all drugs acting via increase in intracellular CAMP are reduced [24].

Third, Metoprolol, through blockade of adrenergic receptors, causes a significant reduction of cardiac norepinephrin spillover, an increase of aerobic metabolic energy production and a reduction of oxygen consumption with a net increase of energy substrate (ATP). Furthermore, this increase could enhance sarcoplasmic reticulum adenosin triphosphatase activity which modulates the activity of the pump adenosine triphosphatase-phospholaman complex in storing Ca++ within the sarcoplasmic reticulum during diastole.

This pump increases cytosolic calcium by a negative feedback mechanism to the sarcolemmal sodium – calcium exchanger. Thus the combined action of metoprolol at different sites allows significant storage of Ca++ in sarcoplasmic reticulum and in consequence, an improvement in the performance in the contracting myocyte [25].

In addition to the improvement in the left ventricular systolic performance, we found that long-term metoprolol therapy in heart failure patients was able to prevent or partially reverse the unwanted diastolic changes in heart failure.

This improvement in diastolic function was manifested in this study, during follow-up, by (1) decrease in the left ventricular early peak diastolic filling velocity (0.78±0.19cm/s Vs 0.73±0.14cm/s with p value >0.05). (2) increase in the diastolic time (153±73ms Vs 188±41ms with p value >0.05).

189
(3) increase in the peak velocity of late diastolic left ventricular filling velocity (0.53±0.24cm/s Vs 0.60±0.16cm/s with p value = 0.003).

Many studies demonstrated how peak velocity and DT of left ventricular early diastolic filling are function of mitral regurgitation, the left chamber's stiffness gradient and relaxation rate of the left ventricle. In patients with heart failure, abnormalities of chamber stiffness and relaxation rate are present and determine contrasting effects on mitral flow pattern [26].

Long-term metoprolol therapy, was shown to restore early diastolic filling by complex interactions between improvement of left ventricular relaxation rate and reduction of chamber stiffness [27].

This effect in early diastolic function was achieved with an improvement in abnormal calcium handling such as reduced calcium sequestration by the sacroplasmic reticulum, which characterizes failing myocardium [27].

Furthermore, progressive sympathetic activation induced a metabolic imbalance in energy substrates with more use of fatty acids than of carbohydrates that, in conditions of oxygen deprivation, causes a decrease in energy production. Metoprolol reduces sympathetic activation and fatty acid oxidation by the failing myocardium and improve myocardial energy production and use, which facilitates the highly energy-dependent diastolic process [27].

Also, long-treatment metoprolol therapy was shown to restore late diastolic filling by complex interaction between a) reduction of the left ventricular early diastolic filling and left ventricular chamber stiffness, representing atrial after load and b) improvement of atrial pump function secondary to reduction of mitral regurgitation secondary to a decrease in left ventricular end-systolic volume, facilitating a decrease in atrial preload and atrial overstretching with an increase in atrial contractility and systolic function [28].

So, the final effect of metoprolol in diastolic function is achieved by different and complex mechanisms and related to the baseline conditions in which abnormalities of chamber stiffness and relaxation may coexist.

In our population, out of 50 heart failure patients who received β-blocker therapy, 42 patients (84%) demonstrated improvement in the left ventricular diastolic filling pattern and only one patient (2%) had a restrictive left ventricular filling pattern develop.

In contrast, majority of patients (40 of 50 patients) who did not receive β-blocker therapy showed no changes in their diastolic filling pattern. (80%).

Of particular interest in this study is that, these improvements in both systolic and diastolic functions in our heart failure population who received β-blocker therapy were related to β₁-adrenoceptor gene polymorphism. The improvement in systolic and diastolic functions were greatest in heart failure patients with Arg389Gly genotype (heterozygote) who received β-blocker therapy, metoprolol.

After long-term treatment with β-blocker, metoprolol, in addition to conventional drugs for heart failure, patients with Arg389Gly genotype showed a higher improvement in ejection fraction (34±4 Vs 40±4) with highly significant p value and a higher incidence in the improvement of diastolic function [24 of 26 patients (92.3%)].

Also, wild type patients who received β-blocker showed a tendency toward improvement in both systolic and diastolic functions, however, these changes were lower in relation to those with Arg389Gly genotype.

These observations may reflect the presence of a relationship between β-blocker therapy and different genotypes of β₁-adrenoceptor gene polymorphism i.e. suggesting that heart failure patients with Arg389Gly genotype might have better response to β-blockade.

Moreover, these observations suggest that mutation in the β₁-adrenoceptor gene might be beneficial to the failing heart and might cause myocardial protection and a more favorable course of the disease. Another possibility is that the mutant receptor might be resistant to down-regulation, and thereby maintain normal receptor function.

Re-hospitalizations are now generally considered in clinical trials as one of the most relevant end points, both for their relation to patient quality of life and for cost implication.

The relation of cardiovascular morbidity, defined as re-hospitalization for heart failure exacerbation and cardiovascular mortality to the presence of β₁-adrenoceptor gene polymorphism at position
389 and β-blocker treatment was also studied in this work aiming at determining whether the expression of this polymorphism represent any prognostic index.

We found that heart failure patients with Arg389Gly genotype (heterozygotes) were associated with statistically significant lower number of cardiovascular re-hospitalization with \( p \) value = 0.033. Also, they were associated with lower incidence of overall cardiac mortality, however, the difference is not statistically significant. (\( p \) value >0.05).

We also demonstrated that, heart failure patients with Arg389Gly genotype and received long-term metoprolol were associated with lowest number of cardiovascular re-hospitalization with \( p \) value = 0.017. Also, they demonstrated highest survival incidence, as non of them died during the follow-up period.

On the other hand, number of cardiovascular re-hospitalization and survival were highest and lowest respectively in heart failure patients with Arg389Arg genotype (wild type) who did not receive β-blocker, metoprolol.

These observations reinforce the previous suggestion mentioned before that the Arg389Gly genotype may be conceptualized as a form of ‘inborn’ β-blockade which is protective in cardiac failure. Also, reinforce the previous conclusion that β-blockade is more effective in heart failure patients with Arg389Gly genotype.

As only 6 patients (6%) out of the one hundred patients died within the follow-up period, the above statistical analysis should be taken cautiously because of the small number of deaths.

**Conclusion**

- **Case-control study demonstrated that the naturally occurring polymorphism in the β1-adrenoceptor gene at 389 is unlikely to be a major causative factor in the development of heart failure, but can be considered as disease modifier.**
- **Individuals with heart failure harboring the Arg389Gly genotype of the β1-adrenoceptor gene might be associated with a more favorable course of the disease and decreased morbidity and mortality risks. These data suggest that the β1-adrenoceptor Arg389Gly variant may ultimately serve a protective effect due to its depressed coupling property.**
- **β-blockade therapy is associated with different response in heart failure patients with different genotypes of β1-adrenoceptor gene. β-blockade might be more effective in heart failure patients harboring Arg389Gly genotype.**
- **Therefore, genetic analysis of β1-adrenoceptor gene could identify heart failure patients with more favorable course of the disease and those with better response to beta-blocker therapy.**

The true significance of these findings needs to be established both by elucidation of the biological mechanisms of the observed differences and further clinical studies carried out prospectively on larger population.

**References**


5-  Ross D: Adrenergic receptor polymorphisms and cardiac function (and dysfunction). Circulation 2001; 103: 1042.


Prognostic Value of Beta₁-Adrenoceptor Gene Polymorphism in Patients


Arrhythmias as Early Post Operative Complications of Cardiac Surgery in Children at Cairo University

YASSER H KAMEL, MD*; MOHAMED SEWIELAM, MD**

**Background:** Arrhythmias are a recognized complication of cardiac operations in pediatrics. However, little is known about the incidence, treatment and risk factors for early postoperative arrhythmias in children after cardiac operations.

**Objective:** The aim of this study was to assess the incidence and type of early post pediatric cardiac surgery arrhythmias and to analyze possible risk factors.

**Methods:** This was a retrospective study conducted on patients who were followed in postoperative clinic at Cairo University Children’s Hospital (CUCH) during the period from September 2007 till January 2009. The collected data were demographic data, diagnosis, pre-operative arrhythmia, cardiac surgical data and postoperative data including presence, type and outcome of arrhythmias. Details of postoperative intensive care course were studied.

**Results:** During the study period, 110 patients were enrolled, including 15/110 who had palliative surgery while 95 out of 110 had corrective surgery. Thirty patients (27.2%) developed postoperative arrhythmias most of them on day one (60%). Of them 20/30 (66.6%) were cyanotic while 10/30 (33.3%) were acyanotic. Two (6.6%) had palliative surgery while 28/30 (93.3%) had corrective surgery. The most common acute post-operative arrhythmias were junctional ectopic tachycardia and Supraventricular tachycardia (33.3%) for each. Out of 95 patients who had corrective surgery, 28 (29.4%) developed arrhythmias most of them (96.4%) within first 48 hours postoperatively. The most common acute post-operative arrhythmias were junctional ectopic tachycardia and supraventricular tachycardia. Both were common early after repair of tetralogy of Fallot (18.1%) and (12.1%) respectively. Risk factors for arrhythmias in corrective surgery were young age, lower body weight and Cyanosis (p<0.05), redo operation (p<0.01), longer cardiopulmonary bypass time (p<0.05), postoperative acidosis, high inotropic support, hypotension and mechanical ventilation (p<0.01), all were identified in a univariate analysis. In the multivariate stepwise logistic regression; cyanosis, was statistically significant (p value <0.005). Longer CPB time, redo operation were statistically significant (p value <0.01) in patients with moderate operative risk (TOF, D-TGA, CAVC) Postoperative higher doses of inotropic support, longer ventilation time were statistically significant (p value <0.001).

**Conclusions:** Lower age, lower body weight, cyanosis, longer cardiopulmonary bypass time, redo procedure, acidosis, electrolyte disturbances, mechanical ventilation and high inotropic support were the risk factors for postoperative arrhythmias. Junctional ectopic tachycardia and supraventricular tachycardia were the most common postoperative arrhythmias.

**Key Words:** Risk factors – Early postoperative – Cardiac arrhythmias – Pediatric.
Postoperative cardiac arrhythmias can be of atrial or ventricular origin. Atrial arrhythmias typically arise after Fontan or Senning type operations, whereas ventricular arrhythmias most often occur after total correction of tetralogy of Fallot [4]. Junctional ectopic tachycardia (JET) may develop after surgery for closure of ventricular septal defects (VSD) and complete atrioventricular block (CAVB) can occur after any operation that interferes with the His-Purkinje system [5]. Arrhythmias that may be tolerated in a normal heart can be a major cause of morbidity and mortality after cardiac operation for congenital heart disease [6]. In the early postoperative period after corrective surgery, arrhythmias may have a major influence on the recovery of the hemodynamically impaired patients and are a prognostic factor for long-term outcome [7]. The aim of the study was to assess the incidence of early postoperative arrhythmias after cardiac operation in a pediatric population, to describe their type and to analyze possible risk factors.

Patients and Methods

This study was a retrospective study conducted on patients who were followed in postoperatively at Cairo University Children’s Hospital (CUCH) during the period from September 2007 till January 2009. Children who had undergone cardiac surgery for corrections of congenital or acquired cardiac disease were enrolled in this study. Data were collected retrospectively from the "pediatric cardiac intensive care unit surveillance data sheet". Each child was monitored routinely in the intensive care during the early postoperative period. Upon detection of a sustained arrhythmia (≥30 seconds duration, recurrences and/or effect on hemodynamic parameters), electrocardiography (ECG) was performed [8]. All the ECG records were assessed by the same pediatric cardiologist. For each case, a demographic data and recorded the cardiac diagnosis, operational procedures, perioperative parameters (cardiopulmonary bypass [CPB] time, aorta clamping time, total surgery time) and postoperative parameters (electrolyte levels, oxygen saturation findings, blood pH, serum calcium, sodium, potassium, magnesium levels and doses of inotropic agents required). Redo-operation, referred to the repeated operation at the same midline incision [9]. Sinus bradycardia, frequent premature atrial or ventricular complexes, conduction defects, atrioventricular (AV) blocks and supraventricular and ventricular tachycardias were considered critical arrhythmias. Supraventricular tachycardia was defined as narrow complex tachycardia with one to one atrioventricular conduction and reentry mechanism. Junctional ectopic tachycardia was defined as a narrow complex tachycardia with (AV) dissociation. Frequent premature supraventricular or ventricular beats were diagnosed if their number exceeded 10 per minute. Sinus bradycardia was defined as an inadequate sinus rate for the age and hemodynamic condition of the patient or as a junctional escape rhythm in the absence of AV block or junctional ectopic tachycardia [8,10]. As estimated normal heart rates are not applicable to children with cardiac dysfunction and in the postoperative state, higher sinus rates than normal were defined as adequate for the postoperative patients [11]. The following minimal rates according to age were considered as bradycardia: 120 to 130 beats/min diurnal rate in neonates, less than 120 beats/min in children aged less than 1 year, 110 beats/min in children aged 3 to 4 years, 100 beats/min in children aged 5 to 7 years, less than 90 beats/min in children aged 8 to 11 years and 85 beats/min in children aged 12 to 15 years [12]. Onset, duration, type of arrhythmia, management and result of management data were collected. The options of treatment were decided for each individual case at the discretion of the management team according to the standard recommendations by the American Heart Association. Junctional ectopic tachycardia was treated by avoidance of hyperthermia, optimizing sedation, pain control, limitation of exogenous catecholamines and administration of antiarrhythmic agents (amiodarone) aiming at optimal heart rate for age and hemodynamic conditions. Amiodarone was our drug of choice for SVT. An initial single 5mg/kg intravenous dose of amiodarone was then followed by intravenous infusion of 10 to 15mg/kg per day. No adverse effects of IV amiodarone therapy, such as hypotension or proarrhythmogenic effect, were observed. Post operative heart block was treated with temporary pacing and observation for recovery was done for 7-14 days before the decision to implant a permanent pacemaker [12].

Statistical analysis:

Statistical calculations were made using the software SPSS for Windows (version 11.0).

Numerical data were expressed as a mean ± standard deviation. Comparison of means for changes in variables was performed using the Paired Student’s t-test, while the non-Paired Student’s t-test was used for numeric comparison.
between two different groups (arrhythmias versus no arrhythmias in open heart surgery patients). Nonparametric test for independent samples (the Mann-Whitney Test) was used to compare linear variables between groups. For categorical variables the Fisher exact test was used. Multivariate stepwise logistic regression was used to assess the risk factors of postoperative cardiac arrhythmias. A p-level of <0.05 was considered statistically significant.

Results

During the study period, 110 patients were enrolled (70 males, 40 females) with a mean age of 2.6±1.5 years. The mean body weight 10.7±2.2kg. 49/110 patients (44.5%) were cyanotic and 61/110 patients were acyanotic (55.5 %). Ventricular septal defect was the most common acyanotic congenital heart diseases 36/61 (59%) and Tetralogy of Fallot was the most common cyanotic congenital heart diseases 33/49 (67.3%). 95/110 (86.3%) of the cardiac surgeries were corrective and 15/110 (13.7%) were palliative cardiac operations. Out of 110 patients 30 developed arrhythmias in the postoperative period (27.2%). Thirty patients (14 females, 16 males; 27.2% of total studied patients) developed rhythm disturbances. 18 cases out of 30 (60%) had arrhythmias on day one, 9 cases (30%) had arrhythmias on day two, 2 cases (6.6%) had arrhythmias from day two to seven and one case (3.3%) after one week. The details are shown in Fig. (1).

Within the corrective cardiac surgery group 95 cases, 28 patients (29.4%) developed arrhythmias most of them occurred within first 48 hours postoperatively Fig. (3).

Supraventricular and junctional tachycardias were the commonest arrhythmias in early postoperative period the details are shown in Fig. (2).

Figure 1: Onset of postoperative arrhythmias.

Out of 30 patients, 20 (66.6%) patients were cyanotic while 10/30 (33.3%) were acyanotic. Two (6.6%) had palliative cardiac surgery while 28 (93.3%) had corrective cardiac surgery.

The two patients 2/15 (13.3%) who developed arrhythmias following palliative cardiac surgery including one patient who had pulmonary artery banding and developed (premature atrial beats) on day one preceded by hyponatremia while the second patient had Blalock Tausung shunt (B-T shunt) and developed (sinus tachycardia) on day 3 that was due to anemia. Both were excluded from our statistical study.

Figure 2: Type and frequency of arrhythmias.

Types of arrhythmias

- JET: Junctional ectopic tachycardia.
- SVT: Supraventricular tachycardia.
- PVC: Premature ventricular-contraction.
- AVB: Atrioventricular block.
- SB: Sinus bradycardia.
- ST: Sinus tachycardia.
- PAC: Premature atrial contraction.

Figure 3: Onset of arrhythmias in corrective cardiac surgery.

Within the corrective cardiac surgery group 95 cases, 28 patients (29.4%) developed arrhythmias most of them occurred within first 48 hours postoperatively Fig. (3).
The commonest arrhythmias in the postoperative period included JET and SVT, 10/28 (35.7%) for each of them. Both were common in the early post operative period following repair of tetralogy of Fallot 6/33 (18.1%) and 5/33 (15.1%) respectively. As shown in Table (1).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Type of arrythmias</th>
</tr>
</thead>
<tbody>
<tr>
<td>(95 Patients)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>JET 10/95 SVT 10/95 AVB 4/95 SB 2/95 PVC 2/95 (10.5%) (10.5%) (4.2%) (2.1%) (2.1%)</td>
</tr>
<tr>
<td>TOF (33 cases)</td>
<td>6 5</td>
</tr>
<tr>
<td>AVC (10 cases)</td>
<td>3 3</td>
</tr>
<tr>
<td>VSD+ASD (10 cases)</td>
<td>3 1 1</td>
</tr>
<tr>
<td>VSD (36 cases)</td>
<td>2 1</td>
</tr>
<tr>
<td>ASD (2 cases)</td>
<td>1</td>
</tr>
<tr>
<td>D-TGA (3 cases)</td>
<td>1</td>
</tr>
<tr>
<td>DORV,TGA,PS (one case)</td>
<td>1</td>
</tr>
</tbody>
</table>

JET : Junctional ectopic tachycardia.
SVT : Supraventricular tachycardia.
PVC : Premature ventricular-contraction.
AVB : Atrioventricular block, Sinus bradycardia.
TOF : Tetralogy of Fallot.
AVC : Atrioventricular canal defect.
D.TGA : Transposition of the great arteries.
ASD : Atrial septal defect.
VSD : Ventricular septal defect.
DORV : Double outlet right ventricle.
PS : Pulmonary stenosis.

Table 1: Details of early postoperative arrhythmia in corrective cardiac surgery are shown in.

Although patients were not classified according to their complexity, arrhythmias were more in patients with (TOF, CAVC, DORV, D-TGA) 20/28 (71.4%) than patients with simple defects (ASD, VSD) 8/28 (28.5%).

The potential risk factors for arrhythmias and perioperative details in corrective cardiac surgery are shown in Table (2).

### Risk factors analysis:

**Preoperative risk factors:**

In a univariate analysis independent risk factors for early postoperative arrhythmias were; lower body weight \((p<0.05)\), younger age at time of surgery \((p<0.05)\) and cyanosis \((p<0.05)\).

**Operative risk factors:**

In a univariate analysis independent risk factors for early postoperative arrhythmias were; Prolonged CPB duration \((p<0.05)\) and a Redo operation \((p<0.01)\).

### Postoperative risk factors:

In a univariate analysis independent risk factors for early postoperative arrhythmias were; High inotropic support on leaving operating room, Hypotension on arrival ICU, ventilation and Acidosis \((p<0.01)\).

In the multivariate stepwise logistic regression, cyanosis was statistically significant \((p value <0.005)\). Longer CPB time and redo operation were statistically significant \((p value <0.01)\). Postoperative higher doses of inotropic support and long ventilation time were statistically significant \((p value <0.001)\).

Treatments of arrhythmias in post corrective cardiac surgery, all cases were successfully treated. Body surface cooling was applied in 5 patients, including 2 with junctional ectopic tachycardia and 3 with supraventricular tachycardia. Antiarrhythmic drug therapy with amiodarone was used in 8 patients, including junctional ectopic tachycardia and 7 with supraventricular tachycardia.
Arrhythmias are serious problems because they cause hemodynamic imbalance, often require aggressive treatment and increase mortality risk [13]. In this study, the incidence of arrhythmia in the 110 cases was 27.2%. It was common after corrective (29.4%) rather than palliative (13.3%) cardiac surgeries. That incidence is close to the rates reported by Pfammater et al, 2001 (27%) [6]. While in the study of Valsangiacomo the incidence of arrhythmias were (48%) and this can be explained by performance of more complex surgical procedures in younger patients in their study [1]. But the incidence in this study was significantly higher than the one reported by Bronzetti who found it (8.9%) as they studied only incidence of Junctional ectopic tachycardia following open cardiac surgery [14]. Where as in this study, the incidence was quite high because the present study included all kinds of abnormal rhythm with and without hemodynamic effects also we are not focused on specific cardiac lesion to provide broader information about the overall spectrum of rhythm disturbances potentially encountered by the pediatric cardiologist, cardiac surgeon and critical care specialist in the immediate postoperative period.

The lower risk of arrhythmia after palliative heart surgery was due to palliative heart surgical technique does not affect the myocardium or interfere with the conduction system; there were also no negative effects of CPB. In contrast, arrhythmias occur more frequently after corrective heart surgery despite the advances in surgical and CPB techniques as well as myocardial preservation. Most of these disturbances are due to direct injury to cardiac tissue from myocardial incision, cannulation, suture affecting atrioventricular conduction and rapid change of intracardiac pressure caused by volume and pressure fluctuation [15].

Previous studies classified arrhythmias as early and late according to the time of onset, early onset arrhythmias was defined as presence of arrhythmias during the first 48 hours postoperatively [16]. In this study within the corrective cardiac surgeries 27 out of 28 (96.4%) developed early onset arrhythmias, the same was reported by other studies this could be expected due to the swelling of the myocardium, unstable hemodynamic status, high doses of inotrope administration and metabolic disturbance were encountered [15].

In the present study the most common forms of arrhythmias in early postoperative period following the corrective cardiac surgery were JET (18.1%) and SVT (15.1%), which were common in early post operative period following repair of tetralogy of Fallot respectively. That were supported with other studies [17,18]. This could be explained by direct trauma or infiltrative hemorrhage of the His bundle secondary to increasing traction through the right atrium for resection of right ventricular outflow tract obstruction. While in the study of Valsangiacomo and colleagues, the most frequent types of arrhythmia were sinus bradycardia, second and third degree AV block and SVT [1], this could be related with the difference in complex surgical interventions between different studies.

This study showed that younger age and low body weight at the time of operation were risk factors for early postoperative arrhythmias and they were statistically significant that could be explained by the fact that complex surgical interventions are more frequent early; moreover, the sensitivity to electrolyte and acid-base disorder is higher early in life [8]. This was reported by the study of Valsangiacomo et al, 2002 [1].

In the current study the more complex the cardiac defects the more frequent early postoperative arrhythmias (TOF, CAVC, DORV, D-TGA) 20/28 (71.4%) than patients with simple defects (ASD, VSD) 8/28 (28.5%). Also presence of cyanosis was a risk factor for early postoperative arrhythmias (66.6%) of arrhythmic patients were cyanotic.

That was supported by the study of Pfammatter and colleagues 2002 who found that the complexity of the surgical procedure was a strong risk factor of postoperative arrhythmias this can be explained by longer CPB time in complex procedure [19].

This study the mean CPB for the patients who developed arrhythmias was 105.4±53.1 and this was longer than in non arrhythmic patients 80.8±35.3 and this was statistically significant so the longer CPB time is a risk factor for arrhythmias this was reported by [8]. This could be explained by the fact that long CPB causes changes in the micro and macro-equilibrium. The arrhythmias might have been increased because of the alterations in the myocardial conduction pathways. Furthermore CPB with ischemia-reperfusion and the related cellular biochemical effects as well as medical
interventions such as electrolyte shifts and catecholamine administration may affect the stability of the cellular membrane and result in an increased myocardial irritability and automaticity [20]. As postoperative arrhythmias appeared frequently in the first 24 hours, factors belonging to the myocardium, CPB and high inotropic requirement, hypotension, electrolytes disturbances, acidosis and longer ventilation in this period should be researched.

In this study among the arrhythmic patients the need for higher dose on inotropes and hypotension were 9 out of 28 patients for each (32.5%) and the presence of acidosis was in 7 out of 28 patients (25%) showed a statistical significance when compared to non arrhythmic patients that was supported with other studies [21,22,23] and this could be explained by the fact that inotropic support, hypotension and acidosis may affect the cellular membrane and result in an increased myocardial irritability and automaticity [8].

This study showed that electrolyte disturbances were not statistically significant in developing arrhythmias which was supported by [24]. While others showed that Low magnesium level was reported as causative in JET appearance [25]. This study showed that the Redo-operations was statistically significant risk factors for early postoperative arrhythmias this could be explained by tissue injury and ionic changes which affected electrical property at cellular level [15,26,27].

Early postoperative arrhythmias influence the long-term outcome of patients with congenital heart diseases, this study showed all reported arrhythmias were transient and their adverse hemodynamic effects could be limited with the therapies used. Thus no life-threatening episodes or deaths were related to postoperative arrhythmias and this can be explained by improved quality of the postoperative intensive care which enables early recognition and immediate treatment of potentially lethal rhythm disturbances. Although development of early postoperative arrhythmias is associated with a longer postoperative stay at the cardiac intensive care unit, a longer ventilation time and most importantly, a higher hospital mortality as reported by the study of Rekawek J et al, 2007 [7]. Which could be explained by more cardiac complexity, younger age at intervention [28].

Among all treatments, Body surface cooling and drug therapy with amiodarone were the most frequently used. The same was reported by previous study [29].

Preventing these arrhythmias will influence the long-term survival of patients with congenital heart diseases. Careful monitoring of these patients especially cyanotic, young patients with lower body weight who are candidate for corrective cardiac surgery with long cardiopulmonary bypass time that might be in need for high inotropic support postoperatively, so medical prevention and early management with appropriate means could improve outcome.

Conclusions

Early postoperative period following cardiac surgery is the most critical period during which arrhythmias mostly happened especially in first 48 hours. Junctional ectopic tachycardia and supraventricular tachycardia were the most common postoperative arrhythmias. Risk factors for postoperative arrhythmias were preoperative including young age, low body weight at the time of operation and the presence of cyanosis. Predisposing operative factors for arrhythmias included redo procedure and long cardiopulmonary bypass time and postoperative risk factors including Acidosis, mechanical ventilation and high inotropic support.

• Recommendation:

Early corrective surgery for congenital heart diseases especially cyanotic group, smooth uncomplicated operative time with early treated any events that might cause prolongation of cardiopulmonary bypass time, early treated any acid base imbalance, minimal effective doses of inotropic drugs in the postoperative time might help in decrease the development of postoperative arrhythmia.

• Acknowledgements:

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Myocardial Performance Index in Patients with Left Ventricular Systolic Dysfunction: Conventional Method Versus Doppler Tissue Imaging

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Background: Left ventricular systolic and diastolic dysfunction are the underlying mechanisms of CHF. Isolated analysis of either mechanism may not be reflective of overall cardiac dysfunction. Myocardial performance (Tei) index has been described which may be more effective for analysis of global cardiac dysfunction than systolic and diastolic measures alone.

Objectives: To compare myocardial performance index (MPI) measured by conventional Doppler and MPI measured by Pulsed wave Doppler tissue imaging (PWDTI) in normal subjects and in patients with left ventricular systolic dysfunction.

Patients and Methods: The study comprised 50 patients with left ventricular ejection fraction (LVEF) <50% & 20 age & sex matched healthy volunteers as a control group. Conventional echocardiography was done to estimate LVEF by Simpson’s rule and LV diastolic filling patterns by assessment of mitral inflow using pulsed wave Doppler (PWD) examination. Tei index was calculated conventionally by measurement of time intervals with PWD and with PWDTI as the average at the four mitral annular sites.

Results: MPI was significantly higher in patients than control subjects both by conventional method (0.48±0.08 Vs. 0.34±0.04, p<0.0001) & PWDTI (0.73±0.1 Vs. 0.40±0.02, p<0.0001). MPI measured by PWDTI (MPI-DTI) showed a stronger negative & more significant correlation with LVEF than conventionally measured MPI in both control group (r=-0.7, p<0.001 & r=-0.47, p<0.05, respectively) and in patients group (r=-0.36, p<0.05 & r=-0.019, p>0.05 respectively). The correlation between MPIDTI & MPI measured by conventional method was stronger and significant in control group compared to patients group (r=0.6, p<0.05 & r=0.035, p>0.05, respectively). The cutoff points of MPI for prediction of LVEF <50%, was (0.47 with 94% sensitivity & 90% specificity for MPIDTI) & (0.37 with 85% sensitivity & 84% specificity for MPI measured by conventional method).

Conclusion: PWDTI provides a simple, rapid, accurate & more reproducible tool for calculation of MPI in comparison to the conventional method. By overcoming the limitation of the conventional method, (MPI-DTI) is considered an effective tool for expression of LV function.

Key Words: Tei index – Doppler tissue imaging – Left ventricular dysfunction.

Introduction

Congestive heart failure (CHF) is a major cause of morbidity and mortality. Previous studies have demonstrated that patients with heart failure (HF) may have gone through a phase of asymptomatic left ventricular dysfunction, where objective LV measurements reveal impairment of cardiac contractility but overt heart failure is not present [1].

Tei index, a recently proposed indicator of combined ventricular systolic and diastolic function, is defined as the ratio of the sum of isovolumic relaxation time and isovolumic contraction time over the ejection time [2]. MPI has previously been shown to be a sensitive independent prognostic indicator in patients with symptomatic HF, dilated cardiomyopathy and postmyocardial infarction [3].

The Doppler components used to calculate the Tei index are obtained sequentially and not on the
same cardiac cycle and its application may be limited by fluctuating cardiac cycle length associated with stressful conditions. To avoid this limitation, Harada et al. [4] obtained the right ventricular Tei index instead by Doppler tissue imaging, which allowed simultaneous measurements of the time intervals of contraction and relaxation from the myocardium. A good correlation was demonstrated between the Tei indices obtained by Doppler tissue imaging and that determined by flow Doppler waveforms. Nevertheless, it is still unknown whether such a good correlation also exists between the left ventricular Tei indices derived by both methods.

**Aim of the work:**

To compare MPI measured by conventional Doppler and MPI measured by Pulsed wave Doppler tissue imaging (PWDTI) in normal subjects and in patients with LV systolic dysfunction.

**Patients and Methods**

The current study included 50 patients with LV systolic dysfunction (defined as LV EF <50% with a disease history >3 months.) admitted to Menoufia university Hospital from June 2007 to May 2008 and 20 healthy normal volunteers as a control group.

**Exclusion criteria:** Patients with the following criteria were excluded from the study:

1- Pericardial effusion.
2- Cardiogenic shock.
3- Restrictive cardiomyopathy
4- Sustained ventricular or supraventricular arrhythmias.
5- Complete (≥120 milliseconds) left bundle or right bundle branch block or complete heart block.
6- Significant valvular lesions.
7- Patients with chronic obstructive pulmonary disease & corpulmonale.
8- Patients with pacemakers.

**For each patient the following was done:**

1- Detailed history talking.
2- Thorough clinical examination.
3- Standard 12 lead Electrocardiogram (ECG).
4- Convensional echocardiographic examination:

Echocardiography was performed with the patients in the left lateral decubitus position. The equipment used was Acuson 128 XP 10 C system equipped with DTI technology. Measurement were performed according to the recommendations of the American Society of Echocardiography [5]. Two-dimensional imaging examination was performed in the standard fashion in parasternal long and short-axis views and apical 4-and 2-chamber views [6]. Pulsed Doppler spectral recordings were obtained in the apical 4-chamber view from a 4mm sample volume placed at the tips of mitral valve.

Echocardiograms were subject to careful visual analysis to detect regional contractile abnormalities. LV systolic and diastolic volumes and ejection fraction (EF) were derived from biplane apical (2- and 4-chamber) views using the modified Simpson’s rule algorithm [7]. The transmitral pulsed Doppler velocity recordings from three consecutive cardiac cycles were used to derive measurements as follows: Peak velocities reached in early diastole (E) and after atrial contraction (A) and deceleration time (DT) was the interval from E-wave to the decline of velocity to baseline. In those cases in which velocity did not return to baseline, extrapolation of the deceleration signal was performed.

