Heart Rate In Heart Failure Management

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Introduction

- Resting heart rate is one of the most easily obtained measures of cardiovascular health.
- In spite that the importance of heart rate (HR) as a prognostic factor and potential therapeutic target has not been formally explored.
- Based on epidemiologic data and inferences from clinical trials most physicians believe that increased resting heart rate is associated with increased total and cardiovascular mortality, in general as well as in coronary artery disease and hypertensive populations.
- Although resting pulse rate can be quickly and reliably assessed, it is often looked as an index of cardiovascular risk factors.
- Heart rate reduction may have direct beneficial effects on clinical outcome in Heart Failure patients.
There is a difference between systolic (HFrEF) and diastolic (HFpEF) heart failure.1

HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction.

2 Owan and Redfield. Progr Cardiovasc Dis 2005; 47:320–32

* Patients with a LVEF in the range of 40–49% represent a 'grey area', which is now defined as HF with mid-range EF (HFmrEF).1

The ejection fraction is usually measured with echocardiography.

Heart failure is the leading CV reason for rehospitalizations

41,413 patients of the Italian National Health Service (INHS) database

Total number of re-admissions during 1 year = 48,549 (2.1 per patient)
CV reasons = 24,723 (50.9%)
Each readmission to hospital among HF patients leads to worse mortality and poorer survival

15 year study from UK from 200-2014, 13416 patients with HF


Heart rate through the cardiovascular continuum:
I. Prognostic importance of heart rate in
   - general population
   - hypertensive patients
   - diabetic patients

Pathophysiological Mechanisms:
II. The role of heart rate in development of atherosclerosis
III. The role of heart rate in stable coronary artery disease
IV. The role of heart rate in acute coronary syndrome
V. The role of heart rate in chronic heart failure
New in stable angina to 7.5 mg, twice daily.


All cause mortality - men with hypertension 35 year follow-up Framingham study (n=2037)

Age adjusted 2-year rate per 1000

60
50
40
30
20
10

65 65-74 75-84 85+

Heart rate (bpm)

Resting heart rate and cardiovascular deaths in type 2 diabetic patients


New in stable angina 5 to 7.5 mg, twice daily
Increased heart rate aggravates ischemia in CAD patients

Heart rate
Systolic wall tension
Contractility
Increased \( O_2 \) demand

Decreased diastole
 Coronary resistance
Decreased perfusion

Cardiac work

 Coronary blood flow
Decreased supply

Ischemia

**Predictor of mortality in CAD patients**

24913 pts from the CASS registry – mean follow up: 14.7 years

Hazard ratio

- Overall mortality
- Cardiovascular mortality

Heart rate (bpm)

Relation between heart rate and long-term mortality in patients after acute myocardial infarction

Prospective long-term observational follow-up study

n=432; 41 months (SD) follow-up; EGG; composite end point (mortality + arrhythmic events)

<table>
<thead>
<tr>
<th>Months follow-up</th>
<th>Patients at risk</th>
<th>% Event-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>308</td>
<td>94.1%</td>
</tr>
<tr>
<td>12</td>
<td>278</td>
<td>93.2%</td>
</tr>
<tr>
<td>24</td>
<td>219</td>
<td>91.4%</td>
</tr>
<tr>
<td>36</td>
<td>173</td>
<td>88.5%</td>
</tr>
<tr>
<td>48</td>
<td>134</td>
<td>84.7%</td>
</tr>
<tr>
<td>60</td>
<td>88</td>
<td>81.9%</td>
</tr>
</tbody>
</table>

P=0.002

Standard 12-lead ECG
HR < 75 bpm
HR ≥ 75 bpm


Plaque Rupture + Thrombosis

Plaque stability ↓

Ischemia

Oxygen consumption ↑
Diasole length ↓
Coronary perfusion ↓

Coronary Artery Disease

Heart Rate

Infarction

Loss of Contractility

Dilatation and “Remodeling”

Heart Failure

Cardiac hypertrophy ↑
Tachycardia/myopathy ↑
Oxygen demand ↑
Ventricular efficiency ↓
Ventricular relaxation ↓

Risk Factors

Atherosclerosis

End-stage Heart Failure

Microalbuminuria ↑
Cuditive stress ↑
Endothelial dysfunction
Arterial stiffness ↑
New in stable angina to 7.5 mg, twice daily

Relationship between cardiac output and heart rate in patients with normal and failing myocardium

 raised heart rate at discharge after acute heart failure is an independent mortality predictor

![Graph showing one-year mortality (%) in different heart rate categories](image1)

![Graph showing relationship between cardiac index and heart rate in normal and failing myocardium](image2)

Guideline recommended treatment goals in heart failure\textsuperscript{1,2}

The goals of treatment in patients with HF are to:\textsuperscript{1}

- improve clinical status, functional capacity and quality of life
- prevent hospital admission
- reduce mortality

\textit{“High resting HR is an independent predictor of cardiovascular and all cause mortality”} \textsuperscript{1}

- JACC 2007
Overactivation of the RAAS and SNS is detrimental in HFrEF and underpins the basis of therapy.

RAAS = renin aldosterone angiotensin system
SNS = sympathetic nervous system
ACEI = angiotensin converting enzyme inhibitor
ARB = angiotensin receptor blocker
MRA = muscarinic receptor antagonist

- The crucial importance of the RAAS is supported by the beneficial effects of ACEIs, ARBs and MRAs.
- Benefits of β-blockers indicate that the SNS also plays a key role.

Does Heart Rate Reduction lead to a decrease in a cardiovascular event and prolongs life in Heart Failure?
PHARMACOLOGICAL HEART RATE SLOWING STRATEGIES

**DRUGS**

- Beta blockers

**Other CV Effects**

- ↓ blood pressure
- ↓ inotropy
- Peripheral vasoconstriction
- ↑ coronary resistance

**Limitations**

- Bronchospasm
- ↓ insulin responsiveness
- AV nodal blockade
- Lethargy / fatigue
- Depression / ↓ sleep
- Sexual dysfunction
- Claudication with PVD
The effect of heart rate lowering on the beneficial action of β-blockade

**Population:**
49 pacemaker-dependent patients with LVSD, LVEF <40%
85% with CAD

**Patient assessment:**
Clinical examination,
Radionuclide ventriculography
Mean follow