"a" interval was measured between cessation and onset of the mitral inflow. Pulsed Doppler study of LV outflow was made by placing the sample volume just below the aortic valve in the five chamber view and "b" interval was measured between onset and cessation of the LV outflow. Intervals "a" and "b" were obtained from the average of three consecutive cardiac cycles. Conventional MPI was obtained as (a-b)/b [8].

5- DTI Examination: DTI of the mitral annulus was obtained from the apical (2- and 4-chamber) views after filters were set to exclude high-frequency signals (which is obtained by activating the DTI mode of the machine). A 5-mm sample volume was placed sequentially at the septal, lateral, inferior and anterior mitral annuli. The resulting velocities were recorded for 3 consecutive cardiac cycles at a sweep speed of 100mm/s. The following measurements were made from the recordings: Peak systolic velocity (Sm), early (Em) and late (Am) diastolic velocities. Analysis was performed for the average of each velocity wave and time intervals measured at the four annular sites [9]. All Doppler echocardiographic and DTI recordings were obtained during normal respiration. The data were stored on a 1/2-inch VHS videotape for subsequent playback, measurement and analysis. DTI isovolumic contraction time (tICT) was...
measured between cessation of A wave and onset of S wave; DTI ejection time (tET) was obtained between onset and cessation of S wave; DTI isovolumic relaxation time (tIRT) was obtained between cessation of S wave and onset of E wave. MPIDTI was calculated as \((tICT + tIRT) / (tET)\) [8].

\[
\text{MPIDTI} = \frac{tICT + tIRT}{tET}
\]

- Student \(t\) test, to compare between two individual groups by measuring the difference between two means.
- Chi square test, to study the relation between two qualitative variables.
- Bivariate Correlation Coefficient (\(r\)) to study the association between two quantitative variables.
- ROC curve was applied to identify the appropriate cutoff point that have the best sensitivity and specificity.
- The level of significance is 95%. So, \(p\) value <0.05 was considered a significant result.

**Results**

The current study included 50 patients with LV systolic dysfunction (defined as LVEF <50% with a disease history >3 months) admitted to Menoufya university Hospital from June 2007 to May 2008 (36 males & 14 females with mean age 54±5.1 years) with different cardiac pathologies referred for echocardiography and 20 healthy normal volunteers as a control group (15 males & 5 females with mean age 52.1±3.4 years).

**Table 1: Demographic data of the study population.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients</th>
<th>Control</th>
<th>(p) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54±5.1</td>
<td>52.1±3.4</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>36/14</td>
<td>72/28</td>
<td>15/5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>30</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>37</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>32</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>+ve family history</td>
<td>20</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>29</td>
<td>58</td>
<td></td>
</tr>
</tbody>
</table>

There was no significant difference between patients and control regarding age or sex (54±5.1 Vs. 52.1±3.4 years, \(p>0.05\)).

As regard risk factors’ prevalence, diabetes mellitus was 60% (30 patients), hypertension was 74% (37 patients), smoking was 58% (29 patients), dyslipidemia was 64% (32 patients) and positive family history was 40% (20 patients) (Table 1).

Myocardial performance index (MPI) measured by DTI was significantly higher in patients group than control group (0.73±0.1 Vs. 0.40±0.02, \(p<0.001\)). Also MPI measured by conventional method, was significantly higher in patients group than control group (0.48±0.08 Vs. 0.34±0.04, \(p<0.001\)).
Myocardial Performance Index in Patients with Left Ventricular Systolic Dysfunction

Ejection fraction measured both by M-mode & Simpson method, was significantly lower in patients group than control group (40.7±4.4 Vs. 64.4±4.8, \(p<0.001\)) & (37.5±4.1 Vs. 61.6±4.8, \(p<0.001\)) respectively. Fractional shortening was significantly lower in patients group than control group (20.2±2.2 Vs 31.6±2.5, \(p<0.001\)) (Table 2).

A highly significant correlation between EF measured by Simpson method and that measured by M-mode in control group (\(r=0.9, p<0.001\)) and in patients group (\(r=0.81, p<0.001\)).

Also there was highly significant correlation between EF measured by Simpson method and fractional shortening in control group (\(r=0.9, p<0.001\)) and in patients group (\(r=0.8, p<0.001\)).

Ejection fraction measured by Simpson method has a strong negative correlation with MPI measured by Doppler tissue imaging (MPI DTI) both in control group (\(r=−0.7, p<0.001\)) and in patients group (\(r=−0.356, p<0.05\)).

Also EF measured by Simpson method has a moderate negative correlation with MPI measured by conventional method in control group (\(r=−0.47, p<0.05\)) but this negative correlation was weaker & non significant in the patients group (\(r=−0.019, p>0.05\)).

Ejection fraction measured by M-mode has a strong negative correlation with (MPI DTI) both in control group (\(r=−0.61, p<0.01\)) and in patients group (\(r=−0.36, p<0.05\)). Also EF measured by M-mode has a strong negative correlation with MPI measured by conventional method in control group (\(r=−0.47, p<0.05\) but this negative correlation was weaker & non significant in the patients group (\(r=−0.09, p>0.05\)).

As regard the whole study population (control & patients), a very strong negative correlation was detected between EF measured by M-mode & each of MPI DTI (\(r=−0.85, p<0.0001\)) and MPI measured by conventional method (\(r=−0.67, p<0.0001\)).

Table 2: Ecocardiographic data in patients and control group.

<table>
<thead>
<tr>
<th>Items</th>
<th>Patients</th>
<th>Control</th>
<th>t. test</th>
<th>p. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPI measured by DTI</td>
<td>0.73±0.1</td>
<td>0.40±0.02</td>
<td>14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MPI measured by conventional method</td>
<td>0.48±0.08</td>
<td>0.34±0.04</td>
<td>7.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ejection fraction (%) by M-mode</td>
<td>40.7±4.4</td>
<td>64.4±4.8</td>
<td>19.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ejection fraction (%) by Simpson method</td>
<td>37.5±4.1</td>
<td>61.6±4.8</td>
<td>19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>20.2±2.2</td>
<td>31.6±2.5</td>
<td>19</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

\(\text{MPI} = \text{Myocardial performance index.}\)

\(\text{DTI} = \text{Doppler tissue imaging.}\)

Table 3: Correlation between EF & MPI in patients and control group.

<table>
<thead>
<tr>
<th>Items</th>
<th>Control</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pearson's correlation coefficient ((r))</td>
<td>p. value</td>
</tr>
<tr>
<td>EF (by Simpson method) &amp; EF (by M mode)</td>
<td>0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EF (by Simpson method) &amp; MPI (by DTI)</td>
<td>−0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EF (by Simpson method) &amp; MPI (by conventional Doppler)</td>
<td>−0.47</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>EF (by M-mode) &amp; MPI (by DTI)</td>
<td>−0.61</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>EF (by M-mode) &amp; MPI (by conventional Doppler)</td>
<td>−0.46</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

\(\text{EF} = \text{Ejection fraction.}\)

\(\text{DTI} = \text{Doppler tissue imaging.}\)
From the above two figures EF could be calculated using the following regression equations:

Using MPI DTI, LVEF could be calculated as follows:

\[ \text{E.F.} = 84 - (57 \times \text{MPI DTI}) \]

Using MPI measured by conventional method, LVEF could be calculated as follows:

\[ \text{E.F.} = 83 - (81 \times \text{MPI conventional method}) \]

A positive correlation was detected between MPI DTI & MPI measured by conventional method but the correlation was stronger & significant in the control group compared to the patients group (\( r = 0.6, p < 0.05 \) & \( r = 0.035, p > 0.05 \), respectively).

As regard the whole study population (control & patients), the significance of correlation was stronger (\( r = 0.6, p < 0.001 \)).

Using ROC curve, the cutoff points of MPI DTI for prediction of LVEF <50%, was (0.47 with 94% sensitivity & 90% specificity for MPI DTI) & (0.37 with 85% sensitivity & 84% specificity for MPI measured by conventional method).

**Reproducibility:** The interobserver and intraobserver variabilities for MPI DTI were compared in 40 consecutive measurements and were 2.2% and 2.9%, respectively compared to 5.7% & 6.3% respectively for conventionally measured MPI, accounting for more reproducibility for MPI DTI.
Figure 6: Correlation between myocardial performance index measured by Doppler tissue imaging (MPI DTI) and measured by conventional method in all study population.

Figures 7-12: Show an example of one of the patients group.

Figure 7: Calculation of EF by Simpson rule.

Figure 8: Calculation of MPI by conventional method.
Figure 9: Calculation of MPI by DTI at the septal mitral annulus.

Figure 10: Calculation of MPI by DTI at the lateral mitral annulus.

Figure 11: Calculation of MPI by DTI at the inferior mitral annulus.

Figure 12: Calculation of MPI by DTI at the anterior mitral annulus.
Discussion

In patients with congestive heart failure, there is no prognostic indicator more important than LV systolic function [10]. LVEF was a strong negative predictor of mortality; low EF predicted a higher incidence of recurrent cardiovascular events, ventricular arrhythmias and cardiovascular death [11-14]. In fact, in stable patients with coronary artery disease (CAD), EF is a stronger predictor of mortality than is the number of diseased vessels [15]. In patients with ischemic cardiomyopathy, EF has a strong influence on mortality from sudden death and ventricular arrhythmias [16]. So an accurate assessment of LV function has a great prognostic importance as a determinant of morbidity and mortality.

In the complete assessment of systolic function in any given patient, preload, afterload, contractility, and myocardial mass should be evaluated. Unfortunately, this is not practical in everyday clinical practice. Contractility is a key determinant of prognosis in most cardiac diseases. However, measurements of contractile function in patients with cardiac disease are laborious and have not gained wide clinical acceptance. Because many current indices of contractile function require load manipulation for their development, these measurements will probably continue to be limited to use as research tools. It should be noted that there has been a marked decline in the number of published papers examining contractile function since 1995 [10]. So there is a strong need for accurate assessment of LV function for accurate diagnosis and treatment.

Tei index obtained from pulsed-Doppler method has been found to be a reproducible and simple index in assessing global LV function [17,18] and it correlates closely with invasive measurements of LV systolic and diastolic function [19,20]. However, its components are sometimes obtained sequentially from different heart beats if mitral inflow and LV ejection signals cannot be clearly recorded simultaneously and its application may be limited by heart rate fluctuation. In contrast, MPIDTI has an inherent advantage of recording its systolic and diastolic velocity signals simultaneously from the same cardiac cycle. Therefore, beat-to-beat variations can be avoided.

**MPI measured by DTI Vs. conventional method:**

The current study was designed to assess LV function in patients with LV systolic dysfunction by MPI using both conventional method & DTI; where MPIDTI and MPI measured by conventional method, was significantly higher in patients group than control group. Also LVEF measured by Simpson method & M-mode was found to have a strong negative correlation with MPI DTI and MPI measured by conventional method both in control group and in patients group. But the strength & significance of correlation was greater with MPID-TI than conventional method and in control subjects rather than patients group; this difference may be attributed to inherent advantage of MPIDTI time intervals, measured simultaneously on the same cardiac cycle. Therefore, beat-to-beat variations can be avoided in contrast to the conventional method which obtain measurements from different cardiac cycles being prone to affection by variation in heart rate & loading conditions. Also the impact of loading conditions and heart rate variability is much less pronounced in control group in comparison to patients with LV systolic dysfunction. In agreement with these findings, Rojo et al [8] found a mild negative correlation between LVEF & MPI \( r=-0.319, \ p<0.005 \) also they reported a mild positive correlation between MPI & wall motion score index \( r=0.258, \ p<0.025 \). Furthermore, Ho-Ming Su et al [23] detected a negative correlation between DTI-derived Tei index and LVEF \( r=-0.384, \ p=0.046 \). This study further demonstrates fair correlations between DTI-derived Tei index and accepted indices of LV diastolic and systolic function acquired from cardiac catheterization. Therefore, DTI-derived Tei index is a reliable index in assessing global LV function. The difference in these cases in the strength of correlation compared to our study, may be attributed to the fact that, assessment of MPI in case of Ming Su et al [23] was performed at the lateral mitral annulus only and at the septal & lateral mitral annuli in case of Rojo et al [8], while in the present study evaluation was performed at the four annular sites and averaged so it gives a better expression of the global LV function which accounts for the stronger correlation in the current study.

Bruch et al [3] postulated that, Tei-Index was significantly correlated with LV end-diastolic pressure \( r=0.46, \ p<0.01 \), but independent of heart rate, systolic or diastolic blood pressure. A significant inverse correlation was observed between LVEF and LV end-diastolic pressure \( r=-0.53, \ p<0.001 \).
Agreement between MPI measured by DTI & conventionally:

A positive correlation was detected between MPIDTI & MPI measured by conventional method but the correlation was stronger in the control group compared to the patients group ($r=0.6$, $p<0.05$ & $r=0.035$, $p>0.05$, respectively). As regard the whole study population (control & patients), the significance of correlation was stronger ($r=0.6$, $p<0.001$).

In agreement with this, Voon et al [2] found that, tissue Doppler Tei index correlated well with the flow Doppler Tei index ($r=0.406$, $p=0.003$).

Detection of LV systolic dysfunction using MPI:

Using ROC curve, the cutoff points of MPIDTI for prediction of LVEF <50%, was (0.47 with 94% sensitivity & 90% specificity for MPIDTI) & (0.37 with 85% sensitivity & 84% specificity for MPI measured by conventional method). Similarly, Bruch et al [3] detected a cutoff point of >0.47 for MPIDTI for identification of congestive heart failure with a sensitivity of 86% and a specificity of 82%. On the other hand, Rojo et al [8] found a cutoff point 0.46 in patients with prior myocardial infarction with a sensitivity of 81% and a specificity of 80%.

Reproducibility: In the current study, the interobserver and intraobserver variabilities for MPIDTI were compared in 40 consecutive measurements and were 2.2% and 2.9%, respectively Compared to 5.7% & 6.3% respectively for conventionally measured MPI, accounting for more reproducibility for MPIDTI. Similarly, Voon et al [2] detected intraobserver and interobserver mean percent error for the flow Doppler Tei index measurement 7% and 5%, respectively. while these values were 5% and 4%, respectively for the tissue Doppler Tei index measurement at the lateral mitral annulus.

Rojo et al [8] Interobserver and Intraobserver variabilities was 8.3%±4% and 7.6%±4.3% for conventionally measured MPI; while these values were 4% and 6%, respectively for the tissue Doppler Tei index measurement at the septal and lateral mitral annuli.

Bruch et al [3] postulated that, conventionally measured MPI intraobserver variability was 3.2±2.4% and interobserver variability was 4.0±2.1%.

Myocardial performance index and LVEF:

In our study, a strong negative correlation was found between LVEF and MPIDTI both in control group ($r=-0.61$, $p<0.01$) and in patients group ($r=-0.36$, $p<0.05$). While these values were ($r=-0.47$, $p<0.05$) and ($r=-0.09$, $p>0.05$) for conventionally measured MPI.

As regard the whole study population (control & patients), a very strong negative correlation was detected between LVEF & each of MPI measured by Doppler tissue imaging ($r=-0.85$, $p<0.0001$) and MPI measured by conventional method ($r=-0.67$, $p<0.0001$).

Depending on this strong correlations, our study was the first one to predict LVEF from MPI (measured by DTI and conventionally) using the following regression equations: LVEF = 84 – (57 x MPIDTI) & LVEF = 83 – (81 x MPI measured by conventional method).

Ming Su et al [23] reported that, the most important finding is the correlation between DTI derived-Tei index with both LV systolic and diastolic function and, like Tei index obtained from pulsed-Doppler method, independent of heart rate and blood pressure. Moreover, its components can be directly measured on the same cardiac cycle without the assistance of ECG. Consequently, MPIDTI is an easily obtainable and useful parameter in assessing global LV function. Previous studies have showed that systolic intervals have a significant correlation with stroke volume, cardiac output and LVEF [24,25]. Ejection time derived from pulsed-Doppler echocardiography has been found to be positively correlated with systolic function(LVEF) and negatively correlated heart rate [19,26].

Study limitations: All DTI measurements were performed with respect to a stationary transducer on the chest wall and data may be affected by the whole heart translation and rotation movements (stationary sample volume positioned within a moving target) but the effect of these movements was minimal and did not dramatically affect DTI measurements except in patients with prominent cardiac translation movements. Another limitation is that, DTI system technique relies on the parallel alignment of the moving object examined. Thus, some of the observed differences in velocity between the walls could be accounted for angulation. These differences could be minimized by choosing myocardial regions of interest within 15-20 degrees

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of the axis of Doppler interrogation. The study population was relatively small and our findings wait for further validation. Also study lacks comparison of the measured echocardiographic findings with an invasive golden standard for further confirmation. However, previous reports [3,23] showed good correlations with invasively measured parameters. Finally, DTI and pulsed Doppler tracings cannot be obtained simultaneously, but meticulous care was taken to measure cycles with identical R-R intervals.

Conclusion

PWDTI provides a simple, rapid, accurate & more reproducible tool for calculation of MPI in comparison to the conventional method. By overcoming the limitation of the conventional method, (MPI-DTI) is considered an effective tool for expression of LV function. Therefore having more clinical diagnostic utility as load-independent tool for assessment of LV function in patients with LV systolic dysfunction.

References


Correlation between Mixed Venous and Central Venous Oxygen Saturation in Patients Undergoing CABG

OSAMA IBRAHEIM, MD*; MOHAMED ESSAM, MD*; AHMAD AL-SHAER, MD*; SAAD SHETA, MD*; KHALID FAROUK, MD*

Objective: To examine the correlation between central venous oxygen saturation (CV\textsubscript{o2}) and mixed venous oxygen saturation (Sv\textsubscript{o2}) and to test the validity of the clinical applicability of substituting CV\textsubscript{o2} for mixed venous oxygen saturation (Sv\textsubscript{o2}) in adult patients with poor myocardial function undergoing coronary artery bypass grafting (CABG).

Methods: Prospective clinical observational study done at King Khalid University hospital, King Saud University, Riyadh, KSA. Forty six adult patients with poor myocardial function as stated by EF<40% scheduled for elective coronary artery surgery were included. Patients were monitored by a pulmonary artery catheter and a central venous catheter with its tip adjusted in the right atrium, so, right atrial blood oxygen saturation (RA\textsubscript{o2}) will be presenting the central venous oxygen saturation (CV\textsubscript{o2}).

Mixed venous oxygen saturation (Sv\textsubscript{o2}) and right atrial oxygen saturation (RA\textsubscript{o2}) were simultaneously measured at 15 and 30 min after induction of anesthesia (T1 & T2), 15& 30 min after initiation of cardiopulmonary bypass (T3 & T4), and 15 min and 30 min after admission to intensive care unit (T5 & T6). Patients who needed IAPB or inotropic support higher than 0.5 ug/Kg/min were excluded.

Results: RA\textsubscript{o2} showed higher reading than Sv\textsubscript{o2} all through our study. Our results showed perfect positive statistically significant correlation between Sv\textsubscript{o2} and RA\textsubscript{o2} at all time points. Individual mean of difference between both readings at study times showed mean of difference (MOD) of 1.97±6.162 and 0.126±3.132 at T1 and T2 simultaneously this MOD was statistically insignificant, but after cardiopulmonary bypass (CBP) was initiated; MOD was 6.682 ± 5.660 and 4.930 ± 4.631 at T3 and T4 with high statistical significance, after cessation of CBP; MOD between Sv\textsubscript{o2} and Scv\textsubscript{o2} continue to have high statistical significance, MOD was 6.1391±3.484 at T5 and at T6 it was 5.2956±4.512.

Conclusions: In coronary artery bypass grafting with poor LV function patient; RA\textsubscript{o2} & Sv\textsubscript{o2} are not interchangeable numerically as they have failed to keep insignificant mean of difference when normothermic CPB was initiated, but had strong positive and significant correlation throughout the operative course. This makes RA\textsubscript{o2} useful in the meaning of trend; these data suggest that RA\textsubscript{o2} is equivalent to Sv\textsubscript{o2} in the course of clinical decisions as long as absolute values are not required.

Key Words: Mixed venous oxygen saturation – CABG.

Introduction

Mixed venous oxygen saturation (Sv\textsubscript{o2}) is a valuable measurement in hemodynamically unstable patients during cardiac surgery [1,2]. This parameter indicates the balance between oxygen supply and demand and thereby provides an index of tissue oxygenation [3]. Furthermore, it allows calculation of tissue oxygen consumption, oxygen extraction ratio, and the degree of pulmonary venous admixture [4].

However, Sv\textsubscript{o2} measurement is obtained only from a correctly positioned pulmonary artery catheter. Significant complications associated with the use of a pulmonary artery catheter (PAC) including pulmonary artery thrombosis, pulmonary infarction, right atrial thrombosis, atrial and ventricular arrhythmias, and right heart valvular damage [5,6]. As such, right atrial oxygen saturation RA\textsubscript{o2} represents an attractive alternative to Sv\textsubscript{o2} because central venous catheterization is easier and less invasive than pulmonary artery catheterization [7].

In a recently published guideline, Sv\textsubscript{o2} and central oxygen saturation (CVO\textsubscript{2}) were declared
Correlation between Mixed Venous & Central

as equivalent for the management of severe sepsis \cite{8}. The clinical applicability of substituting right atrial oxygen saturation (RAO\textsubscript{2}) for mixed venous oxygen saturation (SVO\textsubscript{2}) in different clinical situations still not fully studied. Open heart surgery is a unique clinical situation where there is a great variation during the surgery in hemodynamic and filling indices.

We aimed to examine the correlation between right atrial venous oxygen saturation (RAO\textsubscript{2}) and mixed venous oxygen saturation (SVO\textsubscript{2}), and to test the validity of the clinical applicability of substituting RAO\textsubscript{2} for SVO\textsubscript{2} in adult patients with poor myocardial function undergoing open heart coronary artery bypass grafting surgery (CABG).

Methods

After obtaining approval from the Institutional Review Board at the College of Medicine, King Saud University (Riyadh, KSA) and informed consent from each participant, we studied 46 patients scheduled to undergo coronary artery bypass grafting (CABG) using normo-thermic cardiopulmonary bypass.

The present study is a prospective observational study. Forty six adult patients of either sex, aged above 40 years, suffering from coronary heart disease with poor myocardial function as indicated with EF<40\%, scheduled for elective coronary artery bypass grafting (CABG) surgery were included in the study.

A standardized balanced anesthetic technique was used for all patients; patients were premedicated with lorazepam 2mg orally at the night of surgery and morphine 0.1mg/kg IM preoperatively. On receiving patient in operating room; standard monitoring was instituted. Peripheral venous as well as radial artery cannulae were inserted. Induction of anesthesia followed with sufentanil 1-1.5 µg/kg, midazolam 0.05-0.1 mg/kg and rocuronium 0.9 mg/kg then a maintenance infusion of the same induction agents; Sufentanil 0.2 µg/kg/hr, midazolam 1.5ug/kg/hr and Rocuronium 0.5 mg/kg/hr supplemented with Sevoflurane as required. Induction doses as well as anesthetic maintenance supplementation were guided by BIS monitoring (Aspect Technologies), and signs of lack of analgesia correlated with haemodynamic changes and were managed with a supplementary dose of sufentanil 0.3ug/Kg. A pulmonary artery catheter and a central venous line were inserted after induction of anesthesia enabling monitoring of mixed venous oxygen saturation (SVO\textsubscript{2}), right atrial venous oxygen saturation (RAO\textsubscript{2}) as well as other derived parameters. The lungs were mechanically ventilated with a tidal volume of 8 ml/kg and FiO\textsubscript{2} of 0.4 oxygen in air mixture, while ventilator rate adjusted to maintain a PaCO\textsubscript{2} of 32-36 mmHg.

A 7.5F, PAC (Edwards Lifesciences; Irvine, CA) was inserted through the internal jugular vein using a percutaneous 8.5F sheath introducer (Edwards Lifesciences; Irvine, CA). On the first appearance of right ventricular pressure waves in the distal port, the catheter was withdrawn until the right ventricular waves disappeared. The catheter distance at the entrance of the sheath introducer was noted. The catheter then was advanced; placing the distal port catheter in the pulmonary artery. A 3way CVL (Arrow, Incorp.) then was inserted and advanced till the referenced distance noted while inserting the PA catheter, this position would be approximately 3 to 4 cm above the tricuspid valve. A pressure tracing obtained from the CVL Distal port was used to ascertain correct positioning in the right atrium.

Postoperative portable chest radiograph and the presence of pulmonary artery pressure tracings confirmed the location of the distal PAC port in the pulmonary artery. Immediately after the insertion of the PAC and the CVL, each patient had one set of paired blood samples drawn in random order and in rapid succession from the distal ports of CVL and PAC. The first 2 ml blood drawn for each sample was discarded to prevent contamination with flushing fluid. Blood sampled with the catheter balloon deflated. We then measured the pulmonary artery occlusive pressure (PAOP) and cardiac output (CO) by the thermo dilution method as well as other hemodynamic calculations.

Sets of data were collected 15 & 30 minutes after induction of anesthesia (T1, T2), 15 & 30 minutes after initiation of cardiopulmonary bypass (T3, T4) and 15 min & 30 min post admission to intensive care unit (T5 & T6). Blood samples were drawn simultaneously from the pulmonary artery (PA) and right atrium (RA) at 6 different data points mentioned. A standard volume of 1 ml blood was obtained from each site and oxygen saturation per blood samples was determined immediately (QS 50®; Radiometer, Copenhagen, Denmark). Patients who needed IAPB or inotropic support higher than 0.5 ug/kg/min were excluded.
Data analysis:

Data were analyzed using statistical software package (GraphPad InStat® version 3.00 for Windows, GraphPad Software Inc., San Diego, California, USA) and presented as numbers, mean (SD), or ratio. Data were compared using the parametric or the nonparametric versions of analysis of variance (ANOVA). p value <0.05 was considered significant. Demographic and homodynamic data were compared using the Student t test. p value <0.05 was deemed to denote a significant difference. The correlation between SvO2 and RAo2 was evaluated by linear regression analysis and Pearson test followed by the F test. Mean of difference between simultaneously measured SvO2 and RAo2 individual values were calculated. The Student t test was used to determine whether the mean difference was significantly different from zero.

Results

Patients demographic and operative data are shown in Table (1).

The measured hemodynamic parameters and hemoglobin concentration values are listed in Table (2). Hb% was significantly lower at T3 & T4. Other parameters assessment as CI, PAOP and CVP were not applicable during CBP (T3 & T4).

Our data showed perfect positive statistically significant correlation between SvO2 and RAo2 at all study time points; Table (3) shows the spearman correlation coefficient at different sampling times. RAo2 showed higher values than SvO2 all through our study. Individual mean of difference between SvO2 and RAo2 at each study time was calculated. (MOD) was statistically insignificant at T1 & T2 (1.97±6.162 and 0.126±3.132), but after CBP was initiated; MOD showed statistical significance (6.682±5.660 and 4.9304±4.631 at T3 and T4), and continued to show statistical significance after cessations of CBP (6.1391±3.484 and 5.2956±4.512 at T5 and T6) (Table 4).

Table 1: Demographic and operative data.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>46</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>56.9±6.06</td>
</tr>
<tr>
<td>Sex M/F (n)</td>
<td>28/18</td>
</tr>
<tr>
<td>Preoperative Hb% (g/dl)</td>
<td>12.1±1.57</td>
</tr>
<tr>
<td>Number of grafts</td>
<td>2.8±0.91</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>34.4±4.92</td>
</tr>
<tr>
<td>Cross clamp time (min)</td>
<td>75.5±11.21</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>113±18.51</td>
</tr>
</tbody>
</table>

Data are mean ± SD or number.

Table 2: Hemodynamic parameters and hemoglobin concentrations at the different data points.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>T5</th>
<th>T6</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SaO2 (L/min/M2)</td>
<td>3.19±1.12</td>
<td>3.11±1.13</td>
<td>NA</td>
<td>9.6±0.62</td>
<td>9.42±0.82</td>
<td>9.15±0.79</td>
<td>NS</td>
</tr>
<tr>
<td>CI (L/min/M2)</td>
<td>18.22±6.3</td>
<td>17.25±5.6</td>
<td>NA</td>
<td>NA</td>
<td>4.20±0.81</td>
<td>3.92±0.74</td>
<td>NA</td>
</tr>
<tr>
<td>PAOP (mmHg)</td>
<td>14.7±5.36</td>
<td>16.25±5.36</td>
<td>NA</td>
<td>NA</td>
<td>14.7±8.54</td>
<td>12.71±7.45</td>
<td>NA</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>12.1±1.57</td>
<td>10.52±1.57</td>
<td>10.7±2.41</td>
<td>9.8±2.66</td>
<td>9.9±1.45</td>
<td>10.5±2.47</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are mean ± SD. Significant (p<0.05). NA= Not applicable. NS= Not significant.

Table 3: Correlation between SvO2 at different sampling times.

<table>
<thead>
<tr>
<th></th>
<th>Spearman correlation coefficient r</th>
<th>p (F test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>0.6385</td>
<td>0.001</td>
</tr>
<tr>
<td>T2</td>
<td>0.7714</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>T3</td>
<td>0.526</td>
<td>0.0099</td>
</tr>
<tr>
<td>T4</td>
<td>0.6454</td>
<td>0.0009</td>
</tr>
<tr>
<td>T5</td>
<td>0.8071</td>
<td>0.0001</td>
</tr>
<tr>
<td>T6</td>
<td>0.6170</td>
<td>0.0117</td>
</tr>
</tbody>
</table>

Table 4: Mean of difference (MOD) between SvO2 and RAo2 at different sampling times.

<table>
<thead>
<tr>
<th></th>
<th>SvO2</th>
<th>RAo2</th>
<th>Mean of difference</th>
<th>p value (t test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>81.36±5.17</td>
<td>82.32±6.035</td>
<td>1.977±6.162</td>
<td>0.8986</td>
</tr>
<tr>
<td>T2</td>
<td>81.4±5.17</td>
<td>81.5±3.47</td>
<td>0.126±3.132</td>
<td>0.989</td>
</tr>
<tr>
<td>T3</td>
<td>77.6±6.1</td>
<td>84.3±5.44</td>
<td>6.682±5.660</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>T4</td>
<td>81.5±5.83</td>
<td>85.4±5.03</td>
<td>4.9304±4.631</td>
<td>0.0022</td>
</tr>
<tr>
<td>T5</td>
<td>78.2±5.88</td>
<td>84.3±4.47</td>
<td>6.1391±3.484</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T6</td>
<td>75.6±5.42</td>
<td>80.9±4.82</td>
<td>5.2956±4.512</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are mean ± SD. Significant (p<0.05).
Discussion

In the present study, blood was taken from the right atrium to be representative of central venous blood. A great deal of care was exercised during the insertion of the CVL to position the distal port approximately 3-4 cm above the tricuspid valve. Presumably, this position placed the RAo2 sampling site anterior to the coronary sinus but sufficiently distal into the right atrium to allow for the mixing of superior and inferior vena cava blood.

Results showed a lower value of svO2 compared to RAo2, a possible explanation for the decrease in blood saturation from RAo2 to SvO2 is the myocardial extraction of oxygen as blood flows through the right ventricle into the pulmonary artery. Although, to our knowledge, the rate of O2 diffusion from ventricular blood into the myocardium has not been quantified, we consider this possibility unlikely. A more likely hypothesis is that atrial blood, as it moves toward the pulmonary artery, mixes with blood of lower O2 content; A key element resulted from atrial blood mixing with blood emanating from the Thebesian veins. Although coronary sinus flow may be but a fraction of total blood flow, the effluent from the coronary sinus has very low oxygen saturation, since the heart maximally extracts oxygen from the coronary blood. Although we gave the maximum care positioning the tip of CVL to ensure complete mixing of SVC blood with the IVC blood; this position may not guarantee complete mixing between atrial and coronary sinus effluent blood. We are of the opinion that mixing with coronary sinus blood and thebesian veins blood is most likely explanation for the decrease in blood saturation from RAo2 to SvO2. The step-down from RAo2 to SvO2 propounds the intriguing possibility that differences in blood saturations measured may be related to measures of myocardial O2 utilization. Further studies measuring coronary sinus blood oxygen content and flow are needed to test this hypothesis [9].

Experimental studies in animals showed an excellent correlation between central oxygen saturation and SvO2. Reinhart et al [10] found a Spearman correlation coefficient (r) of 0.97 in anesthetized dogs over a broad range of cardiac respiratory conditions, including hypoxia, hemorrhage, and resuscitation. Schou et al [11] also found a correlation coefficient of 0.97 between CVO2 and SvO2 in pigs that had been subjected to conditions of graded hypoxemia. Of note, both studies found SvO2 to be consistently lower than central venous oxygen saturation [9].

Our data showed perfect positive statistically significant correlation between SvO2 and CvO2 at all data points (Table 3); the findings presented here agree with those of other studies comparing measures of Scvo2 and SvO2 in critically ill patients. Berridge et al [12] found perfect correlation (Spearman correlation coefficients r=0.93) between CVO2 and SvO2 sampled from SVC and the distal PAC port (no=76), Edwards and Mayall13 (no=30), Turnaoglu et al [14] (no=41), and Pieri et al [15] (no=39); who got blood samples from proximal and distal PAC ports showed positive correlation coefficient with r values of 0.56, 0.96, and 0.9 respectively.

In our study, individual mean of difference between both readings at data points showed mean of difference (MOD) of 1.97±6.162 and 0.126±3.132 at T1 and T2 simultaneously this (MOD) was statistically insignificant, but after bypass was initiated; MOD was 6.68±5.660 and 4.930±4.631 at T3 and T4 with high statistical significance, after cessation of bypass; MOD between SvO2 and RAo2 continue to have high statistical significance, MOD was 6.22±3.484 at T5 and at T6 it was 5.29±4.512. The poor agreement between values of SvO2 and RAo2 after initiation of cardiopulmonary bypass presented here may be secondary to the acute changes in hemodynamic accompanying the shift to CPB with hemodilution and the non-pulsatile flow pattern. Schmitz et al [16] showed that, despite normal cardiac index values, CVO2 could not be substituted for SvO2 after cardiac surgery with cardiopulmonary bypass. This agrees with other studies [17-19] comparing measures of CVO2 and SvO2 in critically ill patients. Similarly, poor agreement results appeared with other studies comparing SvO2 and CVO2 in hemodynamically unstable patients. These studies were performed outside the context of cardiac surgery, with heterogeneous groups of patients in septic [20], cardiogenic [21], and neurogenic shock 22 and all reported a poor agreement between SvO2 and CVO2 individual values. In one recent study by Anne-Grethe et al [21], they examined the validity of substituting CVO2 for SvO2 in 20 patients under went different cardiac procedure, the study was in the context of ICU. They sampled patients through a SVC placed CVL catheter and a PA catheter, the study was in the context of ICU, and they concluded that CVO2...
can be used in CABG patient inaccurately but not in AVR patients.

Conclusions

In coronary artery bypass grafting with poor LV function patients; RAo$_2$ & SvO$_2$ are not interchangeable numerically as they have failed to keep insignificant mean of difference at reading times when normothermic CPB was initiated, but had strong positive and significant correlation throughout the operative course. This makes RAo$_2$ a useful tool in the meaning of trend, these data suggest that RAo$_2$ is equivalent to SvO$_2$ in the course of clinical decisions as long as absolute values are not required.

Acknowledgment:

We gratefully acknowledge the technical assistance of Mr. Mohammad Akbar Khan, Chief Cardiac Anesthesia Technician, King Fahad Cardiac Center, Riyadh, KSA, and Mr. Hasan Abo-Kishk, cardiac Anesthesia Technician, King Fahad Cardiac Center, Riyadh, KSA.

References

Transient Ischemic Left Ventricular Dilatation on Tc99m SestaMIBI Gated SPECT is a Sign of Post Stress Induced Left Ventricular Dysfunction

ADEL H ALLAM, MD, FASNC

**Background:** Transient ischemic left ventricular dilatation (TID) has important diagnostic and prognostic value in patients (pts) with known or suspected coronary artery disease. TID has been explained as transient stress induced LV dysfunction and/or sub-endocardial ischemia.

**Methods:** TID was assessed in 394 consecutive pts (336 males; age 52.3±8.5 years) referred for 2-days stress-rest Tc99m SestaMIBI gated SPECT (GSPECT). TID was assessed visually by two experienced observers.

**Results:** 338/394 pts (85.8%) Group (G) 1 showed no TID. G 2 56 pts (14.2%) showed TID. The mean number of perfusion defects was 2.2±1.9 in G1 versus 4.4±1.6 in G2 p<0.0001. The mean number of totally reversible defects was 1.5±1.3 in G1 versus 3.6±1.5 in G2 (p<0.0001). The global post stress EF% was 58.1±11.3% in G1 versus 50.3±8.8% in G2 (p<0.0001). However, the global resting EF% was 56.1±10.8% in G1 versus 54.6±10.6% in G2 (p=NS).

**Conclusion:** TID on stress GSPECT SestaMIBI is a sign of post stress induced LV dysfunction.

**Key Words:** Gated SPECT – SestaMIBI – TID.

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**Introduction**

Over the past 20 years, myocardial perfusion imaging has evolved into a powerful multifaceted tool for the evaluation of coronary artery disease (CAD). The blood flow dependent uptake of a radioactive tracer allows for assessment of regional myocardial perfusion and provides both diagnostic and prognostic information [1,2,3]. Moreover, other parameters, including increased pulmonary uptake and transient ischemic LV dilatation (TID), have also been demonstrated to provide important diagnostic and prognostic information [4,5]. TID refers to an apparent increase in the LV size at stress, relative to the rest images.

Although the specific mechanism leading to TID is still debated, there is little doubt that clinically it signifies severe and extensive CAD and suggests a poor prognosis. It has been suggested that TID can be caused by extensive subendocardial ischemia in the absence of true LV dilation [6,7,8] and that this ischemia simply makes the endocardial border appear to be larger because the subendocardium is not seen. However, supporting the concept that TID represented true ventricular dilation were the original observations in planar studies that volumes calculated from the epicardial borders revealed the finding [9], if the finding was due to diffuse subendocardial ischemia alone, it would have been expected that TID would be observed with the use of endocardial but not epicardial boundaries for the volume calculations.

Most likely, both mechanisms (true dilation and extensive subendocardial ischemia) play a role in producing what is observed as TID. In either case these mechanisms would both be derived from extensive stress-induced abnormality.

In addition, some studies have demonstrated an increased prevalence of LV hypertrophy and elevated LV end-diastolic pressure in patients with TID [10]. It is also possible that in some patients, TID is just a variant of normal LV cavity changes during stress for physiologic reasons that are not yet understood. With the advent of GSPECT simultaneous
assessments of myocardial perfusion and function became possible. Functional parameters as LVEF, EDV and ESV are obtained post-stress and at rest. It has also been shown that transient post-exercise LV dysfunction is indicative of severe coronary stenosis [11,12]. Recently, Druz et al [13] demonstrated that prolonged myocardial stunning also occurs relatively commonly after adenosine stress in patients with CAD and that it occurs in one third of patients with severe stress perfusion defects, consistent with ischemia.

This study will analyzes the relationship between the non-perfusion variable of GSPECT, transient ischemic dilation (TID) and a functional variable, post-stress decrease in the left ventricular (LV) ejection fraction or myocardial stunning (TIS).

Methods

Patient population: The study cohort consisted of 394 patients referred to clinical exercise myocardial perfusion imaging for assessment of coronary artery disease. The study was carried out in a private radiology center (Alfa Scan, Cairo, Egypt) from September 2004 to August 2005. Patients with significant valvular, congenital heart disease, cardiomyopathy, pulmonary hypertension, or intrinsic lung disease were excluded from this study.

Exercise protocol: A baseline 12-lead electrocardiogram (ECG) was recorded. Patients then exercised on a treadmill according to a standard Bruce protocol until fatigue, SOB, chest pain, significant arrhythmias, significant ST-T wave changes, or decrease in systolic blood pressure of greater than 10mmHg below the baseline developed. Heart rate, blood pressure and 12 leads ECG were recorded every 3 minutes. A positive ischemic ECG test was considered if horizontal or downsloping ST segment depression of 1mm or greater occurred.

Tc99m SestaMIBI GSPECT acquisition: A standard 2-day exercise-rest GSPECT Te99m SestaMIBI imaging protocol was used. After symptom-limited exercise on a treadmill according to a Bruce protocol, patients were injected with 20-to-25mCi of Tc99m SestaMIBI at peak exercise. Stress images were acquired after 45-60 minutes. Next day, the resting images were acquired 1 hour after injection with similar dose of Tc99m SestaMIBI used for the stress study. For both studies, Dual Head Toshiba Gama Camera system was used.

GSPECT data analysis: All images were reviewed by two experts. Both were unaware of the other reading results. Qualitative and semi-qualitative analysis of images was performed.

Transient ischemic LV dilatation (TID) was assessed visually by two experienced observers. Exercise-induced left ventricular dilatation was considered if the left ventricle is noted to be larger following exercise than on the resting images.

Increased L/H ratio was assessed with comparison between stress and rest images from a single left anterior oblique frame by two regions of interest on both the left ventricle and the left lung.

Comparison between resting and exercise images is used to detect areas with fixed defects (scar) and those with reversible defects (ischemia). Comprehensive semi-quantitative perfusion defect analysis was using a 13 segments model. The 13 segment scoring model is based on three short axis slices (apical, mid and basal) and an apical segment from vertical long axis slice to represent the entire left ventricle. Each segment had a perfusion scale based on the uptake of each segment: 0=normal, 1=mild reduction of uptake, 2=moderate reduction of uptake, 3=severe reduction of uptake and 4=no uptake. A segment with any degree of reduction on the stress set of images was considered a segment with perfusion defect. Segments with perfusion defects were considered totally reversible if they had normal uptake on the rest set of images, partially reversible if they improved by >1 degree of uptake but did not return to normal on the rest set of images and fixed defects if the degree of uptake did not improve from the stress to the rest set of images. The analysis of the images was interpreted by two observers translating the defect into a percentage [14,15].

The left ventricular ejection fraction (LVEF) calculation was obtained from the stress and rest set of images through the use of an automated, commercially available software (QGS). Transient ischemic stunning (TIS) was considered to be present if stress EF dropped 5% or more from the resting EF value.

Statistical analysis:

Values are expressed as mean ± SD. Analysis of variant (ANOVA test) and paired t test were used to compare between the groups. p value was considered statistically significant when its <0.05.
Results

Three hundred and ninety four consecutive patients underwent a two day stress-rest gated SPECT SestaMIBI scintigraphy. Transient ischemic LV dilatation (TID) was assessed visually by two experienced observers.

Three hundred and thirty six patients were males (85%), the mean age was 52.3±8.8 years. 75 patients having H/O previous MI (19%), 73 patients (18.5%) underwent PCI, while 36 patients (9.1%) underwent CABG. 10 patients (2.5%) had both PCI and CABG. The mean number of risk factors was 2.29±1.2.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Number/394</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>202</td>
<td>51.3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>135</td>
<td>34.3</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>204</td>
<td>51.8</td>
</tr>
<tr>
<td>Smoking</td>
<td>232</td>
<td>58.9</td>
</tr>
<tr>
<td>Family history</td>
<td>132</td>
<td>33.5</td>
</tr>
</tbody>
</table>

Patients included in the study were divided into 2 groups, 338 patients without TID (85.8%) Group 1 and 56 patients (14.2%) showed TID Group 2. Apart from diabetes, no significant difference between the 2 groups regarding basic clinical characteristics.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>52.2±8.9</td>
<td>52.8±7.9</td>
<td>N.S.</td>
</tr>
<tr>
<td>Gender (Males)</td>
<td>84.9%</td>
<td>87.5%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Previous MI</td>
<td>19.2%</td>
<td>17.9%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Mean number of risk factors</td>
<td>2.3±1.1</td>
<td>2.4±1.3</td>
<td>N.S.</td>
</tr>
<tr>
<td>Diabetes</td>
<td>31.7%</td>
<td>50%</td>
<td>0.007</td>
</tr>
<tr>
<td>Hypertension</td>
<td>50.3%</td>
<td>57.1%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Smoking</td>
<td>59.2%</td>
<td>57.1%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>53%</td>
<td>44.6%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Family history</td>
<td>34%</td>
<td>30.4%</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

Resting and exercise ECG data

<table>
<thead>
<tr>
<th>Factor</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting HR</td>
<td>84.4±14</td>
<td>83.5±14</td>
<td>N.S.</td>
</tr>
<tr>
<td>Resting SBP</td>
<td>124±13.8</td>
<td>128±12</td>
<td>0.02</td>
</tr>
<tr>
<td>Resting DBP</td>
<td>82.5±5</td>
<td>84.7±7</td>
<td>0.003</td>
</tr>
<tr>
<td>Resting ECG changes</td>
<td>56.5%</td>
<td>67.9%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Exercise duration</td>
<td>461±126</td>
<td>395±143</td>
<td>0.0005</td>
</tr>
<tr>
<td>Exercise stage (Bruce)</td>
<td>3.1±0.7</td>
<td>2.6±0.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Chest pain at exercise</td>
<td>29.9%</td>
<td>57.1%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Peak HR</td>
<td>153±15.4</td>
<td>146±14.6</td>
<td>0.003</td>
</tr>
<tr>
<td>Peak SBP</td>
<td>170±17.6</td>
<td>164±24.9</td>
<td>0.03</td>
</tr>
<tr>
<td>Peak DBP</td>
<td>85±7</td>
<td>87±8</td>
<td>N.S.</td>
</tr>
<tr>
<td>Peak Double product</td>
<td>26072±3855</td>
<td>24343±4853</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Myocardial perfusion SPECT data

<table>
<thead>
<tr>
<th>Factor</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scan result (+ve)</td>
<td>76%</td>
<td>100%</td>
<td>0.0001</td>
</tr>
<tr>
<td>L/H ratio</td>
<td>0.36±0.06</td>
<td>0.39±0.07</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total number of defects</td>
<td>2.2±1.9</td>
<td>4.4±1.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>Totally reversible defects</td>
<td>1.5±1.4</td>
<td>3.6±1.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Partially reversible defects</td>
<td>0.34±0.8</td>
<td>0.63±0.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Fixed perfusion defects</td>
<td>0.33±0.9</td>
<td>0.2±0.84</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

Functional gated SPECT data

<table>
<thead>
<tr>
<th>Factor</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting EF%</td>
<td>56.1±10.8</td>
<td>54.6±10.6</td>
<td>N.S.</td>
</tr>
<tr>
<td>Resting EDV</td>
<td>102±35.3</td>
<td>98.7±34.6</td>
<td>N.S.</td>
</tr>
<tr>
<td>Resting ESV</td>
<td>47.4±29.4</td>
<td>46.8±27.8</td>
<td>N.S.</td>
</tr>
<tr>
<td>Exercise EF%</td>
<td>58.1±11.3</td>
<td>50.3±8.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Exercise EDV</td>
<td>97.1±34.6</td>
<td>113.6±28.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Exercise ESV</td>
<td>43.7±28</td>
<td>59.2±30.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Resting WMA</td>
<td>0.61±1</td>
<td>1.1±1.2</td>
<td>0.002</td>
</tr>
<tr>
<td>Resting EF% &lt;50%</td>
<td>22.8%</td>
<td>21.4%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Stress EF% &lt;50%</td>
<td>18.3%</td>
<td>42.9%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Δ EF Stress-Rest</td>
<td>1.2±5.7</td>
<td>4.3±5.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>Δ EDV Stress-rest</td>
<td>−4.9±11.3</td>
<td>14.8±15.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>Δ ESV Stress-rest</td>
<td>−4±8.5</td>
<td>12.5±11.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Post Stress 5% drop in EF%</td>
<td>12.1%</td>
<td>51.8%</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Discussion

In 1987 it was postulated that the finding of TID is likely to represent extensive ischemia, because (1) it is reversible, (2) the amount of ischemia has to be large enough to cause true transient ventricular enlargement even in a planar study and (3) such ischemia is likely to be severe, because it lasts for at least one-half hour after stress, a time at which usual exercise-induced ischemia would be expected to have been resolved [16,17]. This hypothesis was supported by observations that TID is predictive of proximal left anterior descending arteries or multiple vessels with greater than 90% stenosis.

It has subsequently been suggested that TID can also be caused by extensive subendocardial ischemia in the absence of true LV dilatation ("apparent TID") [18,19,20] and that this ischemia simply makes the endocardial border appear to be larger because the subendocardium is not seen.
Most likely, both mechanisms (true dilation and extensive subendocardial ischemia) play a role in producing what is observed as TID. However, regardless of the mechanism TID is derived from extensive stress-induced ischemia. In addition, some prior studies have demonstrated that TID may be seen in patients with LV hypertrophy and elevated LV end-diastolic pressure [21]. It is also possible that in some patients with normal LV cavity, TID may occur during stress for physiologic reasons that are not yet understood.

On the other hand although transient post ischaemic stunning (TIS) is a reversible phenomenon, it has the potential of inducing serious hemodynamic consequences [22]. In experimental animal models, the severity and duration of flow deprivation and the size of ischemic region were shown to be among the important factors that determine the severity of myocardial stunning [23]. The exact duration of post ischaemic contractile abnormalities following transient coronary occlusion has been variable in dog models [24]. Myocardial stunning can affect all layers of the myocardium. Recovery, however, was noted to be more rapid in subepicardial tissue than in subendocardial tissue [25]. A close relationship between the degree of myocardial dysfunction and collateral blood flow during the period of ischemia was also found [26].

Recently, TIS has been found in patients with coronary artery disease (CAD) when examined with gated technetium 99m SestaMIBI and Tc-99m Tetrofosmin single photon emission computed tomography (SPECT). TIS was seen in initial images started 30 to 60 minutes after treadmill exercise [27-30] or dipyridamole pharmacologic stress tests [27,29,31] and occasionally persisted for more than 24 hours [31]. The recovery of TIS has been shown to be delayed for at least 30 minutes after the cessation of exercise in previous reports [32-35].

TIS after stress testing is mechanical dysfunction that persists for some time after resolution of stress-induced ischemia despite the absence of any irreversible damage [26].

In this study we used gated SestaMIBI scintigraphy to answer the question if TID was a sign of post stress induced LV dysfunction. Three hundred and ninety four consecutive patients were included in this study, of those three hundred and thirty six patients were males (85%), the mean age was 52.3±8.8 years. 75 patients having H/O previous MI (19%), 73 patients (18.5%) underwent PCI, while 36 patients (9.1%) underwent CAGB. 10 patients (2.5%) had both PCI and CAGB. The mean number of risk factors was 2.29±1.2. The patient population data suggest that this consecutive group of patients referred for non-invasive assessment by MPI have a moderate-high pre-test probability of CAD.

In such a population TID occurred in 14% of the patients. TID was associated with a higher incidence of Diabetes. More severe signs of ischaemia on stress test, patients with TID exercised for a shorter duration and achieved a lower double product; they also showed significantly more chest pain with physical stress.

Also on MPI, TID patients showed more significant ischaemia in the form of larger perfusion defects and larger reversible perfusion defects a finding that has been reported in multiple previous studies. Interestingly the functional indices derived from the gated SPECT studies showed clearly that the post stress EF was significantly lower in TID patients compared to patients showing no TID, although resting EF was not different in the two groups. Also, interestingly enough the phenomenon of TIS was more evident in patients with TID 51.8% Vs 12.1% p<0.0001.

So in conclusion, TID on stress gated SestaMIBI scintigraphy seem to be a sign of post stress LV dysfunction in absence or irreversible damage (post stress stunning). Both findings occur with severe and extensive ischaemia and are poor prognostic signs.

**Limitations:**

Although multiple studies have shown that TID is highly specific for severe and extensive CAD, it is worth considering potential pitfalls. TID may occur in patients who do not have significant epicardial vessel CAD but who may have global subendocardial ischemia [36,37]. Sugihara et al 36 reported on TID in patients with hypertrophic cardiomyopathy. In their study, 24 of 50 patients with hypertrophic cardiomyopathy had TID on stress-redistribution TI-201 imaging. Interestingly, these 24 patients had a higher incidence of exertional chest pain and exercise-induced ECG abnormalities than the 26 patients without TID. Similarly, Robinson et al [37] reported on the presence of TID in patients with hypertensive heart disease and LV hypertrophy. Among 237 consecutive patients, 23 had TID. Of these 23 patients, 9 had no segmental
perfusion defects and multivessel CAD and in 7 patients, there was evidence of LV hypertrophy by either TI-201 or ECG criteria. However, not all patients underwent cardiac catheterization and the details of the nuclear image analysis are not provided. Thus a direct comparison of these reports with the above-referenced studies may not be appropriate.

Other possible mechanisms for falsely increased TID ratios may be related to suboptimal technique. Hansen et al [38] suggest the possibility that errors in slice selection for tomographic analysis may result in erroneously high TID ratios. Mazzanti et al [39] advocate that patients with small left ventricles (LV volume index <30mL/m²) may have abnormally elevated TID ratios despite a low likelihood of CAD. Similarly, the different doses of the administered radionuclide, particularly in single day Tc-99m studies, may result in artifactual TID. Finally, motion artifacts may distort and enlarge the LV cavity, [40] giving the false impression of TID. Therefore the presence of potential technical limitations and artifacts has to be identified and appropriately resolved prior to assessment for TID.

References
Transitient Ischemic Left Ventricle Dilatation on Tc99m SestaMIBI Gated Spect


Stress Tc99m SestaMIBI SPECT Six Months Post Coronary Artery Bypass Grafts Predicts Future Cardiac Events

ADEL ALLAM, MD, FASNC*; AYMAN GHONIEM, MD*; MOSTAFA RADWAN, MD**; NASER RASMI, MD**

Background: Debate exists regarding the optimal time for follow-up SPECT imaging in stable patients (pts) post coronary artery bypass grafts (CABG).

Methods: 44 pts (39 males; age 51±8.2 years) underwent 2-days stress-rest Tc99m SestaMIBI SPECT 6 months post CABG. Clinical evaluation, 12 leads resting ECG and functional assessment using both Echocardiography and Equilibrium Radionuclide Angiography (ERNA) studies were done for all pts. All pts were followed-up for 42.3±4.7 months.

Results: In all 44 pts; 1 cardiac death, 4 non-fatal myocardial infarctions and 8 pts underwent revascularization for progression of cardiac symptoms. By comparing all different variables from clinical evaluation, ECG, Echocardiography, ERNA and stress Tc99m SestaMIBI SPECT, the best predictors for hard cardiac events and revascularization were the summed stress score (p<0.0001), summed difference score (p<0.0001) as well as an ischemia size >10% on the perfusion scan (p<0.005).

Conclusion: Large ischemia on the stress Tc99m SestaMIBI SPECT 6 months post CABG can predict future hard cardiac events and the need for revascularization.

Key Words: SPECT – SestaMIBI – CABG.

Introduction

To better understand the health problems facing Egypt and the rest of the world, the following facts need to be stated:

• Among both men and women, most deaths are due to non-communicable conditions and they account for about 6 out of 10 deaths globally.
• Cardiovascular diseases present the high levels of mortality among men in the low- and middle-income countries with a mortality rate exceeding 1.5 per 1000 adults aged 15-59 years.
• The proportion of deaths in middle- and low-income countries due to non-communicable dis-
most of the household income, such diseases place a heavy burden on their economies. Lost earnings and out of pocket health care payments will undermine their socioeconomic development and hold extensive pressure on governments.

Despite the crucial role of myocardial perfusion imaging in assessment of patients post coronary artery bypass grafts (CABG), debate exists regarding the optimal time for follow-up SPECT imaging in stable patients (pts) post CABG. Angiographic studies addressing follow-up after CABG by angiographic graft patency stated that 10-31% of grafts were occluded at one year, 48% were occluded at 5 years and 81% at 15 years. Scintigraphic data are very well correlating with the angiographic data and are supplying a very good mass of evidence regarding risk stratification post CABG. The question will remain what is the optimal time post CABG for risk stratification by SPECT imaging?

**Aim of the work:**

To assess the prognostic value of SPECT SestaMIBI myocardial perfusion imaging in early (six month) follow-up of post CABG stable patients.

**Methods**

From July 2001 to June 2004 44 patients (39 males; age 51±8.2 years) indicated for CABG according to ACC/AHA practice guidelines underwent CABG at the department of Cardiothoracic surgery Cairo University. Nineteen patients underwent conventional CABG with arterial and venous conduits and 25 patients underwent total arterial revascularization CABG. All patients were subjected to the following:

- Full preoperative assessment including history taking, clinical examination, resting 12-lead ECG, echocardiography, equilibrium radionuclide angiography (ERNA).
- Operative and immediate postoperative data including type & number of conduits, use & type of cardioplegia, cross clamping time, total bypass time and ICU stay data.

Follow-up data at 6 months post CABG including 12-lead ECG, echocardiography and ERNA. 2-days stress-rest Tc99m SestaMIBI SPECT imaging was done for all patients.
**Exercise protocol:**

A baseline 12-lead electrocardiogram (ECG) was recorded. Patients then exercised on a treadmill according to standard Bruce protocol until fatigue, SOB, chest pain, significant arrhythmias, significant ST-T wave changes, or decrease in systolic blood pressure of greater than 10mmHg below the baseline developed. Heart rate, blood pressure and 12-leads ECG were recorded every 3 minutes. A positive ischemic ECG test was considered if horizontal or down sloping ST segment depression of 1mm or greater occurred.

**Tc99m SestaMIBI SPECT acquisition:**

A standard 2-day exercise-rest GSPECT Tc99m SestaMIBI imaging protocol was used. After symptom-limited exercise on a treadmill according to a Bruce protocol, patients were injected with 20-to-25mCi of Tc99m SestaMIBI at peak exercise. Stress images were acquired after 45-60 minutes. Next day, the resting images were acquired 1 hour after injection with similar dose of Tc99m Sesta-MIBI used for the stress study. For both studies, a single head GE Gama Camera system at the Nuclear Cardiology Lab. at Al Azhar University was used.

**SPECT data analysis:**

All images were reviewed by two experts. Both were unaware of the other reading results. Qualitative and semi-qualitative analysis of images was performed.

Transient ischemic LV dilatation (TID) was assessed visually by two experienced observers. Exercise-induced left ventricular dilatation was considered if the left ventricle is noted to be larger following exercise than on the resting images.

Increased L/H ratio was assessed with comparison between stress and rest images from a single left anterior oblique frame by two regions of interest on both the left ventricle and the left lung.

Comparison between resting and exercise images is used to detect areas with fixed defects (scar) and those with reversible defects (ischemia). Comprehensive semi-quantitative perfusion defect analysis was used using a 13 segments model. The 13 segment scoring model is based on three short axis slices (apical, mid and basal) and an apical segment from vertical long axis slice to represent the entire left ventricle. Each segment had a perfusion scale based on the uptake of each segment: 0=normal, 1=mild reduction of uptake, 2=moderate reduction of uptake, 3=severe reduction of uptake and 4=no uptake. A segment with any degree of reduction on the stress set of images was considered a segment with perfusion defect. Segments with perfusion defects were considered totally reversible if they had normal uptake on the rest set of images, partially reversible if they improved by >1 degree of uptake but did not return to normal on the rest set of images and fixed defects if the degree of uptake did not improve from the stress to the rest set of images. SSS is the sum score of all 13 segments on the stress set of images, SRS is the sum score of all 13 segments on the rest set of images. SDS is the difference between the SSS and the SRS. The analysis of the images was interpreted by two observers translating the defect into a percentage [14,15].

All patients were followed-up for 42.3±4.7 months for hard and soft cardiac events.

**Statistical analysis:**

Values are expressed as mean ± SD. Analysis of variant (ANOVA test) and paired t test were used to compare between the groups. p value was considered statistically significant when its <0.05.

**Results**

Forty four patients (39 males, 5 females) were included. Mean age was 51.05±8.2 years. 14/44 (32%) having history of previous MI, 10/44 (22.7%) having previous revascularization.

The mean number of risk factors was 2.43±1.02. 23/44 (52.3%) were diabetics, 16/44 (36.4%) were hypertensive, 15/44 (34.1%) were dyslipidemic, 35/44 (79.5%) were smokers and 18/44 (41%) having a FH of CAD.

Conventional CABG (using both arterial and venous conduits) were done in 19/44 patients (43.2%), while 25/44 (56.8%) underwent total arterial CABG.

**Hard and soft events for all patients.**

<table>
<thead>
<tr>
<th>Event</th>
<th>Number</th>
<th>% of Events</th>
<th>Annual event rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death</td>
<td>1</td>
<td>2.3%</td>
<td>0.66%</td>
</tr>
<tr>
<td>Non fatal MI</td>
<td>4</td>
<td>9.1%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Hard events only</td>
<td>5</td>
<td>11.4%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Revasc. For progression of symptoms</td>
<td>8</td>
<td>18.2%</td>
<td>5.2%</td>
</tr>
<tr>
<td>ICU admission</td>
<td>15</td>
<td>34.1%</td>
<td>9.7%</td>
</tr>
<tr>
<td>Hard and soft events</td>
<td>15</td>
<td>34.1%</td>
<td>9.7%</td>
</tr>
<tr>
<td>Hard events and revascularization</td>
<td>11</td>
<td>25%</td>
<td>7.1%</td>
</tr>
</tbody>
</table>
Patients were followed-up for a mean period of 42.3±4.7 months. None of the 44 patients were lost for follow-up.

In 33/44 patients "75%" (Group 1) no events occurred, while all post CABG events (hard and revascularization) occurred in 11 patients "25%" (Group 2).

Both groups were compared in all parameters including preoperative, operative and postoperative data, provided that there is no statistical significant difference in the mean follow-up period between the two groups.

Table 1: Pre-operative data: Baseline data.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50.3±8.1</td>
<td>53.3±8.2</td>
<td>N.S.</td>
</tr>
<tr>
<td>Gender (Males)</td>
<td>88%</td>
<td>91%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Diabetes</td>
<td>45.5%</td>
<td>72.7%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Hypertension</td>
<td>45.5%</td>
<td>9.1%</td>
<td>0.03</td>
</tr>
<tr>
<td>Smoking</td>
<td>84.8%</td>
<td>63.6%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>33.3%</td>
<td>36.4%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Family history</td>
<td>33.3%</td>
<td>63.6%</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

Table 2: Pre-operative data: Previous events, medications, ECG, Echo & ERNA.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous MI</td>
<td>30.3%</td>
<td>36.4%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Previous revascularization</td>
<td>24.2%</td>
<td>18.2%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>97%</td>
<td>100%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Nitrates</td>
<td>78.8%</td>
<td>82%</td>
<td>0.03</td>
</tr>
<tr>
<td>CC Blockers</td>
<td>78.8%</td>
<td>90%</td>
<td>N.S.</td>
</tr>
<tr>
<td>ECG changes</td>
<td>51.5%</td>
<td>63.6%</td>
<td>N.S.</td>
</tr>
<tr>
<td>ECG% using Echo</td>
<td>56.9±8.1%</td>
<td>53.7±28.7%</td>
<td>N.S.</td>
</tr>
<tr>
<td>FS% using Echo</td>
<td>30.8±5.5%</td>
<td>28.6±5.6%</td>
<td>N.S.</td>
</tr>
<tr>
<td>EF% using ERNA</td>
<td>47.7±23.3%</td>
<td>45.4±14.2%</td>
<td>N.S.</td>
</tr>
<tr>
<td>RWM score using ERNA</td>
<td>4.4±5.2%</td>
<td>9.3±7.9%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Table 3: Operative data: Coronary angiography and surgical data.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diseased vessel in angiography</td>
<td>2.7±0.9</td>
<td>2.4±0.7</td>
<td>N.S.</td>
</tr>
<tr>
<td>Operative type (Total arterial)</td>
<td>51.5%</td>
<td>72.7%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Cardiopulmonary bypass</td>
<td>87.9%</td>
<td>100%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Cross clamping time</td>
<td>34±17.3</td>
<td>38±19.9</td>
<td>N.S.</td>
</tr>
<tr>
<td>Bypass time</td>
<td>67±34.7</td>
<td>69±36.6</td>
<td>N.S.</td>
</tr>
<tr>
<td>Number of conduits</td>
<td>2.7±0.2%</td>
<td>2.5±0.8%</td>
<td>N.S.</td>
</tr>
<tr>
<td>LIMA</td>
<td>93.9%</td>
<td>90.9%</td>
<td>N.S.</td>
</tr>
<tr>
<td>RIMA</td>
<td>6.1%</td>
<td>27.3%</td>
<td>0.05</td>
</tr>
<tr>
<td>Radial artery</td>
<td>84.8%</td>
<td>81.8%</td>
<td>N.S.</td>
</tr>
<tr>
<td>SVG</td>
<td>78.8%</td>
<td>45.5%</td>
<td>N.S.</td>
</tr>
</tbody>
</table>
**Table 4:** Post-operative data: Early post-operative data.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU stay (hours)</td>
<td>29.1±17.6</td>
<td>37±30.3</td>
<td>N.S.</td>
</tr>
<tr>
<td>Mechanical support</td>
<td>100%</td>
<td>100%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Time of mechanical support (hours)</td>
<td>10.9±7.7</td>
<td>9±3.1</td>
<td>N.S.</td>
</tr>
<tr>
<td>Physiological support</td>
<td>45.5%</td>
<td>54.5%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Time of physiological support</td>
<td>9.9±13.8</td>
<td>15.6±27.6</td>
<td>N.S.</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>10.2±5.6</td>
<td>12.7±7.6</td>
<td>N.S.</td>
</tr>
<tr>
<td>Hypotension</td>
<td>9.1%</td>
<td>18.2%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>3%</td>
<td>0%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Wound infection</td>
<td>18.2%</td>
<td>18.2%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Renal complications</td>
<td>9.1%</td>
<td>18.2%</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

**Figure 4:** Operative data: Coronary angiography and surgical data.

**Figure 5:** Post-operative data: Early post-operative data.

**Table 5:** Post-operative data: Six weeks post-operative data.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td>6.1%</td>
<td>9.1%</td>
<td>N.S.</td>
</tr>
<tr>
<td>ECG changes</td>
<td>33.3%</td>
<td>36.4%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Wound infection</td>
<td>0%</td>
<td>0%</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

**Figure 6:** Post-operative data: Six weeks post-operative data.

**Table 6:** Post-operative data: Six months post-operative data.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td>6.1%</td>
<td>27.3%</td>
<td>0.06</td>
</tr>
<tr>
<td>ECG changes</td>
<td>27.3%</td>
<td>27.3%</td>
<td>N.S.</td>
</tr>
<tr>
<td>EF% Echo</td>
<td>59.2±7.7%</td>
<td>53.2±8.6%</td>
<td>0.04</td>
</tr>
<tr>
<td>FS% Echo</td>
<td>31.7±5%</td>
<td>28.1±4.7%</td>
<td>0.04</td>
</tr>
<tr>
<td>Global EF% ERNA</td>
<td>51.4±7.4%</td>
<td>46.5±14.8%</td>
<td>N.S.</td>
</tr>
<tr>
<td>RWM score by ERNA</td>
<td>4.7±4.3%</td>
<td>9.3±11.2%</td>
<td>0.06</td>
</tr>
</tbody>
</table>
Stress Tc99m SestaMIBI SPECT Six Months Post Coronary Artery Bypass

Figure 7: Post-operative data: Six months post-operative data.

Table 7: Post-operative data: Six months exercise ECG data.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RHR</td>
<td>75.5±11</td>
<td>70.2±9.8</td>
<td>N.S.</td>
</tr>
<tr>
<td>RSBP</td>
<td>128.9±14.1</td>
<td>123±17.6</td>
<td>N.S.</td>
</tr>
<tr>
<td>RDBP</td>
<td>82.9±9.5</td>
<td>75.9±11.4</td>
<td>0.05</td>
</tr>
<tr>
<td>Exercise time (seconds)</td>
<td>493±85</td>
<td>430±92</td>
<td>0.04</td>
</tr>
<tr>
<td>Stage of exercise (Bruce protocol)</td>
<td>3.2±0.5</td>
<td>2.9±0.54</td>
<td>N.S.</td>
</tr>
<tr>
<td>Chest pain with exercise</td>
<td>36.4%</td>
<td>54.5%</td>
<td>N.S.</td>
</tr>
<tr>
<td>PHR</td>
<td>150±13</td>
<td>144.5±5.6</td>
<td>N.S.</td>
</tr>
<tr>
<td>PSBP</td>
<td>164±12</td>
<td>162±24.5</td>
<td>N.S.</td>
</tr>
<tr>
<td>Peak double product</td>
<td>24089±2897</td>
<td>23339±3151</td>
<td>N.S.</td>
</tr>
<tr>
<td>ST-T changes</td>
<td>60.6%</td>
<td>90.9%</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Figure 8: Post-operative data: Six months exercise ECG data.

Table 8: Post-operative data: Six months myocardial perfusion imaging data.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSS</td>
<td>11.7±8.3</td>
<td>28.5±8.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>SRS</td>
<td>5.9±7.9</td>
<td>14.7±9.6</td>
<td>0.004</td>
</tr>
<tr>
<td>SDS</td>
<td>5.8±4.6</td>
<td>13.7±5.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ischemia &gt;10%</td>
<td>54.5%</td>
<td>100%</td>
<td>0.005</td>
</tr>
<tr>
<td>Ischemia &gt;20%</td>
<td>39.4%</td>
<td>81.8%</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Long-term adverse outcomes are increasing in the CABG population because multivessel and high-risk angioplasties are becoming common practice, requiring improved surveillance for graft patency, progression of atherosclerotic burden and left ventricular function \[12\]. Although angiography remains the gold standard for determining the status of grafts and native coronaries, it is invasive, expensive and not without risk. MPI is a noninvasive alternative providing information on graft patency, native coronary atherosclerotic progression and prognosis. Lakkis et al \[13\] performed exercise SPECT followed by coronary angiography in 50 symptomatic post-CABG patients (51±47 months). SPECT detected 40 of 48 stenosed grafts (83%) with a high sensitivity for correctly localizing graft stenosis: 82% for the left anterior descending artery, 92% for the right coronary and 75% for the circumflex coronary artery. They concluded that this modality was an excellent method by which to detect and localize graft stenosis after CABG.

SPECT MPI also provides prognostic implications in the CABG population. The incremental prognostic value (beyond that of historical and treadmill exercise test data) of SPECT was displayed in 294 patients 5 or more years after CABG \[7\] Two scintigraphic variables significantly enhanced the predictive ability of hard events (cardiac death and nonfatal MI): The summed reversibility score (odds ratio, 1.13; \(p<.001\)) and the presence of stress-induced increased lung uptake of thallium 201 (odds ratio, 1.77; \(p=0.016\)). During a similar post-CABG time frame, Nallamothu et al \[8\] reinforced the prognostic value of predicting death and MI by SPECT in 255 patients. In this study SPECT added incremental prognostic information to clinical, stress, and angiographic variables. The global \(x^2\) value increased from 3 for clinical variables, to 5 for clinical and stress variables, to 6 for clinical plus stress variables plus angiography and to 14 for clinical, stress variables, angiography and SPECT (\(p=.01\)).

The prognostic capabilities of myocardial perfusion SPECT imaging performed relatively early (within 2 years) after CABG was evaluated by Miller et al \[9\] The 5-year rate of survival free of cardiac death or MI, classified by exercise-induced anginal symptoms or abnormal MPI post exercise segments (or both), was 93% for patients without either of the adverse prognostic variables, 83% for those with 1 variable and 71% for those with both variables. In addition, this early study group was separated by size of the ischemic defect, which correlated with survival free of cardiac death or MI. The 5-year rate of survival free of cardiac death or MI was 72% for patients with a large ischemic defect versus 85% to 89% for the other subsets. For patients with a normal perfusion imaging study, the 5-year event-free survival rate was 92%, yielding an annual hard cardiac event rate of 1.6%.

The decision to risk-stratify post-CABG patients with MPI based on the absence of ischemic symptoms has been debatable. In a study of symptom-free post-CABG patients the presence of any nuclear perfusion defect was strongly predictive of death (9% versus 3% over a period of 3 years, \(p=.0004\)) and of death or nonfatal MI (11% versus 4%, \(p=.0002\)) \[10\]. This study also discriminately stratified patients into low- and high-risk groups by use of 6 variables: increasing age, hypertension, greater time since bypass surgery and absence of an internal mammary artery graft, incomplete revascularization and poor exercise capacity. Reversible nuclear perfusion defects were associated with higher event rates in both the low-risk and high-risk groups, although significance was not found in the high-risk group. These findings support the argument for post-CABG MPI risk stratification regardless of ischemic symptoms.

Taking into account the previously mentioned studies, Zellweger et al \[11\] posed the following question: when should patients undergo stress after CABG? To answer this question, they enrolled 1,765 patients who underwent MPI 7.1±5.0 years after CABG. This group was divided into 2 sub-

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**Figure 9:** Post-operative data: Six months myocardial perfusion imaging data.
groups: Patients undergoing MPI 5 years or less after CABG and those undergoing MPI more than 5 years after CABG. Ischemic symptoms were evaluated and showed no prognostic value (p=11). On the other hand, the annual cardiac death rates increased significantly as a function of the summed stress score (SSS) in both the group undergoing MPI 5 years or less after CABG (p=0.049) and the group undergoing MPI more than 5 years after CABG (p=0.005). In addition, the incremental prognostic benefit, with respect to cardiac death, of nuclear testing when added to the Duke treadmill score was apparent after the global x2 values were evaluated (p<0.05). This study reinforced the idea that MPI is predictive of subsequent cardiac death in post-CABG patients and adds incremental value over clinical and treadmill test information. It also suggested that symptomatic patients at 5 years or less after CABG and all patients at more than 5 years after CABG may benefit from myocardial nuclear perfusion testing.

In all 44 pts included in this study; 1 cardiac death, 4 non-fatal myocardial infarctions and 8 pts underwent revascularization for progression of cardiac symptoms. By comparing all different variables from clinical evaluation, ECG, Echocardiography, ERNA and stress Tc99m SestaMIBI SPECT, the best predictors for hard cardiac events and revascularization were the summed stress score (p<0.0001), summed difference score (p<0.0001) as well as if the ischemia size was >10% on the perfusion scan (p<0.005).

The appropriateness criteria, as well as other clinical statements, are not a perfect fit for every situation. Nearly 1.5 million revascularization procedures, CABG or PCI, are performed each year in the United States [14]. Approximately 25% occur in diabetic patients, who fare worse after either type of revascularization compared with those without diabetes [14,15]. In diabetic patients the detection of angina is difficult, with a significant proportion of them being asymptomatic. These are critical statistics for assessing the risk of cardiac events in the post-revascularization asymptomatic diabetic patient. By use of the appropriateness criteria, such a patient would qualify as "uncertain", whereas other clinicians would consider additional factors such as lipid status, functional capacity and glycemic control to decide whether screening with SPECT MPI is indicated. Clarifications and additions to the existing guidelines would be helpful and most likely are forthcoming.

In this study, chest pain 6 weeks and 6 months post CABG was not a good predictor of hard events and need for revascularization in this study. So our results do not agree with limiting non-invasive assessment to symptomatic post GABG patients. Also, our results shows that a policy of delayed follow-up by MPI 5 years post CABG is not advisable, as the annual rate of hard events or need of revascularization is 7.1% or 35.5% in 5 years. So, it is of paramount importance to schedule stable patients post revascularization in non-invasive risk assessment by MPI.

Conclusion

Exercise myocardial perfusion imaging remains the cornerstone for evaluating patients post coronary artery bypass grafting, not only for diagnosis of post operative residual ischemia, but also for its prognostic value in those patients.

Large ischemia on the stress Tc99m SestaMIBI SPECT 6 months post coronary artery bypass grafting can predict future hard cardiac events and the need for revascularization.

References

tomography (SPECT) perfusion imaging in predicting outcome after coronary artery bypass grafting. Am J Cardiol 1997; 80: 1517-1521.


Study of Asymptomatic Diastolic Dysfunction Among Elderly with Diabetes Mellitus

MOTASSEM S AMER, MD*; TAREK MK ABDEL DAYEM, MD**; SARAH A HAMZA, MD*; DOHA R ALY, MSc*

Objective: The aim of this work was to study the relationship between diabetes mellitus and diastolic dysfunction in the elderly.

Methods: A case control study was conducted among 60 participants divided into two groups, cases (30 diabetic patients) and a control group (30 healthy individuals). Each patient was subjected to comprehensive geriatric assessment, laboratory investigations (blood glucose levels, glycated hemoglobin) and transthoracic echocardiography.

Results: There was a significant difference between cases and controls as regards diastolic dysfunction (p<0.05). There was highly significant relationship between mean duration of diabetes mellitus and the presence of diastolic dysfunction (p<0.01). There was no significant relation between presence of diastolic dysfunction and glycemic control (p>0.05). There was no significant relationship between age and diastolic dysfunction among both cases and controls (p>0.05).

Conclusion: The presence of diabetes mellitus is a risk factor for the development of diastolic dysfunction. The mean duration of diabetes mellitus played a role in the occurrence of diastolic dysfunction.

Key Words: Diabetes mellitus – Diastolic dysfunction – Echocardiography – Age.
on medical treatment for diabetes without any history or clinical data suggestive of other systemic diseases.

**Group B (controls):**
30 healthy elderly subjects matched for age and sex.

**Each patient underwent:**

1- **Comprehensive clinical assessment in the form of:**
History taking, detailed clinical examination and review of investigations.

**Subjects were excluded if they had:**
- Symptoms suggesting cardiovascular disease, including history of effort angina, previous hospitalization for angina, shortness of breath, hypertension, treatment with medications for ischemic heart disease or hypertension.
- ECG changes in study entry or previously.
- History of elevated blood pressure (BP) or a measured BP above 139 systolic or 89 diastolic.
- Entry echocardiogram, or previous evidence of segmental wall motion abnormalities of the left ventricle.
- Previous investigations suggesting ischemic heart disease (e.g. Exercise stress test, stress perfusion study, etc.).

2- **Laboratory investigations:**
Each patient in both groups was tested for diabetes using:
- Fasting blood sugar (FBS).
- Random blood sugar (RBS).
- Glycated heamoglobin (HBA1C)

3- **Transthoracic echocardiography:**
All examinations were performed with the patient resting in the left lateral decubitus position. M mode, two dimensional and Doppler ultrasound examinations were carried out.

Left ventricular systolic function was assessed by measurement of ejection fraction by M mode.

Pulsed wave Doppler measurements were made at the tips of the mitral valve leaflets in the apical four chamber view.

Early diastolic flow (E wave) and atrial contraction (A wave) were measured at the peak velocity. Deceleration time (DT) was measured from the peak of the E wave to the point of interception of the baseline. The area under the curve was measured for both E and A waves, representing peak rapid filling and peak atrial filling, respectively. These measurements were then used to estimate E/A ratio.

The pulsed Doppler sample was then positioned midway between the mitral valve tips and the aortic outflow track so that isovolumetric relaxation time (IVRT) could be measured between the point of aortic valve closure and mitral valve opening.

The isovolumetric contraction time (IVCT) was measured between the point of mitral valve closure and aortic valve opening.

Ejection time (ET) was calculated between the point of aortic valve opening and aortic valve closure.

**Diagnosis of diastolic dysfunction:**
EF≥50% to exclude systolic dysfunction.

**Diastolic dysfunction was classified in 3 categories:**
- Impaired Relaxation: Was defined as an E/A ratio <0.8 and/or DT >240ms with IVRT measurement >90ms.
- Pseudonormal pattern: Was defined as an E/A ratio of 1 to 1.5 and DT >240ms. Confirmation included IVRT <90ms.
- Restrictive pattern: Was defined as DT <160ms with one of the following: E/A >1.5 or IVRT <70ms duration [6].

**Statistical methods:**
The data was analysed with the program Statistical Package for Social Science (SPSS Inc, Chicago, Ill) under windows version 11.0.1. The statistical tests used in this study were Chi-square test, independent sample t test, ANOVA test for determination of variance.

**Results**
The sex distribution among cases were 12 males (40%) and 18 females (60%). In the control group there were 13 males (43.3%) and 17 females (56.7%). There was no significant difference between cases and controls as regards blood pressure (p>0.05). The mean age of cases was 68.1 and the controls was 66.6 years. There was no significant
difference between cases and controls as regards their mean age ($p>0.05$). There was a significant difference between cases and controls as regards the presence of diastolic dysfunction ($p=0.028$) (Table 1).

**Table 1:** Comparison between the two studied groups as regards presence of diastolic dysfunction.

<table>
<thead>
<tr>
<th>Diastolic dysfunction</th>
<th>Diabetics (n=30)</th>
<th>Non diabetics (n=30)</th>
<th>Total (n=60)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic dysfunction</td>
<td>24 (80.0%)</td>
<td>16 (53.3%)</td>
<td>40</td>
<td>0.028</td>
</tr>
<tr>
<td>No diastolic dysfunction</td>
<td>6 (20.0%)</td>
<td>14 (46.7%)</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

There was no significant difference between cases and controls as regards stages of diastolic dysfunction ($p>0.05$) (Table 2).

**Table 2:** Comparison between the two studied groups as regards stages of diastolic dysfunction.

<table>
<thead>
<tr>
<th>Relaxation abnormality</th>
<th>Diabetic</th>
<th>Non diabetic</th>
<th>Total</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic</td>
<td>15 (62.5%)</td>
<td>11 (68.8%)</td>
<td>26 (65%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Non diabetic</td>
<td>4 (16.7%)</td>
<td>2 (12.5%)</td>
<td>6 (15%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psuedonormal pattern</th>
<th>Diabetic</th>
<th>Non diabetic</th>
<th>Total</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic</td>
<td>5 (20.8%)</td>
<td>3 (18.7%)</td>
<td>8 (20%)</td>
<td></td>
</tr>
<tr>
<td>Non diabetic</td>
<td>2 (8.3%)</td>
<td>20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Restrictive abnormality</th>
<th>Diabetic</th>
<th>Non diabetic</th>
<th>Total</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic</td>
<td>14 (53.3%)</td>
<td>14 (46.7%)</td>
<td>28 (70.8%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Non diabetic</td>
<td>2 (8.3%)</td>
<td>12 (44.8%)</td>
<td>14 (36.7%)</td>
<td></td>
</tr>
</tbody>
</table>

*Comparison between cases with and without diastolic dysfunction as regards mean duration of diabetes mellitus revealed that in patients who had diastolic dysfunction the mean duration was 16.25 years, while in those without diastolic dysfunction the mean duration was 5.17 years. There was a highly significant relationship between mean duration of diabetes mellitus and the presence of diastolic dysfunction ($p<0.01$). There was no statistically significant relation between presence of diastolic dysfunction and glyemic control ($p>0.05$), 70.8% of diabetics with diastolic dysfunction showed poor glyemic control (Table 3).

**Table 3:** Comparison between cases with and without diastolic dysfunction as regard their glyemic control.

<table>
<thead>
<tr>
<th>Diabetic dysfunction</th>
<th>Diabetic</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>2 (8.3%)</td>
<td>5 (20.8%)</td>
<td>17 (70.8%)</td>
</tr>
<tr>
<td>Negative</td>
<td>2 (33.3%)</td>
<td>2 (33.3%)</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>7</td>
<td>19</td>
</tr>
</tbody>
</table>

N.B. glycylated haemoglobin levels with HbA1c <7% for good control, 7-7.9% for fair control and ≥8% for poor control [7].

There was no significant relationship between age and diastolic dysfunction among cases ($p>0.05$). There was also no significant relationship between age and diastolic dysfunction among controls ($p>0.05$) (Table 4).

**Table 4:** Comparison between cases with and without diastolic dysfunction as regards their mean age.

<table>
<thead>
<tr>
<th>Diastolic dysfunction</th>
<th>Number</th>
<th>Mean age in years</th>
<th>SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>Positive</td>
<td>24</td>
<td>68</td>
<td>6.101</td>
</tr>
<tr>
<td>Negative</td>
<td>6</td>
<td>68.5</td>
<td>6.921</td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>Positive</td>
<td>16</td>
<td>65.5</td>
<td>5.304</td>
</tr>
<tr>
<td>Negative</td>
<td>14</td>
<td>67.93</td>
<td>6.545</td>
<td></td>
</tr>
</tbody>
</table>

**Discussion**

The hypothesis of this study was that development of diastolic dysfunction among elderly diabetics exceeds that among non diabetics. In the current study it was found that diabetics are at higher risk for developing diastolic dysfunction than non diabetics, a percent of 80% among diabetics versus 53.3% among non diabetics. This can be compared to a study done by Bajraktari et al [8] who found that diastolic dysfunction developed in 66.8% of the diabetic subjects and 33.3% in the control group.

Meanwhile some cross sectional studies discussed the relationship between diabetes and diastolic dysfunction, the prevalence of diastolic dysfunction among young diabetics was 69% [9]. While Zarich et al, found that 29% of diabetic young patients had evidence of diastolic dysfunction. Raev found that the prevalence of diastolic dysfunction among young diabetics was 27% [10,11]. The previous studies showed that diabetics are at higher risk to develop diastolic dysfunction.

The higher percentage of diabetics who developed diastolic dysfunction in this study is due to older age of the studied sample. A descriptive analysis of echocardiographic findings was done in the two studied groups. It was found that of 30 patients with diabetes (50% of patients) had relaxation abnormality, 13.3% of patients had psuedonormal pattern, 16.7% of patients had restrictive pattern and 20% of patients had normal diastolic
function. It was found that of 30 controls 36.7% of controls had relaxation abnormality, 6.7% of controls had pseudonormal pattern, 10% of controls had restrictive pattern and 46.7% of controls had normal diastolic function.

A study performed by Zile and Simsic found that the risk of diastolic heart failure increases with age. It occurs in 15% in patients under 60 years, 35% in patients 60 to 70 years and 50% in patients over 70 years old [12].

In our study there was no significant difference as regards mean age of diabetic patients who developed diastolic dysfunction and those without diastolic dysfunction. This was in contrast to the study of Bajraktari et al, [8] who showed that age was independently associated with increased risk of diastolic dysfunction in NIDDM. This controversy was due to large sample size of their study and exclusion of subjects older than 70 from the study of Bajraktari et al, while in the current study all participants were elderly and the range of age was relatively small.

When the mean duration of diabetes was analyzed, it was found to be higher in the cases with diastolic dysfunction than those without diastolic dysfunction. This high mean duration among cases with diastolic dysfunction was of a highly statistical significance. This result was supported by the study of Bajraktari et al, regarding the effect of the duration of diabetes on the occurrence of diastolic dysfunction [8]. They reported that the duration of diabetes was inversely related with the E/A ratio. Also a study of Annou et al, reported that in NIDDM, LV diastolic dysfunction is correlated with the duration of diabetes [13].

On the other hand, the studies of Gough et al, and Beljic & Mirik reported that diastolic dysfunction developed in newly diagnosed type II diabetic patients free of microvascular complications, without evidence of hypertension and coronary artery disease [14,15].

There was no significant relation between glycemic control (determined by glycosylated hemoglobin) and the development of diastolic dysfunction, although, the diabetics who had diastolic dysfunction were found to have a mean HbA1c higher than in those without diastolic dysfunction.

We observed that, of diabetic patients who developed diastolic dysfunction; 70.8% had poor control of their diabetes, 20.8% had fair control and 8.3% had good control. Yet this was of no statistical significance, probably due to the relatively small number of subjects in each group in our study.

These results agreed with Gough et al, who found that in normotensive patients with type II DM, the diastolic function was impaired and not affected by improvement of glycemic control [14].

Another study by Beljic and Mirik proved that adequate glycemic control for one year did not result in any improvement of diastolic function [15].

Conversely, another study by Grandi, concluded that glycemic control and LV diastolic function were closely related in normotensive type I DM suggesting that diastolic dysfunction could be prevented or reversed in part by maintaining glycemic control [16].

**Conclusion**

The presence of diabetes mellitus is a risk factor for the development of diastolic dysfunction. The mean duration of diabetes mellitus played a role in the occurrence of diastolic dysfunction. It should also be mentioned that every case of newly diagnosed diabetes mellitus should have a routine screening echocardiography and probably repeated during follow-up to evaluate diastolic function of the heart, even if these patients may be asymptomatic.

**Limitations of the study:**

The relatively small number of subjects.

Absence of systematic stress testing, or angiography, to exclude the influence of occult coronary artery disease on the results.

**References**

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6- Zile MR: Heart failure with preserved ejection fraction: is this diastolic heart failure?. J Am Coll Cardiol 2003; 41: 1519.


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Prevalence of Undiagnosed Diabetes and its Impact on the Outcome in Patients Presenting with Acute Coronary Syndrome

NIREEN KHALIFA OKASHA, MD; JOHN GAMIL FAWZY, MSc; MOHAMED TAREK ZAKI, MD; AYMAN SAMIR SADEK, MD

Background: The prevalence of type 2 diabetes, a major risk factor for cardiovascular morbidity and mortality, is rapidly increasing [1]. It has been estimated that 25% of adults with newly discovered diabetes have manifest cardiovascular disease [2] the present study was done to find out the prevalence of undiagnosed type 2 diabetes mellitus in patients presenting with acute coronary syndrome & its effect on in hospital mortality & major in hospital complications [1].

Methods and Results: Total of 100 patients presenting with acute coronary syndrome (58% MI & 42% with unstable angina), classified into two groups:
Group A: (n=45) patients with abnormal glucose metabolism. And further classified into two subgroups; A1: Patients with new onset DM (n=29), A2: patients with impaired glucose tolerance (n=16).
Group B: (n=55) patients with normal glucose metabolism.

Coronary angiography was done to all patients and in hospital stay follow up for morbidity and mortality. Higher incidence of patients with three vessel coronary artery disease was found in newly diagnosed diabetic patients (p≤0.05). Also the incidence of heart failure and ventricular arrhythmia were (p≤0.01) and (p≤0.05) respectively; as compared to patients with normal glucose metabolism regarding the same morbidity variables. The new onset diabetic patients presenting with acute MI; had a high incidence of in hospital re-infarction (p≤0.05) and post infarction angina (p≤0.05) compared to patients with normal glucose metabolism. Higher mortality rate was found among patients with impaired glucose metabolism (13.3%), especially between the newly diagnosed diabetic patients (17.2%), compared to patients with normal glucose metabolism (p≤0.01).

Conclusions: The prevalence of previously undiagnosed DM and impaired glucose metabolism is high between patients presenting with acute coronary syndrome and the incidence of major in hospital complications and mortality is higher in this group. High admission plasma glucose level represents an important marker of poor clinical outcome and high mortality rates, in this group.

Key Words: Diabetes – Acute coronary syndrome.

Type 2 diabetes is a major risk factor for cardiovascular morbidity and mortality [1], it has been estimated that 25% of adults with newly discovered diabetes have manifest cardiovascular disease [2].

Thus, the rapidly expanding population with diabetes will influence cardiovascular morbidity and have a substantial impact on future health cost [2,4].

The risk of myocardial infarction, heart failure and cardiac death is already increased in subjects with moderately elevated blood glucose [5,6] the risk of cardiovascular complications nearly doubles in those with impaired glucose tolerance [7,8].

A substantial proportion of adults, meeting the diagnostic criteria for diabetes remain undiagnosed.
glucose metabolism in patients with acute myocardial infarction (GAMI) study revealed an unexpectedly high prevalence of type 2 diabetes and impaired glucose tolerance amongst patients with myocardial infarction without history of diabetes [9].

The morbidity associated with long-standing diabetes of either type results from a number of serious complications, involving both large- and medium-sized muscular arteries (macrovascular disease), as well as capillary dysfunction in target organs (microvascular disease) [10].

Two large multicentric trials studied the effects of plasma glucose concentrations on long-term complications of diabetes—the Diabetes Control and Complication Trial (DCCT) [10], and the United Kingdom Prospective Diabetes Study (UKPDS) [11] have convincingly demonstrated delayed progression of microvascular complications by strict control of the hyperglycemia.

Admission plasma glucose even after adjustment on HbA1c, is a prognostic factor associated with mortality after acute myocardial infarction [12].

The contribution of undiagnosed diabetes mellitus to total mortality following acute myocardial infarction seems to be underestimated [13].

Patients and Methods

* Patient selection:

This study was conducted on 100 patients presenting with acute coronary syndrome to Police Authority Hospital.

* Inclusion criteria:

1- Patients presenting with acute coronary syndrome.
2- Not previously known to be diabetic.

* Methods:

Every patient was subjected to proper history taking and clinical examination, 12 lead surface ECG, lipid profile and Echocardiography to assess left ventricular functions.

Admission plasma glucose:

By means of glucose oxidase test strips, (normal level up to 200 mg/dl) in accordance with screening recommendations of the report of expert committee of diabetes mellitus, 2003 [14].

Hemoglobin A1c:

HbA1c: (Normal level up to 7%) in accordance with screening recommendations of the report of expert committee of diabetes mellitus, 2003 [14].

Fasting & 2 hours post-prandial blood sugar:

Performed after an overnight fast (FPG <110 mg/dl (6.1 mmol/l) = normal fasting glucose; FPG >110 (6.1 mmol/l) and <126 mg/dl (7.0 mmol/l) = IFG; FPG >126 mg/dl (7.0 mmol/l) = provisional diagnosis of diabetes. 2-h postload glucose (2-h PG) <140 mg/dl (7.8 mmol/l) = normal glucose tolerance; 2-h PG >140 (7.8 mmol/l) and <200 mg/dl (11.1 mmol/l) = IGT; 2-h PG >200 mg/dl (11.1 mmol/l) = provisional diagnosis of diabetes) in accordance with screening recommendations of the report of expert committee of diabetes mellitus, 2003 [14].

Cardiac enzymes:

CK MB {normal level up to 26 u/l}. Troponin T (qualitative test).

*End points:

Daily follow-up with clinical examination, serial ECG and cardiac enzymes follow-up to detect in hospital morbidities and mortality:

In hospital morbidity:

1- Post infarction angina.
2- Re-infarction.
3- Arrhythmias (ventricular).
4- Heart failure.

In hospital mortality:

Follow-up in hospital mortality rate.

Results

Our study included 100 consecutive patients presenting with acute coronary syndrome to Police Authority Hospital (58% presented with myocardial infarction & 42% with unstable angina), 90 males (90%) and 10 females (10%). Their age ranged from 36-82 years with a mean age of 51.64±9.59 years.

Random admission plasma glucose [Random is defined as any time of day regardless to time since last meal] followed on the second day by fasting [Fasting is defined as no caloric intake for at least 8 h] & 2-hours post prandial blood glucose levels; were estimated for all patients [FBS ranged from 70-230 mg/dl with a mean of 114±44.72 while
2- hours PPBS ranged from 96-390 mg/dl with a mean of 173.98±68.21, accordingly patients were classified into two main groups (Recommendations of the report of expert committee of diabetes mellitus, 2003):

1- Group A: included 45 patients (45%) with abnormal glucose metabolism. They were further classified into two subgroups:

   A1: Patients diagnosed as having new onset DM (29 patients= 65.6% of group A) [Random admission plasma glucose concentration >200mg/dl (11.1 mmol/l) followed on the second day by: Fasting plasma glucose >126 mg/dl (7.0 mmol/l) or 2-h post prandial glucose >200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test].

   A2: Patients with impaired glucose tolerance [2-h post prandial glucose >140 (7.8 mmol/l) and <200 mg/dl (11.1 mmol/l)] or impaired fasting plasma glucose [FPG >110 (6.1 mmol/l) and <126 mg/dl (7.0 mmol/l)] 16 patients (34.4% of group A).

2- Group B: included 55 patients (55%) with normal glucose metabolism.

![Figure 1: Study group classification according to fasting and post prandial blood glucose.](image)

Age of the study population ranged from 36-82 years with a mean age of 51.64±9.59 years. Group A included 7 females (15.5%) & 38 males, (84.5%) & Group B included 3 females (5.45%) & 52 males (94.5%).

Clinical and procedural variables between (group A1) and (group B) are indicated in Table (1). Age, sex, cardiovascular risk factors, Lab. investigations, left ventricular function.

### Table 1: Main clinical feasures.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Group A1 no=29</th>
<th>Group B no=55</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;45 years</td>
<td>25 (86)</td>
<td>34 (62)</td>
<td>0.025</td>
</tr>
<tr>
<td>Males</td>
<td>24 (82)</td>
<td>52 (94)</td>
<td>0.10</td>
</tr>
<tr>
<td>Females</td>
<td>5 (16)</td>
<td>3 (6)</td>
<td>0.10</td>
</tr>
<tr>
<td>Smoking</td>
<td>21 (72)</td>
<td>49 (89)</td>
<td>0.10</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (51)</td>
<td>32 (58)</td>
<td>0.32</td>
</tr>
<tr>
<td>BMI</td>
<td>24 (82)</td>
<td>29 (52)</td>
<td>0.01</td>
</tr>
<tr>
<td>Family history of DM</td>
<td>21 (72)</td>
<td>4 (7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Family history of CHD</td>
<td>20 (68)</td>
<td>31 (56)</td>
<td>0.26</td>
</tr>
<tr>
<td>Admission plasma glucose (&gt;200mg/dl)</td>
<td>26 (89)</td>
<td>2 (3)</td>
<td>0.001</td>
</tr>
<tr>
<td>HbA1c (&gt;7%)</td>
<td>19 (65)</td>
<td>0 (0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Triglyceride blood level (150 mg/dl)</td>
<td>26 (89)</td>
<td>26 (47)</td>
<td>0.05</td>
</tr>
<tr>
<td>Total cholesterol (&gt;200 mg/dl)</td>
<td>21 (72)</td>
<td>22 (40)</td>
<td>0.01</td>
</tr>
<tr>
<td>LDL (&gt;100 mg/dl)</td>
<td>26 (89)</td>
<td>17 (30)</td>
<td>0.001</td>
</tr>
<tr>
<td>CKMB (26mg/dl)</td>
<td>0.955±0.237</td>
<td>0.940±0.228</td>
<td>0.56</td>
</tr>
<tr>
<td>Troponin t +ve</td>
<td>12 (41)</td>
<td>31 (56)</td>
<td>0.25</td>
</tr>
<tr>
<td>Total cholesterol (&gt;200 mg/dl)</td>
<td>13 (44)</td>
<td>32 (58)</td>
<td>0.20</td>
</tr>
<tr>
<td>LDL (&gt;100 mg/dl)</td>
<td>26 (89)</td>
<td>17 (30)</td>
<td>0.001</td>
</tr>
<tr>
<td>EF ± SD</td>
<td>51.4±769</td>
<td>52.1±7.218</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Values are given as number (%) or mean±SD.

### Coronary angiography:

Coronary angiography was done to all patients of the two groups. A higher incidence of patients with three vessel coronary artery disease was found in newly diagnosed diabetic patients (A1) (8 patients, 30.7%) compared to patients with normal glucose metabolism (B) (6 patients, 12%) (p<0.05).

While, no significant difference was found comparing newly diagnosed diabetic patients (A1) (8 patients, 30.7%) to patients with impaired glucose tolerance (A2) (3 patients, 18.75%) (p=0.26).

### In hospital morbidity:

The prevalence of major in hospital morbidity variables among different study groups shows the following:
Comparing group A1 & B, a statistically significant predominance of heart failure (10 patients, 34.4%) and arrhythmia (9 patients, 31.03%) \((p \leq 0.05)\) was found among Group A1 patients; compared to Group B [4 patients with heart failure, (7.2%) and 7 patients with ventricular arrhythmia] \((p \leq 0.01)\) & \((p < 0.05)\) respectively.

This study included 58 patients presenting with acute myocardial infarction (28 patients (62.2%) of group A [18 patients subgroup A1 & 10 patients subgroup A2] & 30 patients (54.4%) of group B).

A statistically significant predominance of in-hospital reinfarction and post infarction angina were found among Group A1 patients presenting with acute myocardial infarction; compared to Group B patients presenting with acute myocardial infarction [38.8% Vs 13.3% \((p \leq 0.05)\) & 66.6% Vs 36.6% \((p \leq 0.05)\) respectively.

While no statistically significant difference was found comparing subgroup A1 and A2 regarding the same morbidity variables \((p \leq 0.29)\) & \((p \leq 0.10)\).

**In hospital mortality:**

A statistically significant higher mortality rate was found among Group A1 patients [5 patients, (17.2%)] compared to the control Group B (0%) \((p \leq 0.01)\).

While, no significant difference was found comparing subgroup A1 (17.2%) & A2 (6.2%) regarding mortality rate \((p \leq 0.36)\).

**Relation of admission plasma glucose with in hospital morbidity & mortality:**

We studied the relation between admission plasma glucose & major in hospital morbidity variables [myocardial reinfarction, arrhythmia, post infarction angina & HF] and mortality.

A statistically significant higher admission plasma glucose level was found between patients with arrhythmia \((p=0.017)\), heart failure \((p<0.001)\) and post infarction angina \((p=0.008)\) compared to those without.

Also a statistically significant higher admission plasma glucose level was found between patients who died compared to those who survived \((p=0.015)\) (Table 2).

**Table 2:** The relation between admission plasma glucose & in hospital morbidity variables and mortality.

<table>
<thead>
<tr>
<th></th>
<th>+ ve Mean±SD</th>
<th>- ve Mean±SD</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial reinfarction</td>
<td>169.9±76.78</td>
<td>176.3±84.43</td>
<td>0.818</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td>215.25±14.75</td>
<td>168.8±71.02</td>
<td>0.017</td>
</tr>
<tr>
<td>Post inf. angina</td>
<td>212.77±107.41</td>
<td>162.66±69.35</td>
<td>0.008</td>
</tr>
<tr>
<td>Heart failure</td>
<td>231.47±103.22</td>
<td>166.86±70.89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death</td>
<td>255±82.37</td>
<td>170.63±81.24</td>
<td>0.015</td>
</tr>
</tbody>
</table>

**Relation of HbA1c with in hospital morbidity & mortality:**

We studied the relation between admission plasma glucose & in hospital morbidity variables [myocardial reinfarction, arrhythmia, post infarction angina & HF] and mortality.

HbA1c blood level was significantly higher in patients with in-hospital myocardial reinfarction \((p<0.001)\) compared to those without. Otherwise, no significant relation between HbA1c blood level & other variables (Table 3).

**Table 3:** The relation between HbA1c & in hospital morbidity variables and mortality.

<table>
<thead>
<tr>
<th></th>
<th>+ ve Mean±SD</th>
<th>- ve Mean±SD</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial reinfarction</td>
<td>9.31±2.74</td>
<td>5.89±2.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td>6.49±3.69</td>
<td>6.92±7.1</td>
<td>0.798</td>
</tr>
<tr>
<td>Post inf. angina</td>
<td>6.88±3.64</td>
<td>6.82±7.33</td>
<td>0.966</td>
</tr>
<tr>
<td>Heart failure</td>
<td>6.52±3.6</td>
<td>6.92±7.15</td>
<td>0.806</td>
</tr>
<tr>
<td>Death</td>
<td>5.82±2.21</td>
<td>6.89±6.74</td>
<td>0.697</td>
</tr>
</tbody>
</table>

**Discussion**

Diabetes mellitus and coronary artery disease constitute a serious clinical combination. The morbidity and mortality resulting from cardiovascular complications are high in patients with type 2 diabetes mellitus [15].

Macrovascular complications, especially atherosclerosis, are the major cause of morbidity and mortality in patients with type 2 diabetes mellitus [16].

Glucose intolerance including impaired glucose tolerance and diabetes has emerged as a major
health hazard, because it is causally associated with coronary artery disease [16].

This study included 100 patients presenting with acute coronary syndrome not previously known to be diabetics to the Police Authority Hospital (58% presented with myocardial infarction & 42% with unstable angina). Random admission plasma glucose [Random is defined as any time of day without regard to time since last meal] followed on the second day by fasting [Fasting is defined as no caloric intake for at least 8 h] & 2-hours post prandial blood glucose levels; were estimated for all patients {FBS ranges from 70-230 mg/dl with a mean of 114±44.72 while 2-h PG ranges from 96-390 mg/dl with a mean of 173.98±68.21}. Patients were classified into two main groups according to the Recommendations of the report of expert committee of diabetes mellitus, 2003: 1 Group A: included 45 patients (45%) with abnormal glucose metabolism. They were further classified into two subgroups: {A1: 29 Patients diagnosed as having new onset DM [Random admission plasma glucose >200 mg/dl (11.1 mmol/l) followed on the second day by: Fasting plasma glucose >126 mg/dl (7.0 mmol/l) or 2-h post prandial glucose >200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test] & A2: 16 patients with impaired glucose tolerance [2-h post prandial glucose >140 (7.8 mmol/l) and <200 mg/dl (11.1 mmol/l)] or Impaired fasting plasma glucose [FPG >110 (6.1 mmol/l) and <126 mg/dl (7.0 mmol/l)].

2- Group B: included 55 patients (55%) with normal glucose metabolism. [FPG <110 mg/dl (6.1 mmol/l) and 2-h post load glucose (2-h PG) <140 mg/dl (7.8 mmol/l)].

These results came in consistence with a trial by Ramachandran, A et al [17] which suggested that among 146 Asian Indian subjects admitted with acute coronary syndrome, without history of diabetes mellitus; undiagnosed diabetes was present in 25% of patients; after the exclusion of those with known history of diabetes mellitus.

Norhammar, et al [18], reported that impaired glucose tolerance and diabetes were common in European patients with acute myocardial infarction. In their study, they investigated 181 patients presenting with acute myocardial infarction patients who were not previously known to have diabetes and found that 31% of those patients have undiagnosed diabetes mellitus.

While Conaway et al [19], studied 1,199 patients presenting with acute coronary syndrome and found that 57% of patients had an abnormal glucose metabolism & 14% of patients who did not have a previous diagnosis of diabetes mellitus, met criteria for a new diagnosis of diabetes mellitus compared to 29% in this study. This difference may be attributed to the fact that Darcy G et al excluded those who proved to have stress induced diabetes during hospitalization for the acute coronary syndrome and had normal glucose tolerance curves at follow-up after three months. On the other hand, a recent study has suggested that most patients who have diabetes mellitus that is newly diagnosed during hospitalization for acute coronary syndrome continue to have increased glucose levels after 3 months. This study showed that 33% of the cohort had new diabetes mellitus and another 33% had impaired fasting plasma glucose levels (Tenerz A et al) [20].

Meier J. et al [21]; found that among 129 patients presenting with acute myocardial infarction; oral glucose tolerance test was normal in 47% of patients, 34% had impaired glucose tolerance and 19% were found to have recently diagnosed diabetes.

This study included 90 males & 10 females, their age ranged from 36-82 years with a mean age of 51.64±9.59 years and their body mass index ranged from 24.4 to 34.6 kg/m² with a mean of 28, 652 kg/m². A high prevalence of patients above 45 years of age; with body mass index ≥25 kg/m² & with positive family history of diabetes was found among newly diagnosed diabetic patients compared to patients with normal glucose metabolism (86.2% Vs 61.8%, p<0.01) (82.75% Vs 52.7%, p<0.025) (72.4% Vs 7.2%, p<0.001) respectively. While no significant predominance was found regarding sex (p<0.10), hypertension (51.1% Vs 58.18%, p≤1) & smoking (72.4% Vs 89.09%, p<0.10) in the impaired glucose metabolism group of patients:

These results were found in consistence with the report of the expert committee of diabetes 2003 regarding the steep rise of the incidence of the disease above the age of 45 years & its screening recommendation to all patients above 45 years of age especially with body mass index ≥25 kg/m² [14].

Hashimoto K, et al [22], studied 134 consecutive patients presenting with acute coronary syndrome
who were not previously diagnosed to have diabetes and found that a significant predominance of hypertensive (61%, *p*=0.027); male (80%, *p*=0.018) patients with high body mass index and with positive family history of diabetes mellitus, was found among newly diagnosed diabetic patients (*p*≤0.034 & *p*≤0.028 respectively).

Patients diagnosed to have newly discovered diabetes had significantly higher blood levels of admission plasma glucose (>200mg/dl) and HbA1c (>7%) compared to normal glucose metabolism group of patients (89.65% Vs 3.6%, *p*<0.001 & 65.5% Vs 0%, *p*<0.001 respectively).

HbA1c blood level above 7% was 65.5% sensitive & 98.3% specific for detection of previously undiagnosed diabetics.

Oswald G, et al [23]; studied 397 patients not previously known to be diabetics admitted to hospital with acute myocardial infarction to validate an admission level of HbA1c as a diagnostic test for previously unknown diabetes mellitus and found that HbA1c blood level above 7% was 67% sensitive and 99% specific.

Husband D, et al [24], studied 26 patients not previously known to be diabetics and presenting with acute myocardial infarction, for 2 months and demonstrated that stress hyperglycemia in patients not previously known to be diabetics during acute myocardial infarction is an indicator of pre-existing diabetes mellitus (82%, *p*<0.01).

In the same direction, Hashimoto K, et al 2005 [22], demonstrated that HbA1c blood value was significantly higher in the newly diagnosed diabetic subjects (*p*<0.001).

Newly diagnosed diabetic patients had significantly higher blood levels of triglycerides (>150mg/dl), total cholesterol (>200mg/dl) & low density lipoprotein (>100mg/dl); compared with patients with normal glucose metabolism (89.6% Vs 47.2%, 72.4% Vs 40% & 89.6% Vs 30.9% respectively).

Bartnick M, et al [8], studied 185 patients newly discovered to be diabetics and presenting with acute myocardial infarction and found a statistically significant predominance of high total cholesterol (>200mg/dl) & triglycerides blood levels (>150mg/dl) in the study group compared to control group of patients (*p*<0.008 & *p*<0.001 respectively).

Coronary angiography was done to 92 patients [42 patients of Group A (26 patients of subgroup A1 & 16 patients of subgroup A2) & 50 patients of Group B]. A high prevalence of patients with three vessels coronary artery disease was found in coronary angiography reports of newly discovered diabetics compared to normal glucose metabolism group [30.7% Vs 12%; (*p*≤0.05)].

Hashimoto K, et al [22], found that number of stenosed coronary vessels was significantly higher in the newly diagnosed diabetic subjects than in the normal glucose tolerance subjects (*p*=0.022).

A high in hospital incidence of heart failure & arrhythmia were found to be directly related to high admission plasma glucose level [mean plasma glucose level in patients who developed heart failure & arrhythmias were 231.47±103.22 & 215.25±114.75 and *p* value <0.001 & 0.017 respectively] & and newly diagnosed diabetics [heart failure (10 patients, 34.4%) (*p*≤0.01) and arrhythmia (9 patients, 31.03%) (*p*≤0.05)] Compared to patients with normal glucose metabolism:

Harris M, et al [25] suggests that Onset of NIDDM occurs at least 4-7 years before clinical diagnosis & that significant morbidity is present at diagnosis and for years before diagnosis.

K Foo, et al [26] analyzed the relation between admission plasma glucose & in hospital heart failure in 2127 patients presenting with acute coronary syndromes and he suggested that 25.2% (*p*<0.0001) of patients with high admission plasma glucose not previously known to be diabetics, had in-hospital heart failure.

Zeller M, et al [27], studied 999 patients presenting with acute myocardial infarction; of whom 145 (15%) had impaired glucose tolerance and 473 (47%) normal glucose metabolism. A significant increase in cardiogenic shock (12% Vs 6%, *p*= 0.011) and ventricular arrhythmia (15% Vs 9%, *p*=0.035) were observed in the impaired glucose tolerance Vs normal glucose metabolism group. Impaired glucose tolerance, was a strong independent predictive factor for cardiogenic shock.

Fisman E, et al [28] studied 11, 853 patients with documented coronary artery disease. Patients were divided into 3 groups [normal glucose metabolism impaired fasting blood glucose and newly discovered diabetics] on the basis of their fasting
blood glucose levels at screening. All-cause mortality in the non diabetic group was 14.3% compared to 20.1% in patients with IFG and 24.3% in the newly diagnosed diabetics (p<0.001).

The difference between new onset diabetics mortality rates in both studies (24.3% Vs 17.2%) may be due to lack of follow-up in our study & the small number of patients included.

Meier J, et al [21], studied the survival of 562 patients admitted to the intensive care unit of a medical department with the diagnosis of acute myocardial infarction, which were prospectively evaluated over a span of more than 3 years. Type 2 diabetes had been previously known in 152, while it was newly diagnosed in 83 patients. Survival of all patients with type 2-diabetes was significantly worse than in the remainder of patients (p<0.0001). In patients with impaired glucose tolerance the survival time was significantly shorter than in those with normal glucose tolerance (p=0.029). Even after excluding those patients who had died in the acute post-infarction phase, the difference between patients with normal and with impaired glucose tolerance remain significant (p=0.034).

S Hadjadj, et al [29], studied 146 patients presenting with acute myocardial infarction, four had died by day 5 and 14 by day 28. Admission plasma glucose was higher in patients who had died by day 28 (11.7±5.8 Vs. 8.0±3.3 mmol/L, p=0.002), whereas HbA1c was not (6.4±1.9 Vs. 6.1±0.8%, NS). Admission plasma glucose was significantly higher in those who had died by day 28 after adjustment of HbA1c. A multivariate analysis, including sex, age and heart failure prior to acute myocardial infarction, showed that admission plasma glucose concentration was an independent predictor of survival after acute myocardial infarction.

HbA1c blood level was significantly higher in patients with in-hospital myocardial reinfarction (p<0.001) compared to those without, which signifies the importance of HbA1C as a predictor of myocardial reinfarction.

**Study limitations:**

1- Limited number of patients (especially females 10%).
2- Lack of follow-up after hospital discharge.
3- It included a single medical center.

**Conclusions**

The prevalence of previously undiagnosed diabetes mellitus and impaired glucose metabolism is high between patients presenting with acute coronary syndrome and the incidence of major in hospital complications (heart failure & ventricular arrhythmias) and mortality is higher in this group of patients. High admission plasma glucose level represents an important marker of poor clinical outcome and high mortality rates, in this group of patients.

Hemoglobin A1c blood level >7% was 65.5% sensitive & 98.3% specific for detection of previously undiagnosed diabetics presenting with acute coronary syndrome, also HbA1c blood level was significantly higher in patients complicated with myocardial reinfarction, during hospital admission.

**References**

6- Steinberg HO, Baron AD: Vascular function, insulin resistance and fatty acids. Diabetologia 2002; 45: 623-34.
11- Anonymous: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment


Redo Versus First Percutaneous Balloon Mitral Valvuloplasty for Rheumatic Mitral Stenosis. Analysis of Factors Related to the Redo Procedure

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Background: Percutaneous balloon mitral valvotomy (PBMV) was introduced in 1984 by Inoue. Since then, PMBV has emerged as the treatment of choice for severe pliable rheumatic mitral stenosis. With increasing experience and better selection of patient, the immediate results of the procedure have improved and the rate of complications declined. Restenosis after PMBV ranges from 4 to 70% depending on the patient selection, valve morphology, post procedure MVA and duration of follow-up. The feasibility of redo PMBV is not well known. Aim of our study was to assess the immediate results of repeated percutaneous balloon mitral valvuloplasty in patients with mitral restenosis after previous successful PMBV. Moreover, to compare the outcome to that of the first (PBMV).

Methods: Our study included 70 patients, whom were classified into two groups, 30 patients (group A) who underwent PMBV for the first time and 40 patients (group B) who underwent PMBV as a redo procedure. All patients were subjected to full history taking, general and local examination, resting, 12 leads ECG, echocardiographic examination before and one day after the procedure and transesophageal echocardiography (TEE) 1-2 days before procedure. Multi-track double balloon and Inoue single balloon were used for PMBV.

Results: The immediate outcome of PMBV for patients who had restenosis were satisfactory, with a 92.5% success rate (group B) compared with 93.33% in patients who underwent PMBV as an initial procedure (group A). (p=NS). There was no difference as regard the changes in left atria pressure, mean transmitral pressure gradient and RVSP after PMBV, but only small difference was observed as regard the increase in post PMBV-MVA in favor of group A, where MVA increased from 1.2±1.1 to 1.92±0.4cm² in group A and from 1.03±0.13 to 1.7±0.3cm² in group B (p=0.016). No significant difference was noted as regards the incidence of serious complications between two groups. Factors which determined longer time to redo PMBV or restenosis were: Rhythm (in favor of SR, p=0.009), post procedure increment in MVA (p=0.004), low echo score (p=0.008), and long acting penicillin (in favor of patients receiving LAP, p=0.007).

Conclusion: We conclude that, PMBV should be considered the first option in patients who have restenosis. Prescription of LAP is advisable for patients undergoing PMBV either as a first or a redo procedure.

Key Words: Redo percutaneous balloon mitral valvuloplasty – Mitral stenosis – Mitral valve restenosis.

Introduction

Mitral stenosis (MS) is a narrowing of the inlet valve into the left ventricle that prevents proper opening during diastolic filling. Patients with MS typically have mitral valve leaflets that are thickened, commissures that are fused and/or chordae tendineae that are thickened and shortened [1].

Percutaneous balloon mitral valvuloplasty is the procedure of choice (class I) for symptomatic patients (New York Heart Association Functional Class, or NYHA FC II, III or IV), moderate to severe mitral stenosis and valve morphology favorable for percutaneous balloon valvotomy [2].

In indicated patients, the acute and long term results of balloon mitral valvuloplasty are encour-
aging and it has proven superior to closed commissurotomy [3-4]. The frequency of restenosis of the valve is variable depending on the age and the immediate procedural increment in valve area [5]. Despite the importance of evaluating the repeated balloon mitral valvuloplasty in symptomatic restenosis after a prior successful procedure, there are few trials which targeted this important issue. The aim of our study was to assess the immediate results of repeated percutaneous balloon mitral valvuloplasty in patients with mitral restenosis who had previous procedure of balloon mitral valvuloplasty. Moreover, to compare the results of the redo PBMV to those of the first procedure.

Patients and Methods

The Study population included 70 patients having rheumatic MS. All patients referred to Ain Shams University and National heart institute hospitals and were candidates for percutaneous balloon mitral valvuloplasty over the period from May 2006 to April 2007. Patients were classified into two groups: Group A included 30 consective patients doing the procedure the first time and group B included 40 consecutive patients doing balloon mitral valvuloplasty as a redo procedure after restenosis. Written informed consent was obtained from all patients.

Inclusion criteria: Patients with mitral valve morphology favorable for PBMV and mitral valve area <1.5cm² in symptomatic patients in the absence of left atrial thrombus or moderate to severe mitral regurgitation.

Exclusion criteria: Patients who have unfavorable valve morphology for PBMV (score >12), patients with more than grade two mitral regurgitation, patients with left atrial thrombus on TEE performed within 24h. before the procedure, severe aortic valve disease, or severe tricuspid stenosis and regurgitation associated with mitral stenosis, acute rheumatic activity or infective endocarditis [6] and severe concomitant coronary artery disease requiring bypass surgery.

Methods:

• All patients were subjected to the following: Full history taking, general and local cardiac examination.

• Standard 12 lead electrocardiography was done to all patients at rest on recumbent position with special interest to Rhythm.

• Echocardiographic imaging: All patients were studied with M-mode, two-dimensional and color-Doppler echocardiography before PBMV and one day after the procedure Mitral stenosis: The mitral valve area was measured by the pressure half time method.

• Mitral valve score was assessed by two methods: Wilkins' score: By assessment of valve mobility, thickness, calcification and subvalvular affection according to criteria described by Wilkins and his associates [7]. Rifaie score: By assessment of calcifications of leaflets and commissures and also subvalvular affection according to criteria described by Rifaie and his associates [8].

• Transesophageal echocardiography (TEE): was used in all patients 1-2 days before the procedure for evaluating the LA appendage for the presence of thrombi in th, measuring the inter- atrial septal thickness and the mitral valve annulus.

Percutaneous mitral balloon valvotomy:

Procedure was performed with Inoue balloon, Multi-Track balloon or double balloon technique. Inoue balloon size was selected according to simple formula: Patient's height (in cm) is rounded to the nearest zero and divided by 10 and then 10 is added to the ratio yield the reference (in mm) and using stepwise inflations. Multi-Track balloon was performed with Bonhoeffer Multi-Track system. Balloon size was selected according to mitral valve annulus which was measured by transsesophageal echo-cardiography. The sum of the diameter of the two balloons was then chosen to be 90%-100% of the measured mitral annulus. Immediately before and after valvuloplasty, left and right heart catheterization with determination of intracardiac and intravascular pressure was performed. Transmitral pressure gradient was measured.

Post procedural assessment:

Clinical: Assessment for the presence and the severity of residual stenosis mitral incompetence, systemic and groin complications. A detailed echocardiography and Doppler assessment of the same predilatation variables: e.g. transmitral pressure gradient, mitral valve area, mitral regurgitation, pulmonary artery systolic pressure, let ventricular function & dimensions. Procedural success was defined as MVA > 1.5cm² without mitral regurge > grade II in the absence of serious complications e.g. Cardiac tamponade, cerebral embolism and death.
Statistical methods:

Data were expressed as mean and standard deviation. Categorical variables were compared using the t test. Non categorical variables were compared using the Chi square test. Correlation of variables was done using Pearson correlation coefficient. Multivariate analysis was done for significant variables on univariate analysis, using software of SPSS version 7.

Results

The study included 40 patients (group B) who had mitral restenosis after previous balloon valvotomy underwent percutaneous balloon mitral valvuloplasty as a redo procedure were compared with 30 patients (group A) who underwent it as an initial procedure. The initial procedure in group B was termed B1, whereas the redo data of group B were termed BII.

The age, gender and other clinical data are shown in Table (1). Other pre-procedural and post-procedural hemodynamic and echocardiographic data in groups A and B are shown in Table (2). There was no statistically significant difference between both groups as regard the changes in left atria pressure, mean transmitral pressure gradient and right ventricular systolic pressure (RVSP) after PBMV. Small difference was observed as regard the increase in post PBMV-MV A in favor of group A, where MVA increased from 1.2±1.1 to 1.92±0.4cm² in group A and from 1.03±0.13 to 1.7±0.3cm² in group B.

The Multitrack balloon was used in 23 (76.67%) patients in group A and 25 (62.50%) patients in group B (p>0.05), compared to Inoue technique which was used in 7 (23.33%) patients in group A and 13 (32.5%) patients in group B (p>0.05). Optimal immediate results (defined as an immediate echocardiographic MVA ≥1.5cm² without major complications). Severe MR (≥3/4) after procedure occurred in 2 patients (5%) in group BII and urgent mitral valve replacement was done. While in group B1 no severe MR was reported after procedure (Table 3).

Hemodynamics and procedural variables for the Initial PBMV (group B1) and Redo PBMV (group BII) of the same patients are shown in Table (4).
Redo Percutaneous Balloon Mitral Valvuloplasty

Table 4: Haemodynamics and procedural variables for the Initial PBMV (group B I) and Redo PBMV (group B II) of the same patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group A</th>
<th>Group B II</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMG Before</td>
<td>17.78±6.161</td>
<td>16.29±5.234</td>
</tr>
<tr>
<td>MMG After</td>
<td>5.78±2.973</td>
<td>5.74±2.686</td>
</tr>
<tr>
<td>MVA Before</td>
<td>0.97±0.123</td>
<td>1.03±0.138</td>
</tr>
<tr>
<td>MVA After</td>
<td>1.90±0.354</td>
<td>1.71±0.302</td>
</tr>
<tr>
<td>% of mean increase ± SD in MVA</td>
<td>96.235±37.084%</td>
<td>68.074±31.371%**</td>
</tr>
<tr>
<td>Difference in MES2 between group B I and group B II</td>
<td>7.30±1.364</td>
<td>7.76±1.214</td>
</tr>
</tbody>
</table>

* p<.05 compared with control subjects.
** p<.001 compared with control subjects.
MES1 (Rifaie score).
MES2 (Wilkins’ score).

Factors affecting time to redo percutaneous balloon mitral valvuloplasty after first successful procedure in group B:

There was a positive correlation between mitral valve area gained after percutaneous mitral valvuloplasty and the freedom from redo procedure (p=0.004), also there was a positive correlation between mitral valve morphology and the freedom from repeat surgery (p=0.008). There was a significant relationship between rhythm and the freedom from redo procedure in favor of patients in SR (p=0.009). Moreover, there was a significant relationship between long acting penicillin therapy and the freedom from redo procedure in favor of patients receiving long acting penicillin therapy (p=0.007).

By multivariate analysis of the different factors which determine time to redo procedure or restenosis, it was found that MV morphology (MES 2) is the most powerful predictor; (p=0.008). (Tables 5-9).

Table 5: Showing relationship between time to redo percutaneous mitral valvuloplasty and mitral valve area after initial procedure and MES2 at the time of initial PBMV.

<table>
<thead>
<tr>
<th>Time to redo PBMV</th>
<th>r</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MES 2 at the time of initial PBMV</td>
<td>-0.634</td>
<td>0.008*</td>
</tr>
<tr>
<td>MVA after initial PBMV</td>
<td>0.522</td>
<td>0.004*</td>
</tr>
</tbody>
</table>

* p<.05 compared with control subjects.
MES2 (Wilkins’ score).

Table 6: Showing relationship between time to redo procedure and rhythm.

<table>
<thead>
<tr>
<th>Rhythm</th>
<th>Time to redo PBMV (years)</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range (years)</td>
<td>Mean±SD</td>
</tr>
<tr>
<td>SR</td>
<td>3.000-10.000</td>
<td>6.800±2.121</td>
</tr>
<tr>
<td>AF</td>
<td>1.000-10.000</td>
<td>4.867±2.200</td>
</tr>
</tbody>
</table>

Table 7: Showing relationship between time to redo procedure and long acting penicillin therapy in group B.

<table>
<thead>
<tr>
<th>LAP</th>
<th>Time to redo PBMV (years)</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range (years)</td>
<td>Mean±SD</td>
</tr>
<tr>
<td>No</td>
<td>1.000-10.000</td>
<td>4.938±2.112</td>
</tr>
<tr>
<td>Yes</td>
<td>4.000-10.000</td>
<td>7.214±2.155</td>
</tr>
</tbody>
</table>

Table 8-9: Showing that MES is the most powerful predictor of redo PBMV.

<table>
<thead>
<tr>
<th>Unstandardized Coefficients</th>
<th>B</th>
<th>Std. Error</th>
<th>Beta</th>
<th>t</th>
<th>p</th>
<th>value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Constant)</td>
<td>13.635</td>
<td>2.472</td>
<td>5.516</td>
<td>0.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MES2 at the time of initial PBMV</td>
<td>-1.146</td>
<td>0.374</td>
<td>-0.634</td>
<td>-3.066</td>
<td>0.008</td>
<td></td>
</tr>
</tbody>
</table>

Table 10: Showing the relationship between MVA gained after PBMV to balloon technique.

<table>
<thead>
<tr>
<th>MVA after PBMV</th>
<th>Multi track</th>
<th>Inoue</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td>t</td>
<td>p value</td>
</tr>
<tr>
<td>Group A</td>
<td>1.939±0.450</td>
<td>1.871±0.180</td>
<td>0.385</td>
</tr>
<tr>
<td>Group BII</td>
<td>1.736±0.352</td>
<td>1.704±0.205</td>
<td>0.302</td>
</tr>
</tbody>
</table>

Table 11: Showing the relationship between MVA gained after PBMV to MES1 & MES2.

<table>
<thead>
<tr>
<th>MVA after PBMV</th>
<th>r</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MES1</td>
<td>Group A</td>
<td>-0.420</td>
</tr>
<tr>
<td>Group BII</td>
<td>-0.578</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>MES2</td>
<td>Group A</td>
<td>-0.441</td>
</tr>
<tr>
<td>Group BII</td>
<td>-0.397</td>
<td>0.011*</td>
</tr>
</tbody>
</table>
Relationship between MVA gained after balloon mitral valvuloplasty to valve morphology and balloon type:

There was no significant difference as regard the type of the balloon used in procedure to increase MVA. However; there was a significant relationship between the increase in MVA and the mitral valve echo score (Tables 10,11).

Complications:

In group A, one patient developed cerebral thromboembolic event and died after two days. While two patients developed minor complications; one patient had a significant hematoma and one patient developed rapid atrial fibrillation and required DC shock.

In group BII, two patients had severe mitral regurgite after the procedure: One patient required emergency cardiac surgery and one patient was kept on medications. While three patients developed minor complications; one patient developed ventricular tachycardia and required DC shock, one patient had drug reaction and one patient had vasovagal reaction. There was no significant difference between the two groups either in major or minor complications.

Discussion

Percutaneous balloon mitral valvotomy (PBMV) was introduced in 1984 by Inoue who developed the procedure as a logical extension of surgical closed commissurotomy. Since then, it has emerged as the treatment of choice for severe pliable rheumatic mitral stenosis. With increasing experience and better selection of patient, the immediate results of the procedure have improved and the rate of
Redo Percutaneous Balloon Mitral Valvuloplasty

complications declined. Complication rates compare favorably to those reported after surgical commissurotomy [3]. Several randomized trials reported similar hemodynamic results with percutaneous balloon mitral valvuloplasty and surgical commissurotomy [3-4]. Restenosis after PMBV ranges from 4 to 70% depending on the patient selection, valve morphology, post procedure MVA and duration of follow-up [9].

The aim of our study was to assess the immediate results of repeated percutaneous balloon mitral valvuloplasty in patients with mitral restenosis after previous successful PMBV.

Our study included 70 patients from those referred to Ain Shams University and National heart institute, Cairo, Egypt and were candidates for percutaneous balloon mitral valvuloplasty over the period from May 2006 to April 2007. Patients were classified into two groups, 30 patients (group A) underwent the procedure for the first time and 40 patients (group BII) underwent a redo procedure for mitral restenosis after previous successful percutaneous balloon mitral valvuloplasty.

The immediate outcome of PMBV for patients who had restenosis was satisfactory, with a 92.5% success rate (group BII) compared with 93.33% in patients who underwent PMBV as an initial procedure (group A), (p=NS). This finding concurs with the study done by Fawzy et al [10], where he found the immediate success rate 93% in patients who underwent PMBV as a redo procedure and 96% in patients in patients who underwent PMBV as an initial procedure (p=NS). Also this result is consistent with the study done by Jang et al [12], Iung et al [11]. But this is different from the study done by Pathan et al [13], where the success rate was 75% and this is because they included older patients at a mean age of 58 years with more deformed valves; 50% had Wilkins's echocardiographic score >8 and 77% had valve calcification [13].

The mean mitral gradient decreased significantly in both groups, It is decreased from 16.2±5.8 to 5.6±2.4mm Hg in group A and from 16.29±5.2 to 5.74±2.68mm Hg in group BII, without significant difference (p=0.870). This is consistent with the study done by Fawzy et al [10], where mean transmitral gradient decreased from 14±2 to 5±2mm Hg in the group underwent percutaneous balloon mitral valvuloplasty for the first time and from 15±3 to 6±3mm Hg in the group underwent a redo procedure (p=0.13). Also this is consistent with the study done by Iung et al [11] and Jang et al [12].

The right ventricular systolic pressure (RVSP) decreased significantly in both groups. It is decreased from 52.3±19.28 to 40.6±16.3mm Hg in group A and from 47.6±12.9 to 37.1±11.2mm Hg in group BII, without significant difference (p=0.338). This is consistent with the study done by Pathan et al [13], where pulmonary artery pressure decreased from 49±17 to 40±14mm Hg in the group which underwent percutaneous balloon mitral valvuloplasty for the first time and from 49±21 to 41±18.2mm Hg in the group underwent a redo procedure (p=0.79). Also this is consistent with the study done by Iung et al [12] and Jang et al [11].

The final mitral valve area increased significantly in both groups, it increased from 1.2±1.1 to 1.92±0.4cm² in group A and from 1.03±0.13 to 1.7±0.3cm² in group BII and as shown, it is small but significant difference observed in the final MVA that favored group A (p=0.016). This concurs with that obtained by Fawzy et al [10], where MVA increased from 0.83±0.02 to 1.8±0.5cm² in the group under-went percutaneous balloon mitral valvuloplasty for the first time and from 0.78±0.16 to 1.6±0.6cm² in the group underwent it as a redo procedure and also significant difference in the final mitral valve area was in favor of the group underwent the procedure for the first time (p=0.01).

In our study, there was also a significant difference in the percentage of mean increase in favor of group A; (97.71±51.81% in group A Vs. 68.074±31.371% in group BII, p=0.004).

Fawzy et al, found that these differences were no longer observed when patients who had favorable echocardiographic scores were compared; as 50% of patients had mitral valve echo score >8 in the redo group, while only 34% of patients had score >8 in the first group. In our study there was no significant difference in the score between the two groups, but the difference in the final mitral valve area in favor of group A may be due to the larger baseline MVA in group A as it was 1.2±1.1cm² VS. 1.03±0.13cm² in group BII and the possibility of more fibrosis in the group underwent redo PMBV [10].

When comparing the initial available data of the first procedure of group B (group BI) to their redo data obtained in this study (group BII), the mean mitral gradient decreased significantly after
procedure, without significant difference between both groups ($p=0.9$). But there was a small but significant difference as regard the final mitral valve area, $[1.7±0.3cm^2$ (group BII) Vs. $1.9±0.35cm^2$ (group BI), $p=0.012$] and also the percentage of mean increase in MVA was strikingly different in favor of the initial procedure, ($96±37\%$ in group BI Vs. $68±31\%$ in group BII, $p=0.001$).

By retrospective analysis of the available data of group B, we found some important factors that determine the time to redo percutaneous balloon mitral valvuloplasty or restenosis e.g. post procedure increment in mitral valve area and low echo score were important factors that predict freedom from restenosis. As regard post procedure mitral valve area, $p=0.004$ and as regard mitral echo score, $p=0.008$ and this is consistent with Ben Farhat et al [14].

We found also that, patients in sinus rhythm were free from restenosis more significantly than those in AF ($p=0.009$) and this is consistent with that found by Langerfeld et al [15], as they reported that, presence of chronic AF before percutaneous balloon mitral valvuloplasty to be an independent predictor of restenosis. Another important factor that significantly determine the freedom from restenosis is long acting penicillin therapy (LAP) ($p=0.007$) and this is may be explained by prevention of rheumatic fever recurrence which may be a possible cause of restenosis after procedure.

This finding is supported by the study done by Nigri et al [16], where they found that one of the potential mechanisms responsible for more rapid restenosis after valvuloplasty is rheumatic fever recurrence. By multivariate analysis of the different factors which determine time to redo PBMV or restenosis, it was found that MV morphology (mitral echo score 2) is the most powerful predictor of redo procedure; ($p=0.008$).

Other investigators found also other important factors which determine rate of restenosis e.g. Kang et al [17] found the development of commissural splitting and commissural mitral regurgitation (CMR) were a significant independent predictors of restenosis-free survival and serial post-procedural mitral valve areas were significantly different between patients with and without CMR after PBMV. The annual decrease of post dilation mitral valve area was also significantly smaller in the patients with, than those without, CMR. Langerveld et al [18] found the presence of high transmitral gradient immediately after dilatation to be an independent predictor of restenosis.

The achievement of complete commissurotomy with development of CMR or larger post-PBMV mitral valve area is important to optimize the long-term results of PBMV [17]. In our study there was no difference in obtaining larger post-PBMV mitral valve area as regard the type of balloon used whether Inoue balloon or multi-track system; $p=0.703$ in group A and $p=0.764$ in group BII. This concurs with the study done by Kang et al [17] where he found that, the Inoue and double-balloon techniques were equally effective in commissurotomy and produced similar, excellent long-term results. In fact, the production of post-PBMV mitral valve area was largely dependent on the mitral valve morphology and this consistent with the study done by Wilkins et al [19], Fawzy et al [10] and Pathan et al [13]. Turgeman et al [20] reported that valve morphology is the main predictor of first PBMV and commissural morphology and chordae tendineae length are better predictors of outcome than Wilkins's echocardiographic score in patients with mitral restenosis.

In our study there was no significant difference as regard the incidence of major complications between group A and group BII ($p=0.97$). Two patients in group BII developed severe mitral regurgle (≥3/4), one of them had severe regurgle 4/4 and underwent urgent mitral valve replacement, this patient had significant subvalvular disease, mitral valve echo score 1 and 2, 6/12 and 10/16, respectively. The second patient had severe mitral regurgle 3/4 and was kept on medical treatment and follow-up. In group A: one patient developed cerebral thromboembolic stroke and died after two days, although his transesophageal echo done and no left atrial or left atrial appendage thrombi have been detected. This insignificance in complications between both groups concurs with the study done by Fawzy et al [10].

In conclusion, the present study showed good immediate outcome for redo percutaneous balloon mitral valvuloplasty and the low risk of incidence of in-hospital adverse events. The results of redo PBMV are comparable to that of the first procedure.

It is clear that the mitral valve morphology gets worse by time so that the mitral valve area obtained by the redo PBMV may be a little bit less than the initial one. A new finding in this study was that using long acting penicillin may be usefull in delaying mitral restenosis.
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References


Predictors of Immediate Failure of Percutaneous Balloon Mitral Valvuloplasty, Insights from a Pooled Analysis of Egyptian Experience

HANY M AWADALLA, MD; FSCAI

**Background:** Rheumatic mitral stenosis (MS) is still common in Egypt. Percutaneous balloon mitral valvuloplasty (PBMV) is commonly offered as a palliative treatment modality in such patients. Multiple studies have examined factors that affect the success in patients with mitral stenosis.

**Objective:** To demonstrate the impact of pre-procedural variables on the success rate of PBMV in the Egyptian experience.

**Methods:** 2170 Patients with mitral stenosis of rheumatic origin were enrolled, 291 males and 1879 females. Percutaneous mitral valvuloplasty was performed utilizing either Double Balloon technique or Inoue Balloon technique. Success was defined as a combination of postprocedural mitral valve area of ≥1.5cm², AND post-PBMV MR <3 Seller’s grade.

**Results:** The study population included 1879 females and 291 males whose age ranged from 11-69 years with mean age of 28.6±9.9 years. The mitral valve area increased from a mean value of 0.95cm² to 1.94cm² (p<0.0001). A successful PBMV, defined as a postprocedural MVA of ≥1.5cm², AND post-PBMV MR <3 Seller’s grade, was attained in 2000 patients (92.1%) [Group 1]. In this group, the MVA increased from 0.95cm² preprocedure to 1.99cm² postprocedure. Failure of PBMV was observed in 170 patients (7.8 %) [Group 2]. In this group, the MVA increased from a mean of 0.85cm² preprocedure to a mean of 1.28cm² postprocedure. Univariate predictors of failure were: Older age (p=0.002), female gender (p=0.01), a higher echo score (p=0.001), higher degree of mitral calcification (p=0.001), baseline atrial fibrillation (p=0.03), higher left atrial dimension (p=0.005) and a preprocedural mitral regurgitation ≥ 2 (p=0.03). Multiple stepwise logistic regression analysis identified female gender, mitral calcification and baseline atrial fibrillation as independent predictors of immediate procedural failure of PBMV.

**Conclusion:** Pre-BMV clinical and echocardiographic variables identify patients who would benefit from PBMV. The current analysis underscores the importance of scrutinizing such variables closely before performing PBMV, to identify patients who are less likely to benefit from such a procedure.

**Key Words:** Left atrial size – Atrial fibrillation – Mitral regurgitation – Mitral stenosis – Balloon mitral valvuloplasty.

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**Introduction**

Balloon mitral valvuloplasty (BMV) has been established to be an effective non-surgical therapeutic technique that can be used as an alternative measure for symptomatic relief in patients with MS and favorable anatomy [1]. BMV results in an immediate improvement in the mitral valve area (MVA) and pulmonary artery (PA) pressure with substantial further improvement at 6 months follow-up [2-4]. Previous scoring and evaluation systems have focused on the anatomy and pathology of the mitral valve leaflets and the subvalvular apparatus [5,6]. It is possible that other factors may influence the success and complication rate in patients not directly related to the mitral valve complex. These factors may include age, sex, rhythm, left atrial (LA) dimensions and left ventricular size, New York Heart Association (NYHA) functional class, a history of previous mitral commissurotomy (MC), inter-atrial septum (IAS) anatomy, IAS thickness and geometry and MV plane relationship to the IAS plane and IAS puncture site [6].

**Objective:**

To study the impact of pre-procedural variables on the success rate of PBMV in patients with rheumatic MS in the Egyptian experience.
Methods

Study population:

This is a pooled analysis of all observational and case-control studies of PBMV performed between 1991 and 2005 from nine Egyptian centers for which data were available. Using the primary patient-level data from each study, data were combined to obtain a pooled estimate of the results of PMV in Egypt. All demographic, clinical, and technical data were collected using the “Data Collection Form” and entered into a computerized database. Data obtained from all patients were statistically analyzed. Continuous variables were compared using analysis of variance (ANOVA) for repeated measures. The Fischer-exact chi square test with was used for comparison of categorical variables. p-value <0.05 was considered statistically significant. All data were expressed as mean ± standard deviation (mean ± SD) or number (%) as appropriate. A logistic regression model was used to analyze factors independently associated with failure of BMV (age, female gender, higher echo-score, higher degree of mitral calcification and subvalvular affection, baseline atrial fibrillation, higher left atrial dimension and preprocedural mitral regurgitation ≥2).

Technique of PMV:

PMV was performed using the double-balloon or the Inoue techniques, as previously described [7-10]. Left ventriculography was performed before and after PMV to assess the severity of mitral regurgitation (MR) using the Sellers’ classification [11]. The effective balloon-dilating area (EBDA) of the balloons used was calculated with standard geometric formulas and normalized by body surface area (EBDA/BSA) as previously described [8,12]. Severity of mitral valve calcification under fluoroscopy was graded from 0 (none) to 4 (severe), as previously described [8,13].

Results

All patients included in the current analysis had rheumatic mitral stenosis, 1879 females (86.6%) and 291 males (13.4%). The age range was 11 to 69 years, with a mean age of 28.6±9.9 years. Data on mitral valve morphology were available in 1849 patients (85%). The mean echoscore was 7.05±1.87cm² for the entire study cohort. The mitral valve area was assessed by at least two techniques: Mitral valve pressure half time and mitral valve planimetry in parasternal short axis view. The mean preprocedural mitral valve area assessed by pressure half time was 0.95±0.18cm², as opposed to 0.94±0.18cm² by planimetry (p>0.05). Choice of technique for mitral valvuloplasty was operator’s preference and availability of equipment. Table (1) summarizes the baseline clinical, echocardiographic and hemodynamic variables among 2170 patients included in the current analysis.

Among 2170 patients included in the current analysis, 618 patients (28.5%) were in atrial fibrillation (AF), 1552 (71.5%) patients were in sinus rhythm (NSR). Patients in sinus rhythm had a baseline mitral valve area of 0.95±0.28cm², as opposed to 0.93±0.2cm² in patients in atrial fibrillation cm² (p=NS). Post-valvuloplasty mitral valve area was 1.95±0.39cm² for patients in NSR, as opposed to 1.91±0.39cm² for patients in AF (p<0.05). Patients in AF were older (32±10.9 years Vs. 27.2±9.1 years, p<0.01), had a higher echoscore (7.6±1.98 Vs. 6.8±1.7, p<0.05), a higher degree of mitral calcification (1.6±1.1 Vs. 0.95±1, p<0.05), were more commonly males (15.8% Vs. 12.4%, p=NS), had a higher percentage of previous surgical commissurotomy (9.7% Vs. 4.2%, p<0.05) and a higher degree of prevalvuloplasty mitral regurgitation (0.43±0.55 Vs. 0.32±0.52, p<0.05).

Among 2170 patients included in the current analysis, 1879 were females (86.6%) and 291 were males (13.4%). Males were marginally younger (28.5±10.8 Vs. 28.6±9.7, p=NS), had more frequent atrial fibrillation (33.7% Vs. 27.8%, p<0.05), had a higher prevalence of previous mitral commissurotomy (3.8% Vs. 6.1%, p<0.05), higher total score (7.5±1.8 Vs.7.1±1.5, p=NS), higher degree of mitral calcification (1.3±1 Vs. 1.1±1, p=NS), smaller LA dimension (45±7.7mm Vs. 46.6±6.5mm, p=NS), a lower pre-valvuloplasty mitral valve area (0.91±0.16cm² Vs. 0.95±0.27cm², p=NS) and a lower degree of pre-valvuloplasty mitral regurgitation (0.29±0.47 Vs. 0.36±0.54, p=NS). Tables (2,3) summarize the differences in baseline clinical and echocardiographic variables among patients in sinus rhythm versus atrial fibrillation, as well as among male and female patients.

Among 2170 included in this analysis, the mitral valve area increased from a mean value of 0.95±0.26m² to 1.93±0.39cm² (p<0.0001). Success, defined as a combination of mitral valve area ≥1.5cm² AND post-PBMV MR < 3 Seller’s grade, was observed in 92.2% (n=2000) [Group 1], while in 7.8% of patients (n=170), one or both criteria were not fulfilled [Group 2]. In group 1, the MVA
increased from 0.95±0.26cm² preprocedural to 1.99±0.35cm² postprocedural (p<0.05), whereas in group 2, the MVA increased from 0.85±0.18cm² preprocedural to 1.28±0.21cm² postprocedural. Table (4) summarizes differences in baseline clinical and echocardiographic variables between groups 1 and 2.

**Table 1:** Baseline clinical, echocardiographic and hemodynamic variables among 2170 patients included in the current analysis.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>28.6±9.9</td>
</tr>
<tr>
<td>Male Gender n (%)</td>
<td>291 (13.4%)</td>
</tr>
<tr>
<td>Previous Commissurotomy</td>
<td>125 (5.8%)</td>
</tr>
<tr>
<td>Sinus Rhythm</td>
<td>1550 (71.4%)</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>620 (28.6%)</td>
</tr>
</tbody>
</table>

**Echocardiographic Assessment:**

- MVA by 2D: 0.94±0.18
- MVA by PHT: 0.95±0.18
- Mean Pressure Gradient: 16±5.5
- Mitral Regurgitation: 0.35±0.5
- Left Atrial Dimension: 46.4±6.8
- Total Echoscore (TTE): 7.05±1.87
- Thickness: 2.1±0.6
- Mobility: 1.89±0.6
- Calcification: 1.1±1.1
- Subvalvular affection: 2.1±0.9

**Invasive assessment:**

- LAP (mmHg): 27.9±7.6
- MPAP (mmHg): 18.4±6.2
- LVEDP (mmHg): 11.1±4.6
- mPAP (mmHg): 44.8±15.6
- sPAP (mmHg): 64.1±18.8
- RAP (mmHg): 9.6±4.4

**Table 2:** Baseline clinical and echocardiographic variables among 2170 patients included in the current analysis; comparison between patients with a baseline sinus rhythm (NSR) as opposed to patients with atrial fibrillation (A Fib).

<table>
<thead>
<tr>
<th>Variable</th>
<th>NSR</th>
<th>A Fib</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>1552 (71.5%)</td>
<td>618 (28.6%)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Age (years)</td>
<td>27.2±9.1</td>
<td>32±10.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Male Gender n (%)</td>
<td>193/1552 (12.4%)</td>
<td>98/618 (15.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Prev. Commissurotomy n (%)</td>
<td>65/1552 (4.2%)</td>
<td>60/618 (9.7%)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**Echocardiographic assessment:**

- MVA by 2D: 0.95±0.28cm² 0.93±0.20cm² NS
- Mitral Regurgitation: 0.32±0.52 0.43±0.55 <0.05
- Left Atrial Dimension: 46±6.8 47±8.2 <0.05
- Total Echoscore (TTE): 6.8±1.8 7.6±1.98 <0.05
- Calcification: 0.95±1 1.6±1.1 <0.05

**Table 3:** Baseline clinical and echocardiographic variables among 2170 patients included in the current analysis; comparison between male and female patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Males</th>
<th>Females</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>291 (13.4%)</td>
<td>1879 (86.6%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Age (years)</td>
<td>28.5±10.8</td>
<td>28.5±7.7</td>
<td>NS</td>
</tr>
<tr>
<td>Atrial Fibrillation n (%)</td>
<td>98/291 (33.7%)</td>
<td>522/1879 (27.8%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Prev. Commissurotomy n (%)</td>
<td>11/291 (3.8%)</td>
<td>114/1879 (6.1%)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**Echocardiographic assessment:**

- MVA by 2D: 0.91±0.16cm² 0.95±0.27cm² NS
- Mitral Regurgitation ≥2: 0.29±0.47 0.36±0.54 NS
- Left Atrial Dimension: 45±7.7 46.6±6.5 NS
- Total Echoscore (TTE): 7.5±1.8 7±1.85 NS
- Calcification: 1.3±1 1.1±1 NS

**Table 4:** Baseline clinical and echocardiographic variables among 2170 patients included in the current analysis; comparison between group 1 (successful PBMV) and group 2 (unsuccessful PBMV).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (n=2000)</th>
<th>Group 2 (n=170)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>28.3±9.87</td>
<td>30.6±10</td>
<td>0.002</td>
</tr>
<tr>
<td>Male Gender n (%)</td>
<td>273 (13.7%)</td>
<td>18 (10.6%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Previous</td>
<td>107 (5.4%)</td>
<td>18 (10.5%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Commissurotomy</td>
<td>1445 (72.3%)</td>
<td>107 (62.9%)</td>
<td>0.029</td>
</tr>
<tr>
<td>Sinus Rhythm</td>
<td>555 (27.7%)</td>
<td>63 (37.1%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>0.36±0.24</td>
<td>0.36±0.24</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Echocardiographic assessment:**

- MVA by 2D: 0.94±0.26 0.85±0.18 NS
- Mitral Regurgitation ≥2: 21/1069 (1.96%) 3/58 (5.2%) 0.03
- Left Atrial Dimension: 46±6.9 49±6.7 0.005
- Total Echoscore (TTE): 7±1.8 7.6±2.05 0.001
- Thickness: 2.1±0.61 2.05±0.59 NS
- Mobility: 1.87±0.63 1.88±0.61 NS
- Calcification: 1.08±1.03 1.74±1.3 0.001
- Subvalvular affection: 2.06±0.85 2.04±0.9 NS

Univariate analysis demonstrated that failure of PBMV was significantly correlated with older age (p=0.002), female gender (p=0.01), a higher echo score (p=0.001), higher degree of mitral calcification (p=0.001), baseline atrial fibrillation (p=0.03), higher left atrial dimension (p=0.005) and a preprocedural mitral regurgitation ≥2 (p=0.03). Multiple stepwise logistic regression analysis demonstrated that female gender, mitral
calcification and baseline atrial fibrillation were independent predictors of failure of PBMV. Univariate and multivariate predictors of failure are summarized in Tables (5,6).

Pre and Post-PBMV MVA as well as success rates for PBMV were stratified according to the total echoscore. Table (7) and Fig. (1) summarize these findings. Table (8) and Fig. (2) demonstrate success rates for PBMV in relation to cutoff points of the total echoscore (8≥8), calcification (2≥2), mobility (2≥2), thickening (2≥2) and subvalvular affection (2≥2). Tables (9-11) and Figs. (3-5) shed some light on the outcomes of PBMV in patients with differing degrees of mitral calcification, thickening, mobility and subvalvular affection. Mitral calcification appears to have had the greatest impact on the outcome of PBMV among the four criteria included in the Wilkin’s score. This is clearly demonstrable statistically, as mitral calcification remained as an independent predictor of failure of PBMV.

**Table 5**: Univariate predictors of immediate failure of PBMV.

<table>
<thead>
<tr>
<th>Variable</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older Age</td>
<td>0.002</td>
</tr>
<tr>
<td>Female Gender</td>
<td>0.01</td>
</tr>
<tr>
<td>Higher Total Echoscore</td>
<td>0.001</td>
</tr>
<tr>
<td>Higher Degree of Mitral Calcification</td>
<td>0.001</td>
</tr>
<tr>
<td>Baseline Atrial Fibrillation</td>
<td>0.03</td>
</tr>
<tr>
<td>Preprocedural Mitral Regurgitation</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**Table 6**: Independent predictors of immediate failure of PBMV (multiple stepwise logistic regression analysis).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>6.08</td>
<td>3.5 12.2</td>
<td>0.015</td>
</tr>
<tr>
<td>Mitral Calcification</td>
<td>3.01</td>
<td>1.6 4.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>Baseline AF</td>
<td>2.26</td>
<td>1.4 3.1</td>
<td>0.014</td>
</tr>
</tbody>
</table>

**Table 7**: Pre and Post-PBMV, Success rates for PBMV stratified according to the total echoscore.

<table>
<thead>
<tr>
<th>Total Echoscore</th>
<th>Success Rate</th>
<th>Pre-MVA (Mean ± SD)</th>
<th>Post-MVA (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>93.5% (29/31)</td>
<td>1.01±0.25</td>
<td>2.2±0.4</td>
</tr>
<tr>
<td>4</td>
<td>95% (75/79)</td>
<td>1.02±0.22</td>
<td>2±0.4</td>
</tr>
<tr>
<td>5</td>
<td>93.7% (224/239)</td>
<td>0.99±0.2</td>
<td>2±0.45</td>
</tr>
<tr>
<td>6</td>
<td>96.7% (412/426)</td>
<td>0.95±0.18</td>
<td>1.96±0.3</td>
</tr>
<tr>
<td>7</td>
<td>94% (364/387)</td>
<td>0.95±0.17</td>
<td>1.98±0.4</td>
</tr>
<tr>
<td>8</td>
<td>89% (273/306)</td>
<td>0.94±0.2</td>
<td>1.93±0.89</td>
</tr>
<tr>
<td>9</td>
<td>94.6% (178/188)</td>
<td>0.92±0.18</td>
<td>1.9±0.3</td>
</tr>
<tr>
<td>10</td>
<td>84.6% (110/130)</td>
<td>0.88±0.16</td>
<td>1.84±0.37</td>
</tr>
<tr>
<td>11</td>
<td>81% (38/47)</td>
<td>0.86±0.22</td>
<td>1.75±0.46</td>
</tr>
<tr>
<td>12 or higher</td>
<td>84% (21/25)</td>
<td>0.89±0.17</td>
<td>1.75±0.45</td>
</tr>
</tbody>
</table>

**Figure 1**: Success rates for PBMV stratified according to the total echoscore.

**Table 8**: Success rates for PBMV in relation to the total echoscore, calcification, mobility, thickening and subvalvular affection.

<table>
<thead>
<tr>
<th>Echoscore</th>
<th>% of PBMV Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤8</td>
<td>93.7% (1374/1465)</td>
</tr>
<tr>
<td>&gt;8</td>
<td>88.9% (346/389)</td>
</tr>
<tr>
<td>Echo-Calcification ≤2</td>
<td>94.3% (931/987)</td>
</tr>
<tr>
<td>Echo-Calcification &gt;2</td>
<td>75% (107/142)</td>
</tr>
<tr>
<td>Echo-Mobility ≤2</td>
<td>92% (904/982)</td>
</tr>
<tr>
<td>Echo-Mobility &gt;2</td>
<td>91.2% (136/149)</td>
</tr>
<tr>
<td>Echo-Thickness ≤2</td>
<td>91.6% (826/902)</td>
</tr>
<tr>
<td>Echo-Thickness &gt;2</td>
<td>93.4% (214/229)</td>
</tr>
<tr>
<td>Echo-Subvalvular ≤2</td>
<td>92.7% (752/811)</td>
</tr>
<tr>
<td>Echo-Subvalvular &gt;2</td>
<td>90.9% (319/351)</td>
</tr>
</tbody>
</table>

**Figure 2**: Success rates for PBMV in relation to the total echoscore, calcification, mobility, thickening and subvalvular affection.
Table 9: Mitral Calcification Vs. mitral thickening in successful and failed cohorts.

<table>
<thead>
<tr>
<th></th>
<th>MV Thickening (Mean ± SD)</th>
<th>MV Calcification (mean ±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful PBMV + MV Thickening ≤2</td>
<td>1.83±0.37</td>
<td>0.95±0.98</td>
</tr>
<tr>
<td>Successful PBMV + MV Thickening &gt;2</td>
<td>3.1±0.26</td>
<td>1.6±1.1</td>
</tr>
<tr>
<td>Successful PBMV (Entire Cohort)</td>
<td>2.09±0.61</td>
<td>1.09±1.05</td>
</tr>
<tr>
<td>Failed PBMV + MV Thickening ≤2</td>
<td>1.83±0.38</td>
<td>1.5±1.28</td>
</tr>
<tr>
<td>Failed PBMV + MV Thickening &gt;2</td>
<td>3.1±0.35</td>
<td>2.8±1</td>
</tr>
<tr>
<td>Failed PBMV (Entire Cohort)</td>
<td>2.04±0.61</td>
<td>1.74±1.3</td>
</tr>
</tbody>
</table>

Table 10: Mitral Calcification Vs. mitral mobility in successful and failed cohorts.

<table>
<thead>
<tr>
<th></th>
<th>MV Mobility (Mean ± SD)</th>
<th>MV Calcification (Mean ±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful PBMV + MV Mobility ≤2</td>
<td>1.7±0.48</td>
<td>1.01±1.03</td>
</tr>
<tr>
<td>Successful PBMV + MV Mobility &gt;2</td>
<td>3±0.12</td>
<td>1.6±1</td>
</tr>
<tr>
<td>Successful PBMV (Entire Cohort)</td>
<td>1.87±0.63</td>
<td>1.09±1.05</td>
</tr>
<tr>
<td>Failed PBMV + MV Mobility ≤2</td>
<td>1.71±0.46</td>
<td>1.67±1.31</td>
</tr>
<tr>
<td>Failed PBMV + MV Mobility &gt;2</td>
<td>3</td>
<td>2.15±1.34</td>
</tr>
<tr>
<td>Failed PBMV (Entire Cohort)</td>
<td>1.89±0.61</td>
<td>1.74±1.3</td>
</tr>
</tbody>
</table>

Table 11: Mitral Calcification Vs. mitral subvalvular affection in successful and failed cohorts.

<table>
<thead>
<tr>
<th></th>
<th>MV Subvalvular (Mean ± SD)</th>
<th>MV Calcification (Mean ±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful PBMV + MV Subvalvular ≤2</td>
<td>1.63±0.6</td>
<td>1.0±1</td>
</tr>
<tr>
<td>Successful PBMV + MV Subvalvular &gt;2</td>
<td>3.1±0.25</td>
<td>1.25±1.1</td>
</tr>
<tr>
<td>Successful PBMV (Entire Cohort)</td>
<td>2.1±1.8</td>
<td>1.09±1.05</td>
</tr>
<tr>
<td>Failed PBMV + MV Subvalvular ≤2</td>
<td>1.43±0.64</td>
<td>1.8±1.3</td>
</tr>
<tr>
<td>Failed PBMV + MV Subvalvular &gt;2</td>
<td>3.2±0.37</td>
<td>1.63±1.34</td>
</tr>
<tr>
<td>Failed PBMV (Entire Cohort)</td>
<td>2±1</td>
<td>1.74±1.3</td>
</tr>
</tbody>
</table>
Predictors of Immediate Failure of Percutaneous Balloon Mitral Valvuloplasty

Discussion

This study confirms earlier reports that BMV results in good immediate hemodynamic and clinical improvement in most patients with mitral rheumatic stenosis [14,15]. This study identifies clinical and morphological factors that help predict immediate results after BMV. They include pre-BMV variables that were predictors of an unsuccessful procedure: Older age \( (p=0.002) \), female gender \( (p=0.01) \), a higher echo score \( (p=0.001) \), higher degree of mitral calcification \( (p=0.001) \), baseline atrial fibrillation \( (p=0.03) \), higher left atrial dimension \( (p=0.005) \) and a preprocedural mitral regurgitation \( \geq 2 \) \( (p=0.03) \). The use of these factors in conjunction with the Echo score allows optimal selection of patients for BMV.

The wide use of PMC stresses the need to identify the predictive factors of the immediate results to improve the selection of candidates for this technique. Analyses of the predictors of immediate results of PMC have been performed in different single- or multi-centre series [16-19]. In multi-centre series, however, differences between centres, in particular in patient selection, grading of baseline characteristics and the experience of the operators, may influence the identification of the predictive factors.

Echocardiographic evaluation of the mitral valve is essential to predict immediate and long-term follow-up results of candidates for BMV. Echocardiographic assessment of risk scores involving semi-quantitative assessment of leaflet thickening, subvalvular change, leaflet mobility and valve calcification, emphasized the importance of these characteristics [20]. It is now accepted that a favorable clinical and procedural outcome may be predicted in many subjects depending on the precise assessment of valve and commissural morphology and a number of clinical and procedural variables [21].

Meanwhile, data from large series indicate that the prediction of outcome following PBMV is multifactorial and based not only on morphological characteristics of the valve but also on a number of clinical and procedural variables, including age, functional class, effective balloon dilating area and the final valve area [22,23]. Thus, balloon dilatation may well provide good immediate results in patients with adverse anatomy if other characteristics are favorable. Conversely, if other characteristics are not in favor, then mitral surgery should be considered as an alternative [19].

Another important factor influencing case outcome is the experience of the clinical team. In the study by Rihal et al [23], unfavorable outcomes appeared to be related to three factors: Presence of thick, calcified valve leaflets with extensive subvalvular involvement, poor general medical status and operator inexperience [23]. Several series have confirmed that complication rates are lower in high volume centers. BMV should be restricted to groups whose experience of transseptal catheterization has been positive and who have been able to carry out an adequate number of procedures to maintain technical competence [23].

Several studies have demonstrated that the degree of mitral commissural calcification is a stronger predictor of the outcome and early restenosis than the Wilkin’s score [24-27]. Rifaie et al, have devised a score that includes commissural calcification and subvalvular affection as the only anatomical variables affecting immediate outcome following PBMV. This score was validated on at least 162 patients [25,27]. In the current analysis, calcification was identified as an independent predictor of procedural failure. Calcification was associated with a three fold increase in the odds of failure after correction for baseline variables.

In the current analysis, female gender was identified as the strongest independent predictor of failure of PBMV. After correction for baseline variables, female gender was associated with a six folds increase in the odds of immediate failure. There are scarce, yet similar data in the literature as to the effect of gender on the outcome of PBMV. Palacios et al [14] have identified male gender as both a univariate and independent predictor of immediate success following PBMV. This is despite that fact that calcification of the valves tends to occur later in women than in men, providing a longer time window in which balloon valvuloplasty can be performed. One likely explanation for the worse outcomes in females in the current analysis is the possibility that most valvuloplasties performed during the early learning curve of the procedure in Egypt were on females, which might have reflected on outcomes. Another explanation is the possibility that since males in this analysis had more unfavorable clinical and morphologic baseline characteristics, their procedures were assigned to more experienced operators. The impact
of operator experience on outcome of PBMV has been well documented in the past [23].

This study identified AF as significantly associated with a higher incidence of immediate procedural failure. Stepwise logistic regression analysis identified AF as a strong independent predictor of procedural failure. AF was associated with approximately two increases in the odds of failure, after correction for baseline variables. Previous studies on the effect of AF on the immediate success and long-term outcome after BMV were controversial. The negative influence of AF was also demonstrated in a group of patients with echocardiographic scores ≥10, where AF was the only predictor of sub-optimal result [28], as well as in a subgroup of patients with previous surgical commissurotomy, where AF was an independent predictor of immediate and short-term outcome. Awadalla et al. reported that AF unfavorably influences the immediate outcome of BMV, even after correction for associated unfavorable clinical and morphologic features [29]. Hung et al. (1991) reported that AF was an independent predictor of suboptimal immediate result but not an independent predictor by multivariate analysis [15]. Lung et al. (1996) identified sinus rhythm as univariate predictor of good functional results five years after a successful procedure, but the multivariate analysis failed to demonstrate rhythm as an independent predictor of long-term success [20]. Pan et al. (1993) identified the presence of AF as an independent predictor of late success [30]. Conversely, in the larger series from the NHLBI registry of percutaneous balloon mitral commissurotomy, AF was not an independent predictor of procedural success or long-term outcome at 4 years of follow-up [18]. Other reports also did not reveal any association between AF and suboptimal immediate or long-term outcome after percutaneous balloon valvuloplasty [31]. The inconsistency of the results of these studies is more likely explained by the size of the patient population included in each study as well as different baseline clinical and morphologic characteristics of the patients. Leon et al. (1999), reported that BMV in patients with AF resulted in inferior immediate and long-term outcomes, as reflected in a smaller post-BMV mitral valve area (1.7±0.7 Vs. 2±0.7cm²; p<0.0001) and a lower event free survival (freedom of death, redo-BMV and mitral valve surgery) at a mean follow-up time of 60 months (32% Vs. 61%; p<0.0001). These results led them to conclude that patients with AF have worse immediate and long-term outcomes after BMV [28]. However, they found that in patients in AF, severe post-BMV mitral regurgitation (≥3+) (p=0.0001), echocardiographic score >8 (p=0.004) and pre-BMV NYHA class IV (p=0.046) were identified as independent predictors of combined events at follow-up. They concluded that the presence of AF by itself does not unfavorably influence the outcome, but is a marker for clinical and morphologic features associated with inferior results after BMV [28].

In the present study MR was associated with a higher incidence of procedural failure in univariate analysis. This is in accordance with the report by Zhang et al., (1998) [32]. A possible explanation may be that, in the presence of pre-existing MR, operators may have a tendency to perform BMV with as small a risk of increasing the MR as possible by the adaptation of an undersized, less aggressive "palliative approach". This palliative approach is generally supported by the use of smaller balloons, less inflations and a ready acceptance of a suboptimal final valve area (1.0-1.5cm²), especially when initial dilatation is associated with the development of mild, well tolerated mitral regurgitation [32]. This may translate into less success in dilating the valve. This hypothesis needs to be tested in a prospective study that looks at the final balloon to annulus ratio, the balloon inflation pressures and the number of inflations, in order to evaluate the independent effect of MR on success.

**Conclusion**

In conclusion, the present study demonstrated that failure of PBMV was significantly correlated with: Older age (p=0.002), female gender (p=0.01), a higher echo score (p=0.001), higher degree of mitral calcification (p=0.001), baseline atrial fibrillation (p=0.03), higher left atrial dimension (p=0.005) and a preprocedural mitral regurgitation ≥2 (p=0.03). Multiple stepwise logistic regression analysis demonstrated that female gender, mitral calcification and baseline atrial fibrillation were independent predictors of failure of PBMV.

This study emphasizes the need to adopt a new scoring system that incorporates clinical as well as anatomic variables related to mitral valve morphology as predictors of outcome following PBMV. Among these morphologic variables, mitral calcification remains the most reliable (and independent) predictor of failure of percutaneous mitral valvuloplasty.
References


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27. Awadalla H, Abdel-Rahman M, El-Nammwas W, Esmat E, Rifaie O: The value of a novel echocardiographic score of the mitral valve in predicting the outcome of percutaneous balloon mitral valvuloplasty, comparison with


Terlipressin Salvage in Catecholamine Resistant Septic Shock Patients

HATEM ELATROUSH, MD

**Background:** Severe sepsis is characterized by stimulation of series of inflammatory cascades leading to extensive cardiovascular derangements. Septic shock is characterized by arteriolar and venous vasodilation. Patients generally have a high cardiac output (CO) and low systemic vascular resistance (SVR). Effective hemodynamic and cardiac support is of crucial importance in the management of septic shock patients. Treatment is aimed at maintaining oxygen delivery above a critical threshold and at increasing mean arterial pressure (MAP) to a level that allows appropriate distribution of CO for adequate organ perfusion. In addition to an appropriate antimicrobial therapy, fluid expansion and vasopressors are the pivotal parts in the current treatment of sepsis. Terlipressin is a synthetic analogue of vasopressin. It has a similar pharmacodynamic profile but different pharmacokinetic properties. The half-life of arginine vasopressin is only 6 min, whereas that of terlipressin is 6 h.

**Objective:** This study was designed to evaluate, in septic shock patients with severe hypotension resistant to high-dose catecholamines and fluid resuscitation, the hemodynamic effects of terlipressin. The impact on renal, hepatic and pulmonary functions was also evaluated.

**Methods:** Seventeen patients were enrolled. The cause of septic shock was a documented infection in all patients. All patients presented with hypotension that failed to respond to fluid loading and high dose norepinephrine (>0.6 mcg · kg⁻¹ · min⁻¹). All patients had a systemic arterial catheter, a pulmonary artery catheter (Swan-Ganz catheter, Baxter Edwards) and esophageal Doppler probe to measure cardiac output and stroke volume. Hemodynamic parameters were calculated according to standard formulas. Full laboratory study was done for every patient. Transthoracic echocardiography was done to evaluate left ventricular functions and cardiac output was measured form Doppler data.

**Results:** After the introduction of terlipressin, significant increases in MAP, SVR and PVR were observed. The effect was consistent over the study period. Compared with the period when norepinephrine was used alone, CI and HR were significantly decreased. Stroke volume index remained constant and when plotted against PAOP (an index of preload), no significant changes were observed when terlipressin was added. Values of bilirubin, AST and ALT were significantly increased. Thrombocytes were significantly decreased and no change was observed in prothrombin time and PaO₂/FiO₂. Serum lactate concentrations were significantly decreased at 12 and 24 h. Urine flow (UF) was significantly improved. After use of terlipressin, the norepinephrine infusion rate was significantly decreased. Five out of 17 patients died of late multiple organ failure state during their intensive care unit stay (between day 5 and 12).

**Conclusion:** In conclusion, the use of terlipressin was associated with a significant increase in MAP in study patients with severe hypotension despite the use of high-dose norepinephrine and fluid resuscitation. Concomitantly a decrease in HR and CI was observed. Renal function, assessed by UF and serum creatinine level was improved.

**Key Words:** Terlipressin – Norepinephrine – Severe sepsis – Hypotension.
therapy, fluid expansion and vasopressors are the pivotal parts in the current treatment of sepsis [3]. Among catecholamines, norepinephrine is often favored because of its reliable effectiveness to achieve and maintain an adequate MAP in septic shock patients [4-8]. However, despite the use of high doses, norepinephrine may fail to restore blood pressure in some patients and alternative vaspressors such as epinephrine or phenylephrine are required but are not always effective [9,10]. Over time, vascular responsiveness to catecholamines diminishes and patients may die in intractable shock states [9,10]. The vascular hyporeactivity to catecholamines is caused, among other mechanisms, by excessive nitric oxide formation associated with an activation of ATP-sensitive K+ channels and reduction in Ca2+ entry through voltage-gated Ca2+ channels [11,12]. Thus, the search for alternative vaspressors, used alone or in combination with standard therapies, is of great importance.

Vasopressin has been studied in several clinical trials [12-14]. This drug mediates vasoconstriction via V1 receptors, coupled to phospholipase C and increases intracellular Ca2+ concentration. This action is not impaired during sepsis and thus, vasopressin has been shown effective to reverse catecholamine-resistant hypotension in septic shock patients [15-17]. Terlipressin is a synthetic analogue of vasopressin. It has a similar pharmacodynamic profile but different pharmacokinetic properties. The half-life of arginine vasopressin is only 6min, whereas that of terlipressin is 6h [15].

This study was designed to evaluate, in septic shock patients with severe hypotension resistant to high-dose catecholamines and fluid resuscitation, the hemodynamic effects of terlipressin. The impact on renal, hepatic and pulmonary functions was also evaluated.

Material and Methods

Informed consent was obtained from a next-of-kin before study enrollment.

Patient eligibility:

Recruited patients had to present a septic shock with hemodynamic instability (MAP <55mmHg) not responding to high dose norepinephrine (>0.6mcg · kg⁻¹ · min⁻¹) and adequate fluid resuscitation. Patients were considered to have refractory hypotension if they failed to respond within 60min to maximized therapy. Before and during norepinephrine infusion, patients received crystalloid fluid expansion to raise pulmonary artery occlussion pressure (PAOP) between 12 and 15mmHg. Norepinephrine was started at the dose of 0.2mcg · kg⁻¹ · min⁻¹ with 0.2mcg · kg⁻¹ · min⁻¹ increment every 10 minutes if no adequate response up to 0.6mcg · kg⁻¹ · min⁻¹. All patients received broad-spectrum antibiotic coverage. All patients received corticosteroids (hydrocortisone 50mg q.i.d.).

Exclusion criteria:

Patients were not eligible if they were pregnant, had known hypersensitivity to norepinephrine or terlipressin, had acute coronary artery disease, had Raynaud’s phenomenon, systemic sclerosis, esophageal disease, hepatic failure, or severe bleeding.

Patients:

Seventeen patients were enrolled. Clinical characteristics are presented in Table (1). The cause of septic shock was a documented infection in all patients. All patients presented with hypotension that failed to respond to fluid loading and high dose norepinephrine (>0.6mcg · kg⁻¹ · min⁻¹).

Measurements:

All patients had a systemic arterial catheter, a pulmonary artery catheter (Swan-Ganz catheter, Baxter Edwards) and esophageal Doppler probe to measure cardiac output and stroke volume. Hemodynamic parameters were calculated according to standard formulas. Full laboratory study was done for every patient including serum electrolytes, CBC, liver function tests, renal function tests, coagulation profile, arterial and venous blood gases. Transthoracic echocardiography was done to evaluate left ventricular functions and cardiac output was measured form Doppler data. Systemic vascular resistance (SVR) was calculated as the MAP minus.

Right atrial pressure divided by CO and multiplied by 80. Pulmonary vascular resistance (PVR) was calculated as the mean pulmonary artery pressure (PAP) minus pulmonary artery occlusion pressure divided by CO. Heart rate and intravascular pressures were recorded continuously. An indwelling urinary catheter was inserted in each patient. Baseline measurements were obtained at the highest dose of norepinephrine used (mean highest dose: 3.8mcg · kg⁻¹ · min⁻¹). Patients received a bolus of 1mg terlipressin (terlipressin acetate) every 12 hours for 48 hours. After stabilization, norepinephrine was titrated down to main-
tain MAP at a level determined by the attending physician (>65mmHg). Fluids were given to maintain PAOP constant. APACHE II and SOFA scores were used to evaluate the severity and expected outcome respectively. All data was measured at inclusion and every 12 hours for 24 hours.

**Statistics:**

Results are presented as mean ± SD. Two-way ANOVA for repeated measurements with post hoc Bonferroni tests were used. A \( p \) value less than 0.05 was chosen to reject the null hypothesis.

**Results**

Clinical characteristics of the study patients are presented in Table (1). Hemodynamic parameters are summarized in Table (2). After the introduction of terlipressin, significant increases in MAP, SVR and PVR were observed (Fig. 1). The effect was consistent over the study period. Compared with the period when norepinephrine was used alone, CI and HR were significantly decreased. Stroke volume index remained constant and when plotted against PAOP (an index of preload), no significant changes were observed when terlipressin was added (Fig. 2). Values of bilirubin, AST and ALT were significantly increased (Table 3). Thrombocytes were significantly decreased and no change was observed in prothrombin time and PaO\(_2\)/FiO\(_2\) (Table 3). Serum lactate concentrations were significantly decreased at 12 and 24h. Urine flow was significantly improved. After use of terlipressin, the norepinephrine infusion rate was significantly decreased (Table 2). Five out of 17 patients died of late multiple organ failure state during their intensive care unit stay (between day 5 and 12).

**Figure 1:** Significant increase in mean arterial blood pressure after starting terlipressin infusion.

**Figure 2:** Left ventricular function points during infusion of norepinephrine or terlipressin. SVI, stroke volume index; PAOP, pulmonary artery occlusion pressure. No significant change was observed.
Terlipressin Salvage in Catecholamine Resistant Septic Shock Patients

Table 1: Clinical characteristics of the 17 study patients (mean ± SD).

<table>
<thead>
<tr>
<th></th>
<th>Terlipressin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>55±14</td>
</tr>
<tr>
<td>Male/female</td>
<td>9/8</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>28±6</td>
</tr>
<tr>
<td>SOFA score</td>
<td>11±3</td>
</tr>
<tr>
<td>Type of infection:</td>
<td></td>
</tr>
<tr>
<td>Bronchopneumonia</td>
<td>5</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>6</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>2</td>
</tr>
<tr>
<td>Soft tissue infection</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 2: Hemodynamic variables (mean ± SD).

|                      | Norepinephrine | Terlipressin |
|----------------------|---------------|
|                      | 12h           | 24h          |
| HR (beats/min)       | 126±10        | 102±12*      |
| MAP (mmHg)           | 59±14         | 76±11*       |
| V O 2 (L·min⁻¹)      | 8±1.5         | 6±1.2**      |
| SVI (ml·beat⁻¹·m⁻²)  | 39±3          | 40±3         |
| PAOP (mmHg)          | 11±2          | 11±2         |
| SVR (dyn·s·cm⁻⁵)     | 513±87        | 992±90*      |
| PVRI (dyn·s·cm⁻⁵·m⁻²)| 295±137       | 330±117      |
| Norepinephrine (µg·kg⁻¹·min⁻¹) | 3.8±1.3 | 2.3±1.9** |

*p<0.01 versus norepinephrine.

Table 3: Laboratory parameters (mean ± SD).

|                      | Norepinephrine | Terlipressin |
|----------------------|---------------|
|                      | 12h           | 24h          |
| Bilirubin (mg·L⁻¹)   | 13.7±2.6      | 20.2±16.1*   |
| AST (U·L⁻¹)          | 105±90        | 210±167*     |
| ALT (U·L⁻¹)          | 83±89         | 223±192*     |
| Thrombocytes (1000 cells·L⁻¹) | 135±77 | 113±100* |
| Prothrombin time (s) | 26±19         | 27±15        |
| PaO₂/FiO₂             | 223±88        | 228±53       |

*p<0.01 versus norepinephrine.

AST = Aspartate aminotransferase.
ALT = Alanine aminotransferase.

Discussion

The main findings of the present study are the following: (a) in septic shock patients with hypotension not responding to high-dose norepinephrine and fluid resuscitation, MAP was significantly increased by the use of terlipressin; (b) the increase in MAP was accompanied by a significant decrease in CI; (c) mesenteric circulation was not evaluated, but liver function was affected with increases in bilirubin, AST and ALT; (d) renal function was improved with a significant increase in UF. In the treatment of septic shock it is essential to preserve sufficient tissue oxygenation [2-4]. This goal can be achieved only with an appropriate MAP and an adequate CI. In their study O’Brien et al, observed in septic shock patients a decrease in cardiac output after injection of a bolus of 1 or 2mg of terlipressin [15]. They did not report data on oxygen delivery and VO₂. In the present study, CI was also decreased after the onset of terlipressin. A simultaneous decrease in HR probably explains the decrease in CI because SVI remained unchanged. Also, myocardial performance assessed by SVI plotted against PAOP was not altered (Fig. 2). When terlipressin is used, CI should be closely monitored because significant modification of this parameter could cause or worsen sepsis-related alterations in organ function. In the study by O’Brien et al, a reduction in HR was also observed [15]. Terlipressin, increases vagal and decreases sympathetic tone by acting on VI brain receptors [16]. In clinical practice, in using terlipressin, one should remember that with respect to the impact on CI, it could be of interest to keep MAP in the lower part of the normal range (±70mmHg) to limit the effects on the baroreflex.

We did not study mesenteric perfusion but observed some abnormalities in liver function such as an increase in bilirubin, AST and ALT. This point should be further evaluated. Splanchnic hemodynamics should be evaluated during terlipressin use.

In the present study, lactate concentrations were decreased during the use of terlipressin. This decrease could be, at least in part, related to the reestablishment of UF and the concomitant improvement in renal function, although most lactate is cleared by the liver.

Several laboratory parameters were affected during the use of terlipressin [16]. Values of bilirubin, AST and ALT were significantly increased, and thrombocytes were significantly decreased. The respective effects of the drug itself and the natural history of the septic state cannot be determined because of the design of the present study. Pulmonary function assessed by PaO₂/FiO₂ ratio was not affected during terlipressin use.
In the study patients, during terlipressin use, renal function, as assessed by urine flow, serum creatinine, was significantly improved. Studies have already demonstrated the beneficial effects of norepinephrine on renal function during septic shock [5-7,17-22].

On the basis of evaluation of left ventricular function points, no significant changes in ventricular function were observed when terlipressin was used in the study patients. Thus, cardiac function was not altered by terlipressin, given the lack of difference in preload and the observed increase in afterload. This is of crucial importance because cardiovascular dysfunction is a major determinant of the elevated mortality in septic shock patients [23,24]. Potent vasopressors, such as norepinephrine or terlipressin, should not be considered in patients with high SVRI. The elevated cardiac afterload obtained by straining the myocardium could be very deleterious in cases of severe cardiac dysfunction. This point is crucial. If considered, terlipressin must be used only to restore normal values of SVRI and/or MAP in patients with marked and documented vasodilation. When terlipressin is used, a slight but significant decrease in CI was observed in the present study. This point should be kept in mind, and the minimal effective dose of terlipressin should be used to avoid a marked effect on CI.

Candidates for this study were nonresponders to high levels of norepinephrine with a PAOP between 12 and 15 mmHg. Recent guidelines recommend achieving a central venous pressure between 8 and 12mmHg in septic patients and starting therapy with vasopressor agents when appropriate fluid challenge fails to restore adequate blood pressure and organ perfusion [25]. The volume status of our patients was in agreement with these recommendations and consequently, we did volume expand patients sufficiently.

The present study has several limitations. First, the study had an open-label design with no control group. A time effect with a favorable evolution of the patients cannot be ruled out [26]. Terlipressin was considered as a last-resort therapy and our goals were to investigate changes in systemic hemodynamics and in different organ functions. Second, we studied a small number of patients. A far greater number of patients will be needed to demonstrate a potential survival benefit. A further concern is that the study duration was short, focused on indices of hemodynamic stability and measures of organ function. No conclusion can be drawn from the present study on whether terlipressin increases survival of septic shock compared with conventional catecholamine therapy.

In conclusion, the use of terlipressin was associated with a significant increase in MAP in study patients with severe hypotension despite the use of high-dose norepinephrine and fluid resuscitation. Concomitantly a decrease in HR and CI was observed. Cardiac performance was not altered, but close monitoring of CI and possibly the additional use of a positive inotropic agent should be considered. The effects of terlipressin on the splanchnic circulation deserve to be evaluated by further studies. Renal function, assessed by UF and serum creatinine level was improved.

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Terlipressin Salvage in Catecholamine Resistant Septic Shock Patients


Value of Proximal Isovelocity Surface Area in Assessing Mitral Valve Area in Rheumatic Mitral Stenosis Patients

TAREK KHAIRY ABD EL-DAYEM, MD*; ALAA M OMAR, MSc**; AYMAN S SADEK, MD*; HALAH RASLAAN, MD**; ASHRAF AL-SHERBINY, MD**

Introduction: The method of choice for measurement of mitral valve area (MVA) is still a challenge for echocardiographers since each method has its inherent limitations. More recently, the proximal isovelocity surface area (PISA) method has been proposed as an alternative method for calculating MVA. This method should be attractive in mitral stenosis (MS) quantification but is seldom used in routine practice due to the perception of being technically difficult and time consuming; requiring several technical measurements.

Aim of the Work: To evaluate the accuracy of PISA performed by trans-thoracic echocardiography (TTE) in measuring MVA in rheumatic MS patients with or without associated aortic regurgitation (AR), and to attempt to simplify the equation.

Patients, Methods, and Results: The study included 30 patients with MS, divided into 2 groups: Group I included 16 MS patients without aortic regurgitation (AR), and Group II included 14 MS patients with any degree AR. MVA was calculated for all subjects using planimetry (PLN), Pressure half time (PHT), Continuity equation (CONT) and PISA methods. MVA for all methods was compared with PLN which was taken as the golden standard. In the current study we attempted to simplify the calculations by using a constant aliasing velocity = 33 cm/second for all patients. Moreover, mitral valve angle in rheumatic MS patients was observed to be between 100 to 110 degrees. Multivariate stepwise regression analysis revealed that there was highly significant positive correlation among cases of Group I between PISA and PLN ($p<0.001$, Beta co-efficient= 0.78), and a significant positive correlation between CONT and PLN ($p<0.05$, Beta co-efficient= 0.21) and PHT and PLN ($p<0.05$, Beta co-efficient= 0.23). In Group II (cases with AR), there was a highly significant positive correlation found by multivariate stepwise analysis between PISA and PLN ($p<0.001$, Beta co-efficient= 0.95). However, in the group with AR, PHT and CONT overestimated the MVA with no correlation to PLN method.

Conclusion: PISA can be an easy, non-invasive method for measuring MVA in patients with pure rheumatic MS without AR being as accurate as PLN, PHT, and CONT. In patients with rheumatic MS and associated AR, PISA is as accurate as PLN, and is considered to be the only comparable method to PLN in such patients.

A constant aliasing velocity of 33 m/sec. and a constant mitral valve angle of 100-110 degrees can be used to simplify calculations promoting more widespread implementation.

Key Words: Proximal isovelocity – Rheumatic mitral stenosis.
in patients with an irregular mitral valve orifice and/or with severe calcification using 2-DE [2,4].

PHT has been reported to be inaccurate for calculating MVA in patients with aortic regurgitation (AR) and/or left ventricular stiffness [5]. Moreover, the PHT method is inaccurate for measuring the MVA immediately after percutaneous mitral valvuloplasty [4,12].

More recently, the proximal isovelocity surface area (PISA) method has been proposed as an alternate method for calculating the MVA [6]. Applying the PISA method may be a unique way of measurement of MVA, because this method would have the advantage of using forward flow across the valve regardless of the presence of mitral regurgitation [7].

The orifice area is estimated by the formula:

\[ \text{Area} = 2 \times \pi \times r^2 \times \left( \frac{V_{\text{ali}}}{V_{\text{max}}} \right) \]

Where \( r \) is the radius of PISA, \( V_{\text{ali}} \) is the aliasing velocity, and \( V_{\text{max}} \) is the maximum velocity across the orifice [10]. This formula is valid for planar orifices. If the blood moves through a conical tunnel, this formula is modified to become: \( \text{Area} = 2 \times \pi \times r^2 \times \left( \frac{V_{\text{ali}}}{V_{\text{max}}} \right) \times \left( \frac{\theta}{180^\circ} \right) \). Where \( \theta \) is the angle of the top of the segment and \( \pi = 3.14 \) [10].

In MS, the orifice is almost always at the end of such a conical segment because of the restricted mobility of the valve necessitating the use of \( \theta/180^\circ \) correction for estimation of the MV orifice [6,8].

Despite its theoretical advantages, the PISA method is seldom used in routine practice for the assessment of MS severity. One reason may be that this method is reputed to be technically demanding and time-consuming since it requires several measurements, in particular an angle correction. This angle cannot be obtained using machine’s built-in software and requires a manual measurement using a protractor and a print-out [16]. Other reasons for its rare implementation, include the complex equation used in calculation, and the lack of a fixed way of choosing the optimum aliasing velocity necessary to obtain a clear cap that is suitable for the accurate radius measurements.

Aim of the Work:

We attempted to evaluate the accuracy of PISA compared to PLN, PHT, and CONT, performed by trans-thoracic echocardiography, in measuring MVA in patients with rheumatic MS, with or without associated AR, and to suggest a simplification of the equation.

Patients and Methods

The study included 30 patients with rheumatic MS referred to Ain Shams University Hospital, Cardiology department in the period from January 2005 to August 2006. The patients were divided into 2 groups:

1- Group 1: 16 MS patients without AR.
2- Group 2: 14 MS patients with any degree AR.

The inclusion criteria were:

1- Age range from 15-75 years.
2- Rheumatic MS.
3- Good quality echocardiographic imaging of the mitral valve apparatus.

Exclusion criteria were:

1- Poor echogenicity or inconclusive planimetry assessment method.
2- Affection of tricuspid or pulmonary valves.

The entire patient population underwent:

1- History taking and physical examination.
2- 12 lead ECG.
3- Echocardiography by 2-DE, Doppler ultrasound and color flow mapping using Vivid-5 echocardiography machine (General Electric medical systems, Horton, Norway) with a multifrequency phased array transducer of 1.7-2.5 MHz. MVA was measured in each patient by 4 methods: 2-DE planimetry, Pressure half time, Continuity equation and PISA, 2-DE planimetry method was taken as the golden standard. If the patient’s cardiac rhythm was atrial fibrillation (AF), the measurements and calculations were done in 5 consecutive beats and the mean value was considered as MVA [8].

Planimetry:

Short axis views of the mitral valve (MV) were obtained from the parasternal transducer position and the smallest orifice of the MV was identified by scanning from left atrium towards the direction of the left ventricular apex. The gain settings were adjusted up to the lowest level at which the cir-
cumference of the mitral orifice was still visible. After identification of the frame with the orifice at its maximal opening in early diastole, MVA was measured by planimetry of its contours [9].

**Pressure-half time:**

Doppler echocardiographic recordings of the trans-mitral blood flow velocity were made by continuous wave Doppler in the apical four chamber view. MVA was then determined by the PHT formula: MVA = 220/P1/2 [1,2].

**Continuity equation:**

The Doppler approach to measuring blood flow is a general formula that is possible to measure blood flow/area across all four valves: Flow at any point = CSA x VTI x HR [13].

Where:

- VTI: Velocity time integral.
- CSA: Cross sectional area.
- HR: Heart rate.

CSA = πr² and π = 3.14

As 𝑟 = 1/2 D, and D is the dimension actually measured, this formula can be simplified to be as follows: CSA = 0.785 x D² [11].

We used the application of the continuity equation for calculation of the MVA using mitral flow and LVOT flow, the cross sectional area of the LVOT was calculated and VTI of both mitral and LVOT flow was determined and MVA was calculated by the following formula:

\[
MVA = \frac{CSA_{LVOT} \times VTI_{LVOT}}{VTI_m} = 0.785\times(LVOTd)^2\times VTI_{LVOT}/VTI_m [11]
\]

Where:

- LVOTd: Left ventricular outflow tract diameter.
- VTI_{LVOT}: VTI of LVOT flow.
- VTI_m: VTI of mitral flow.

To measure flow through LVOT the Doppler recording is performed using apical five chamber view and the sample volume is positioned below the level of the aortic annulus. Cross sectional area is measured by recording the parasternal long axis view and determining the diameter of the left ventricular outflow tract diameter (LVOTd). VTI of the LVOT and Mitral flow were calculated by tracing the flow envelope of the LVOT flow and Mitral flow respectively.

**PISA:** (Figs. 1,2,3)

Color flow mapping of the mitral flow was done in the apical window with color gain adjusted to eliminate random color in areas without flow, from this window the four chamber view provided the most consistent image of the largest proximal convergence radius and allowed the proximal flow to be viewed nearly parallel to the ultrasonic beam. This view was scanned to image the largest proximal flow convergence region, and the aliasing velocity was reduced by shifting the color baseline to maximize the area of the image [7,10]. After a small pilot study, we opted to use a fixed aliasing velocity (V_{al}) of 33 m/sec. for all patients.

The maximal radius of the proximal flow convergence region was measured in early diastole from the first aliasing boundary to the tips of mitral valve in a direction parallel to that of the flow. The funnel angle α containing the flow convergence region was measured in the same frame using a manual off-line analysis system. Mitral valve area was then calculated by continuity as follows [15,16].

\[
MVA = 2\pi r^2 \times \frac{V_{al}}{V_{max}} \times \frac{\alpha}{180}
\]

Where:

- r = PISA radius.
- V_{al} = Velocity of aliasing.
- V_{max} = Maximal flow velocity across mitral valve.
- α = The funnel mitral valve angle containing the flow convergence region.

**Statistical methodology:**

Data analysis was done using the software Statistical Package for Social Science version 11 (SPSS Inc., Chicago, IL, USA). Quantitative variables were tabulated as mean and standard deviation (SD), and qualitative variables as number and percentage (%). Chi-square and paired t-tests were used to compare same group qualitative and quantitative variables respectively. The Unpaired t-test was used to compare quantitative variables between two independent groups. Correlation co-efficient test was used to rank different parameters against each other positively or inversely. Multivariate analysis was used to examine the effect of different independent variables using stepwise technique. \( p < 0.05 \) was considered significant, \( p < 0.01 \) highly significant.
**Value of Proximal Isovelocity Surface Area**

### Results

Tables (1,2) summarize the patients’ demographic data and the measured study variables respectively and the relation between them in both study groups.

**Table 1:** Age and gender distribution among both study groups.

<table>
<thead>
<tr>
<th>Study group</th>
<th>Age (years)</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1: N=16</td>
<td>34.3±10</td>
<td>Male: 9 (56.3%)</td>
</tr>
<tr>
<td>Group 2: N=14</td>
<td>33.9±10.4</td>
<td>Male: 5 (35.7%)</td>
</tr>
<tr>
<td>Significance</td>
<td><em>p</em>&gt;0.05</td>
<td><em>p</em>&gt;0.05</td>
</tr>
</tbody>
</table>

**Table 2:** Echocardiographic variables among both study groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I No = 16</th>
<th>Group II No = 14</th>
<th><em>p</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angleº</td>
<td>112±8.2</td>
<td>109±4.1</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>V$_{max}$ (m/sec)</td>
<td>232.7±47.7</td>
<td>225.3±48.7</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>r (cm)</td>
<td>1.31±0.2</td>
<td>1.37±0.2</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>VTI$_M$</td>
<td>75.3±16</td>
<td>77.2±32</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>VTI$_{LVOT}$</td>
<td>24.9±9.5</td>
<td>27.6±10.2</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>LVOTd</td>
<td>1.86±0.21</td>
<td>1.99±0.27</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>MVA (PLN)</td>
<td>1.008±0.3</td>
<td>1.09±0.3</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>MVA (PISA)</td>
<td>0.99±0.29</td>
<td>1.09±0.31</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>MVA (PHT)</td>
<td>1.01±0.5</td>
<td>1.18±0.30</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>MVA (CONT)</td>
<td>0.9±0.30</td>
<td>1.2±0.43</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Aliasing velocity (V$_{al}$) of 33m/sec was used for all patients in both groups.

There was no statistically significant difference between the studied groups regarding the angle, V$_{max}$, r, VTI$_M$, VTI$_{LVOT}$ and LVOTd, by unpaired-t-test (*p*>0.05).

In both studied groups, MVA measured by PISA versus PLN method was compared, with no statistically significant difference between both methods (*p*>0.05). Similarly, there was no statistically significant difference between MVA calculated by PLN and PHT, and between MVA calculated by PLN and CONT in group I (*p*>0.05).

However, there was a statistically significant difference (*p*<0.05) between MVA calculated by PLN and PHT as well as between PLN and CONT in group II (with AR) due to overestimation of MVA using PHT and CONT, compared to cases without AR (group I).

For cases without AR (Group I), a comparison between the different methods versus planimetry
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(gold standard) by multivariate stepwise regression analysis found that there was highly significant positive correlation between PISA versus PLN ($p<0.001$, Beta co-efficient= 0.78), and a positive correlation between CONT ($p<0.05$, Beta co-efficient= 0.23), as well as PHT ($p<0.05$, Beta co-efficient= 0.21) versus PLN.

In group II (with AR), multivariate stepwise regression analysis found a highly significant positive correlation between PISA versus PLN ($p<0.001$, Beta co-efficient= 0.95), however there was no correlation between planimetry and either PHT or CONT, as they overestimated the MVA.

MVA by PISA was more closely correlated to MVA by PLN in Group II (Beta co-efficient 0.95) than in group I (Beta co-efficient= 0.78).

Discussion

Mitral stenosis is one of the leading causes of congestive heart failure in developing countries. The treatment of mitral stenosis depends upon its severity which can be measured either by transmirtal pressure gradients or by measuring MVA at the orifice [14]. Measurement of MVA by echocardiography is still a challenge for echocardiographers; because each method has its own limitations [1].

In spite of many limitations; Gorlin's formula was the reference method to calculate MVA, however this method was not used as gold standard in our study because it is invasive, technically difficult, requiring accurate measurement of cardiac output, diastolic filling period, and mean pressure difference across the mitral valve. Instead, planimetry was used as the gold standard. Planimetry was used as the gold standard in the studies by Genc et al 2004 [14], Bennis et al 2002 [15] and Ikawa et al 2001 [17].

We attempted to evaluate the accuracy of PISA performed by trans-thoracic echocardiography in measuring MVA in patients with rheumatic MS with or without associated AR, and to suggest a way to simplify the calculation.

In all 30 patients included in our study, MVA was calculated using planimetry (PLN), pressure half time (PHT), continuity equation (CONT) and PISA. All the results were then statistically compared to PLN. In patients without AR there was no statistically significant difference between the result of each method and PLN ($p>0.05$). Multivariate stepwise regression analysis there was high
positive correlation between PLN and PISA (beta co-efficient 0.78, $p<0.001$) as well as positive correlations between PLN and CONT (beta co-efficient 0.21, $p<0.001$) and PLN and PHT (beta co-efficient 0.23, $p<0.001$).

Our findings are similar to those of Rodriguez et al 1993, who found good correlation between PISA and PLN in cases with no AR with correlation coefficient ($r=0.91$, $p=0.001$) [11]. Similar results were reported by Ikawa et al 2001, who concluded that MVA by the PISA method correlated well with planimetry both in patients with AR ($r=0.90$, $p<0.001$), and those without AR ($r=0.92$, $p<0.001$) [17]. Bennis et al 2002 concluded that MVA calculated using the PISA method correlated well with PLN MVA ($r=0.93$, $p<0.0001$). The correlation was also valid in patients with AF ($r=0.93$, $p<0.0001$), with MR ($r=0.94$, $p<0.0001$), with Wilkins score >8 ($r=0.92$, $p<0.0001$), as well as in patients with commissural calcification ($r=0.90$, $p<0.0001$) [18]. Genc et al 2004 found good correlation of planimetry to PISA with $r=0.72$, $p=0.002$ [14].

Our results, along with the previous studies’ comparable results, give more evidence for the general use of PISA in calculating MVA as it shows that PISA is comparable to other usually used methods.

In the current study, MVA in patients with AR measured by PISA method was compared to MVA by PLN and it was found that there was no statistically significant difference between both methods in both study groups ($p>0.05$).

This was also confirmed by previous studies by Ikawa et al, 2001, who reported an $r$ value = 0.9, Genc et al, 2004 who found $r=0.77$ [14], and Bennis et al, 2003, who found $r=0.93$ [15].

On the other hand, in the presence of AR, MVA measured by PHT method or continuity equation overestimated MVA with statistically significant difference compared to planimetry ($p<0.05$).

Multivariate stepwise regression analysis established a high positive correlation between PLN and PISA (beta co-efficient 0.95, $p<0.0001$), this correlation was even evident in patient with AR. However no correlation could be obtained in case of PHT and CONT due to the out of range overestimation.

As is the case in our study, Ikawa et al, 2001 found that MVA by PHT method did not correlate well with planimetry ($r=0.57$, $p<0.05$) in patients with associated AR. The PHT method in their study produced a significant overestimation (24%) of MVA when compared to planimetry in these patients. Genc et al, 2004 also reported significant overestimation of MVA by PHT ($p<0.01$) and by linear regression analysis correlation co-efficient was 0.57 [14,17].

A possible explanation for the overestimation of MVA in case of AR when measured by PHT is that ventricular diastolic filling retrograde from the aorta causes a decline in the mitral gradient because it increases the left ventricular diastolic pressure, this leads to an artificial decrease in PHT, and causes an overestimation of MVA [18,19].

Supporting data were recently published by Messika-Zeitoun et al, 2008 where he stated that the continuity equation should not be used in case of AR [20].

These results support the concept that PHT and CONT methods should not be relied upon in the measurement of MVA in patients having associated AR because of the overestimation of MVA giving false impression of milder disease that may mis-guide the treatment plans.

PISA, being as accurate as PLN in this group of patients, gives a good option for an easy reproducible tool to measure MVA at least in comparison with the widely used PLN method.

It is to be noted that the closer relation noticed in case of Group II (with AR) (Beta co-efficient 0.95, $p<0.0001$) than in Group I (Beta co-efficient 0.78, $p<0.0001$) using multivariate stepwise regression analysis, gives an indication that the use of PISA to measure MVA in MS patients with AR maybe of more accuracy than in patients with pure MS.

Despite the theoretical advantages, the PISA method is seldom used in routine practice for the assessment of MS severity. One reason may be that this method is reputed to be technically demanding and time-consuming since it requires several measurements, in particular an angle correction. This angle cannot be obtained using machine’s built-in software and requires a manual measurement using a protractor [16]. Other reasons include the complex equation used in calculation and the lack of a fixed way of choosing the aliasing
velocity suitable for obtaining a clear cap that is suitable for the radius measurements.

In our study we have tried to simplify the calculations by using a constant aliasing velocity of 33 m/second for all patients in the two study groups. In the preparatory stage for the study we have tried many different velocities ranging from 20 m/sec to 40 m/sec and we found that in almost all patients it was enough to decrease the velocity to 33m/sec to obtain a PISA cap clear enough to measure the radius easily. Other studies have used different methods for determination of aliasing velocity. Ikawa et al, in 2001 have used a velocity of 10% of the peak transmitral velocity [17], Bennis et al, used velocities ranging from 21-29 m/sec with a mean of 23±3 [15], Robert et al used a velocity 18-30 m/s [13] and Rodriguez et al 1990, who used velocities ranging from 19-43 m/s [11].

Also in our study, mitral valve angle was found to be 109±4.1 in group I and 112±8.2 in group II. There was no statistical difference between both groups. Comparable results were found in previous studies. Rodriguez et al 1990 reported mitral valve angle of 118±15. Robert et al 1995 who reported mitral valve angle of 128±15 [11]. Bennis et al 2002 also reported mitral valve angle of 113±7 [15].

In our study we observed that the mitral valve angle usually fluctuates around 110 degrees and so we concluded that in the calculation of MVA by PISA it is possible to use a constant of 100–110 for the mitral valve angle alleviating the need for its manual measurement. Recently, supportive data were obtained by Messika-Zeitoun et al 2006, who have concluded that the angle formed by the mitral leaflet only slightly changes in between patients and that the use of a fixed angle value of 100 degrees provides an accurate estimation of the MVA by the PISA method in patients with MS. He also stated that this simplification would facilitate and extend the use of the PISA as an additional method for the assessment of MS severity in routine practice [16].

Our study contributes to the simplification of MVA assessment by PISA by confirming that a fixed postulated angle can be factored in the equation (without manual measurement) with a resultant consistent good correlation with other methods of MVA estimation. In addition, using a fixed aliasing velocity will decrease time needed for performing the measurement.

Limitations:
1- Absence of a true golden standard for the calculations.
2- Small study sample.

Conclusion
1- PISA is a sensitive and reliable method for calculating MVA in patients with rheumatic mitral stenosis especially if accompanied with AR which will give it the advantage over the commonly used PHT method which overestimates MVA in the case of AR.
2- A constant of 100-110 could be used instead of the manual measurement of the mitral valve angle.
3- A preset velocity of aliasing of 33 m/s could be used constantly for all patients with resultant clear PISA cap, and easy, accurate measurement of the radius in most patients.

References
Value of Proximal Isovelocity Surface Area


Detection and Characterization of Pediatric Cardiac Tumours with Magnetic Resonance Imaging

NOHA H BEHAIRY, MD*; KHALED H ELKAFFAS, MD*; RANYA A HEGAZY, MD**

Objective: Primary cardiac tumors are rare in pediatrics with variable clinical presentations. The aim of our study is to show the value of magnetic resonance imaging in detection and characterization of pediatric cardiac masses.

Material and Method: We prospectively examined 20 patients ranging in age between 2mo-12yrs diagnosed as having a cardiac mass by transthoracic echocardiography. Clinical examination, chest X-ray, transthoracic echocardiography and CMRI using T1 & T2 weighted images, (STAIR and bFFE were sometimes used) and post enhancement with intravenous gadolinium-based contrast material were performed for all patients. Proof of diagnosis was obtained by follow-up, surgical excision and/or biopsy.

Results: MRI detected the site, number, size and extracardiac extension of the cardiac tumors. MRI characterized the masses and suggested a diagnosis in all 20 cases, as such: Rhabdomyoma (n=10), fibroma (n=3), myxoma (n=1), thrombus (n=1), fibroelastoma (n=1), schwannoma (n=1), angiosarcoma (n=1) rhabdomyosarcoma (n=1) and hemangiosarcoma (n=1). 19 were tumors (16 were benign masses and 3 were malignant) and 1 was a nonmalignant mass (thrombus).

Conclusion: CMRI can accurately characterize the mass, detect site, size, extracardiac invasion and multiplicity of the lesion, hence it is considered an indispensable complementary diagnostic tool to echocardiography in diagnosing cardiac and pericardial masses.

Key Words: Cardiac masses – Magnetic resonance imaging – Echocardiography – Tumors.

Introduction

Cardiac tumours are benign or malignant neo-plasms arising primarily in the inner lining, muscle layer, or the surrounding pericardium of the heart. They can be primary or metastatic. Primary cardiac tumors are rare in pediatric practice with a prevalence of 0.0017 to 0.28/10,000 in autopsy series. The vast majority of primary cardiac tumors in children are benign, whilst approximately 10% are malignant. Secondary malignant tumors are 10-20 times more prevalent than primary malignant tumors [1].

Rhabdomyoma is the most common cardiac tumor in childhood accounting for more than 60% of all primary cardiac tumors [2]. Other tumors include fibromas, hemangioma, germ cell tumors, histiocytoid cardiomyopathy and sarcomas [3]. Pericardial neoplasms also affect the heart and may mimic cardiac neoplasia. The two most common pericardial tumors are teratoma and malignant mesothelioma.

The clinical presentations vary widely from asymptomatic presentation to life threatening cardiac events [4]. The diagnosis and management of primary cardiac neoplasms has been greatly facilitated by the development of noninvasive cardiac imaging. Echocardiography is the primary modality for imaging intracardiac disease. It provides high-resolution and real-time images [5]. It has the limitation of being operator dependant with limited acoustic window.

Magnetic resonance imaging provides a non-invasive and three-dimensional assessment of masses involving the cardiac chambers, the pericardium and the extracardiac structures. Therefore, it has become an established method for the yielding of
complimentary diagnostic information and to guide surgeons in the design of an appropriate therapeutic strategy. Furthermore, magnetic resonance imaging has a soft tissue contrast superior to that of echocardiography allowing characterization of tumor tissue [6,7].

**Material and Methods**

Twenty patients ranging in age between 2 months and 12 years were diagnosed with cardiac masses by transthoracic echocardiography at our institution in the 4 year period between July 2004 and July 2008. All patients were examined by history taking, clinical examination, chest X-ray, 12 lead ECG, transthoracic echocardiography and magnetic resonance imaging. The study was approved by the scientific committee in the Medical School at Cairo University.

*Transthoracic Doppler echocardiography:*

Transthoracic echocardiographic examinations were carried out in all patients. The equipment used for all echocardiographic examinations was Hewelett Packard (Sonos-4500), using an 8 and 4MHz transducer, capable of performing 2D studies, continuous and pulsed Doppler and color flow Doppler. The site, size, mobility, attachment, extension, multiplicity and sonographic texture of masses were documented.

*Magnetic resonance imaging:*

All patients were imaged by a Philips Gyroscan Intera 1.5 tesla super conducting magnet using the synergy body coil and ECG triggering.

Patients were examined in supine position; ECG leads and respiratory trigger were applied and adjusted until a good signal is obtained. Children under 5 years were sedated using a regular dose of chloral hydrate which was well tolerated with no reported side effects. Endotracheal intubation was not needed in any case.

*MRI protocol:*

Multiple stack survey providing coronal, transverse and sagittal images with consequent transverse, sagittal and/or coronal views were taken in the following sequences:

- T1 weighted images with TR/TE = 600-750/25-30, T2 weighted images with TR/TE = 1300-1700/75-85. Fat suppression images were obtained in cases of fatty lesions, 156x256 matrix. Gradient echo sequences bFFE was performed for most patients with TR/TE = 3.2/1.7, 215-256x256 matrix and 50º flip angle.

- 5-8mm slice thickness, 10-14 slice numbers encompassing the heart and mediastinum with 300-350mm FOV according to the body dimensions was performed for all patients. Post enhancement with intravenous gadolinium-based contrast material was performed for all patients (0.1mm/kg) in transverse, sagittal or coronal views. The site, size, multiplicity, extension and tissue characterization by studying the signal intensity of the mass at different sequences were documented. Vascularity of the mass was determined by the degree and pattern of contrast enhancement. Extracardiac structures as the lungs, mediastinum, great vessels, dorsal vertebrae and thoracic cage were visualized to detect any associated condition.

Patients were followed, the outcome and pathology findings were reported for each case.

**Results**

Twenty patients (2 months-12 yrs) of age diagnosed as having cardiac or pericardial masses by echocardiography were studied. 8 of the patients were females and 12 were males.

*Clinical findings:*

Patients showed variable initial clinical presentations; shortness of breath (n=8), arrhythmias (n=5), cardiac murmur (n=4), syncope (n=2) and seizure (n=1).

Chest X-ray demonstrated cardiomegaly in 11 patients and pericardial effusion in 2, while 7 children showed no abnormal findings.

*MRI findings:*

Nineteen cases showed intracardiac masses with 12 seen in the LV, 4 in the RV, 2 in the IVS (interventricular septum) and one at the pulmonary valve. 1 case was pericardial in location.

MRI detected the size, site, vascularity of the masses and characterized them into different types; most of them were tumors (16 benign and 3 malignant) and 1 non tumoral as shown in Tables (1,2,3).

Regarding the multiplicity of the lesions; MRI detected two cases with multiple left ventricular lesions diagnosed as Rhabdomyomatosis in a patient with tuberous sclerosis and the other was multiple thrombosis at the RV and TV in a pediatric patient with abnormal protein C.
Although echocardiography diagnosed one patient as having multiple masses suspicious of rhabdomyomatosis, MRI proved it to be a solitary intramural mass with characteristic signal of an IVS fibroma. Seven of the cardiac masses (rhabdomyomas) were part of tuberous sclerosis diagnosis and one patient with schwannoma had neurofibromatosis Table (4).

9 cases (45%) including three cases of rhabdomyoma, two cases of fibroma, myxoma, schwannoma, angiosarcoma and hemangiosarcoma, were surgically excised and/or biopsied. Tissue pathology obtained; confirmed our diagnosis.

Patients diagnosed as rhabdomyomas were followed by echocardiography and MRI, six showed regression in size. Hemodynamically insignificant, very small (e.g. Fibroelastoma) or intramural masses (e.g. Fibroma), were followed as surgery was not feasible. All three patients with malignant masses died within weeks after diagnosis.

Table 1: Cardiac masses in the different age groups.

<table>
<thead>
<tr>
<th>AGE</th>
<th>Diagnosis</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants 2mo-2yrs</td>
<td>Rhabdomyoma</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Fibroma</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Fibroelastoma</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Rhabdomyosarcoma</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Angiosarcoma</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Hemangiosarcoma</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Thrombus (RA and TV)</td>
<td>1</td>
</tr>
<tr>
<td>Children (3-12yrs)</td>
<td>Rhabdomyoma</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Myxoma</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Fibroma</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Schwannoma</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2: Site and Characters of the cardiac masses by echocardiography and MRI.

<table>
<thead>
<tr>
<th>Echocardiographic findings</th>
<th>MRI findings</th>
<th>Diagnosis</th>
<th>No.</th>
<th>Site of the mass</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1wIs</td>
<td>T2wIs</td>
<td>Post contrast</td>
<td>Special</td>
</tr>
<tr>
<td>Hyperechoic</td>
<td>Iso-</td>
<td>High</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Narrow stalk, hypo</td>
<td>Iso</td>
<td>Heter</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Echogenic-heterog.</td>
<td>Iso</td>
<td>Low</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Elongated, mobile</td>
<td>Iso</td>
<td>Low</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Heterogenous</td>
<td>Iso</td>
<td>High</td>
<td>+++</td>
<td>bFFE</td>
</tr>
<tr>
<td>Large heterogenous mass</td>
<td>Heterhigh</td>
<td>Heterhigh</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>filling LV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogenous infiltrating</td>
<td>Heter high</td>
<td>Heter High</td>
<td>++++</td>
<td></td>
</tr>
<tr>
<td>mass</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echogenic infiltrating mass</td>
<td>High</td>
<td>Infiltra</td>
<td>High</td>
<td>+++</td>
</tr>
<tr>
<td>Heterogenous-hypoechoic</td>
<td>Low</td>
<td>Lower</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>mass</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Classification of cardiac and paracardial masses.

<table>
<thead>
<tr>
<th>Type</th>
<th>No.</th>
<th>Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary benign tumors</td>
<td>16</td>
<td>Rhabdomyoma, Myxoma, Fibroma, Fibroelastoma, schwannoma</td>
</tr>
<tr>
<td>Primary Malignant tumors</td>
<td>3</td>
<td>Rhabdomyosarcoma, angiosarcoma, hemangiosarcoma</td>
</tr>
<tr>
<td>Non tumoral masses</td>
<td>1</td>
<td>Thrombus</td>
</tr>
</tbody>
</table>

Table 4: Associations of the cardiac masses.

<table>
<thead>
<tr>
<th>Cardiac Mass</th>
<th>No.</th>
<th>Associated Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhabdomyoma</td>
<td>7</td>
<td>Tuberous Sclerosis</td>
</tr>
<tr>
<td>Schwannoma</td>
<td>1</td>
<td>Neurofibromatosis</td>
</tr>
<tr>
<td>Fibroma</td>
<td>1</td>
<td>Vertebral anomalies, Vascular anomalies (persistent left SVC, hypoplastic left pulmonary artery and intermitted hepatic segment of the IVC)</td>
</tr>
</tbody>
</table>

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Detection & Characterization of Pediatric Cardiac Tumors

Discussion

Echocardiography is considered the procedure of choice for diagnosing intracardiac tumors. This technique is noninvasive and may provide information on the size, mobility, shape and location of cardiac masses. However, it has the limitation of poor echogenicity in 30% of patients, absent tissue characterization and poor evaluation of pericardium/extracardiac structures. Moreover, bone and lung interference remains a major limitation of echocardiography and renders this real-time imaging technique suboptimal in patients with narrow rib spaces [8,9].

At present, MRI is definitely one of the preferred imaging modalities in the evaluation of patients with suspected cardiac masses. Major advantages of this technique are: The excellent spatial resolution; the large field of view; the inherent natural contrast between flowing blood and the surrounding heart chambers, vessel walls and tumor masses, without the need for contrast agents; the multiplanar imaging capability and the ability to administer paramagnetic contrast agents in order to obtain a better detection of the tumor borders and the degree of tumor vascularization. These advantages are important in planning the patient’s therapy, particularly if surgical intervention is being considered. Using MRI, cardiac tumors can be depicted with a very high accuracy [8].

Spin echo (SE) sequences provide detailed morphological information of the heart, the great vessels and the adjacent structures. T1-weighted images provide a better signal-to noise ratio and excellent soft tissue contrast between epicardial fat, myocardium and rapidly flowing blood. T2-
weighted images have an increased image contrast, which may be helpful for tissue characterization [6].

According to Hoffmann et al [6]; the major tasks of magnetic resonance imaging in diagnosing cardiac masses are: To confirm or exclude a mass suspected by X-ray or echocardiography, to assess the location, mobility and its relationship to surrounding tissues, to image the degree of vascularization, which allows differentiation between benign and malignant masses, to distinguish solid from fluid lesions, and to determine tissue characteristics and the specific nature of a mass; all of which were confirmed in our study.

Unlike two-dimensional echocardiography, magnetic resonance imaging has, to some extent, the potential for tissue characterization by comparing the T1 and T2 values of the mass to a reference tissue [10].

Rhabdomyomas being the commonest cardiac tumor in early childhood, [11] represented 50% of the pediatric tumors diagnosed in our study (10 cases) (Fig. 1). Associated tuberous sclerosis was found in 7 cases of rhabdomyomas, while six of them showed regression in size on follow-up examination which were the most important differential features from fibroma according to Bader et al [12]. The remaining three cases were pathologically proven.

Intracardiac fibroma was diagnosed in three pediatric patients on bases of being solitary, intramural in location and being hypointense on T1, lower on T2 with no contrast enhancement detected as reported by Araoz and Sharon [7] (Figs. 1, 2). None of them had associated Gorlin syndrome. Although one of them was a unique case of IVS fibroma associated with vertebral and vascular anomalies (persistent left SVC, hypoplastic left pulmonary artery and interrupted hepatic segment of the IVC). The patient had normal CT and MRI of the brain, normal hands and genitalia with no basal cell carcinomas, thus Gorlin syndrome was excluded.

Papillary fibroelastomas are rare cardiac benign tumors, but they are the most common primary tumor of the cardiac valves [7]. We diagnosed one case in a seven month old male child which was discovered accidentally during routine check up. A murmur was heard on the pulmonary valve area. MRI depicted a small 12mm elongated mobile mass at the pulmonary valve that was isointense in both T1 and T2 weighted images and low in gradient echo sequences.

The case diagnosed as schwannoma was part of a known neurofibromatosis systemic disease in a 12yr old child. The mass filled the RV and extended upwards towards the pulmonary artery obstructing the outflow tract showing intense contrast enhancement. The mass was surgically excised; however recurrence was detected on follow-up.

Although MRI can suggest the diagnosis of malignant cardiac masses, the signal features of malignant tumors are ambivalent and do not permit a tissue diagnosis [6]. Two masses showed malignant behavior suggestive of cardiac sarcoma evident by broad based masses occupying most of the affected cardiac chamber, infiltration of the myocardium with pericardial extension, heterogeneous MR appearance and high vascularity as reported by Best et al [13]. They were pathologically proven to be angiosarcoma and heamangiosarcoma respectively.

Since rhabdomyosarcoma is the most common cardiac malignancy in infants and children [14]; MRI diagnosed one case of rhabdomyosarcoma in a two month old infant which was huge occupying the whole LV, obstructing both outflow and inflow with evident infiltration to the myocardium (Fig. 3). The mass showed the same signal characteristics as reported by Yousem et al [15]. However, the diagnosis couldn't be pathologically confirmed since the patient died 2 days after the examination. We presented 1 case of pathologically proven cardiac myxoma.

Since nontumoral masses usually require medical (or no) treatment, accurate differentiation between the two conditions is important.

Thrombi can be misinterpreted as a cardiac tumor on echocardiography [16]. However on CMRI thrombus has a characteristically low signal on gradient echo sequences (Fig. 4) with isointense or low signal on T1 weighted images and low signal on T2 weighted images with no contrast enhancement [8]. We reported one case which was confirmed by dissolving of the masses on follow-up after medical treatment.

Conclusion

Cardiac masses are rare but can be well characterized and often confidently diagnosed with
magnetic resonant imaging, allowing the differentiation between tumoral and nontumoral masses, hence facilitating the choice for medical or surgical treatment which is hence an indispensable diagnostic modality in these patients.

CMRI can accurately detect site, size, extracardiac invasion and multiplicity of the lesion, hence it is considered a valuable complementary diagnostic tool to echocardiography in diagnosing cardiac and pericardial masses.

Acknowledgement:
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Brugada Syndrome: A Four-Case Clinical Experience 1st Egyptian Report
HESHAM AL-AASSAR, MD

Brugada syndrome is characterized by a distinctive electrocardiographic pattern (right bundle branch block and ST segment elevation in precordial leads) and a high risk of cardiac arrest from malignant dysrhythmia. The genetic basis is a molecular defect of the cardiac sodium channel and the pattern of inheritance is autosomal dominant.

We are reporting our experience with four patients who are survivors of sudden cardiac death (SCD) and their ECG during sinus rhythm showed manifestations of Brugada syndrome, all of them received an implantable cardioverter defibrillator (ICD).

Key Words: Brugada syndrome.

Introduction

In 1992, Brugada and Brugada [1] described eight patients who were resuscitated from cardiac arrest without demonstrable structural heart disease but who presented right bundle branch block (RBBB) and ST segment elevation in leads V1-V2-V3. These cases established this electrocardiographic (ECG) pattern as a distinctive new syndrome associated with augmented risk of sudden death. The prototypical case of Brugada syndrome has been associated with alterations in the SCN5A gene.

Patients with Brugada syndrome are prone to develop ventricular tachyarrhythmias that may lead to syncope, cardiac arrest, or sudden cardiac death [2,3,4]. Intrahisian conduction delay and atrial fibrillation may also be manifestations of the syndrome [5,6]. Brugada syndrome is genetically determined and has an autosomal dominant pattern of transmission in about 50% of familial cases. About 5% of survivors of cardiac arrest have no clinically identified cardiac abnormality; about half of these cases are thought to be due to Brugada syndrome [7].

<table>
<thead>
<tr>
<th>Table 1: ECG variants of brugada syndrome.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>J wave amplitude (mm)</td>
</tr>
<tr>
<td>T wave</td>
</tr>
<tr>
<td>ST-T configuration</td>
</tr>
<tr>
<td>ST segment, terminal portion</td>
</tr>
</tbody>
</table>

Brugada et al [8] proposed that asymptomatic patients are at high risk of cardiac arrest (approximately 60% of patients within 1 year from the diagnosis); thus justifying aggressive therapy such as the implantation of a cardioverter-defibrillator. A prospective study [9] reported that in asymptomatic patients the risk of cardiac arrest is infrequent enough to justify postponing implantation of a cardioverter-defibrillator. Many factors (medications, bradycardia, temperature changes) could precipitate malignant dysrhythmia in these patients.

The differential diagnosis of sudden cardiac death in an otherwise presumably healthy subject is varied, but includes such entities as acute cardiac ischemia due to atherosclerosis or coronary anomaly, hypertrophic cardiomyopathy, catecholaminergic polymorphic ventricular tachycardia, long QT syndrome and arrhythmogenic right ventricular cardiomyopathy (ARVC).
Patients and Methods

Our experience concerns 4 patients with Brugada Syndrome. The diagnosis of the syndrome was obtained by ECG; All patients (Table 2) were (3m, 1f), mean age 25.25±4 y; Every patient presented ST segment elevation in precordial leads between 0.1 and 0.2mV (Fig. 1) and incomplete right bundle branch block.

Structural heart disease or coronary artery disease were excluded by noninvasive tests and the absence of creatine phosphokinase elevations. All patients had a history of aborted sudden cardiac death (SCD) and syncopes caused by torsades de pointes.

All patients received an implantable cardioverter defibrillator (ICD).

Table 2: Demographic characteristics, history and risk stratification of the patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Presentation</th>
<th>ST segment elevation</th>
<th>Risk stratification</th>
<th>Others</th>
<th>ICD (cardioverter-defibrillator)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>38</td>
<td>Male</td>
<td>SCD</td>
<td>0.1</td>
<td>High</td>
<td>–</td>
<td>Yes</td>
</tr>
<tr>
<td>Patient 2</td>
<td>26</td>
<td>Male</td>
<td>SCD</td>
<td>0.15</td>
<td>High</td>
<td>–</td>
<td>Yes</td>
</tr>
<tr>
<td>Patient 3</td>
<td>21</td>
<td>Male</td>
<td>SCD</td>
<td>0.15</td>
<td>High</td>
<td>Dextrocardia</td>
<td>Yes</td>
</tr>
<tr>
<td>Patient 4</td>
<td>16</td>
<td>Female</td>
<td>SCD</td>
<td>0.2</td>
<td>High</td>
<td>–</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Case (1):
Palestinian pt (MS) 38 years old male presented to our center by a history of twice cardiac arrest and has been resuscitated, unfortunately he has a residual quadriplegia and permanent tracheostomy, his ECG showed typical pattern of Brugada syndrome and his echocardiography was within normal. He received an ICD and follow-up for 36 months showed that he developed 6 attacks of VF which has been successfully terminated by the ICD (Fig.1).

Case (2):
Palestinian pt (MO) 26 years old male presented to our center by a history of cardiac arrest and has been resuscitated, his ECG showed typical pattern of Brugada syndrome and his X-ray and echocardiography showed dextrocardia and situs inversus totalis. He received an ICD and he escaped follow-up (Fig. 2).

Case (3):
Egyptian pt (AA) 21 years old male, medical student referred to our center following cardiac arrest during his final oral exam. and has been resuscitated, unfortunately he remained on mechanical ventilation for 3 weeks and he developed bilateral pneumothorax and tracheoesophageal fistula, his ECG showed typical pattern of Brugada syndrome and his echocardiography was within normal. He received an ICD and follow-up for 12 months showed no attacks of VT/VF (Fig. 3).

Case (4):
Egyptian pt (FA) 16 years old female referred to our center by a history of cardiac arrest while playing sports witnessed by the doctor who started successful resuscitation, her ECG showed typical pattern of Brugada syndrome and her echocardiography was within normal. She received an ICD and follow-up for 6 months showed that she developed no attacks of VT/VF (Fig. 4).
Results

All patients were followed-up from 6 months to 36 months. During follow-up patient no. (1) developed 6 attacks of ventricular fibrillation (VF) which has been successfully terminated by the implanted ICD. All other patients did not develop any episode of VT/VF and one pt is lost follow-up.

Discussion

The prevalence of Brugada syndrome has not been accurately estimated but, according to previous studies, the disease is not uncommon. The incidence may be even more frequent in the younger population and it is the most common cause of sudden death in individuals younger than 50 years without underlying cardiac disease in the Japanese population [11] and in South Asia [12]. Roberts and Brugada [13] report an estimated incidence of this form of sudden death between 26 and 38 per 100,000 people per year.

Risk stratification in these patients is important for defining treatment: e.g., the choice of cardioverter-defibrillator implantation [9]. Brugada et al [14] proposed a risk stratification scheme based on screening with programmed electrical stimulation of asymptomatic patients, but this test is not reproducible and it is useless for risk stratification [9,15,16]. Other authors proposed different criteria for risk stratification but they all need to be confirmed: Priori et al [15] proposed S wave width 0.08s in V1 and ST elevation 0.18mV in V2; Atarashi and Ogawa [16] proposed ST elevation >0.15mV at baseline with pilsicainide-induced additional ST elevation >0.1mV and Morita et al [10] proposed the simultaneous presence of syncope and ST segment elevation at ECG baseline.

All our patients presented an ECG pattern of Brugada syndrome at rest, incomplete right bundle branch block, and different level of ST elevation from V1 to V3.

Many drugs can have a proarrhythmic effect. In patients with Brugada syndrome, Class I antiarrhythmic drugs [17] sodium channel blockers (specifically procainamide and ajmaline) can induce ST segment elevation because they interact directly with the receptors affected by the syndrome. The muscarinic and α-adrenergic receptor agonists cause an increase in ST segment elevation [18] in the general population and in many cases of Brugada syndrome [9]. Psychotropic [19] drugs also have electrophysiologic effects: Amitriptyline induces cardiac sodium channel blockade but also causes the reduction in the inward sodium current and a prominent outward current (several mutations on the SCN5A gene produce the same effects).

Brugada syndrome is an increasingly recognized disorder. The ECG pattern should alert the clinician to suspect possible Brugada syndrome. If this finding is confirmed further investigation is justified. However, there is a degree of genetic heterogeneity and some patients affected by the syndrome do not show the typical ECG pattern. Follow-up data indicate that the risk of ventricular tachyarrhythmia is minimal in the absence of a resting ECG abnormality. Risk stratification criteria currently do not allow identification of patients who run the risk of malignant arrhythmias.

References

Brugada Syndrome: A Four-Case Clinical Experience 1st Egyptian Report


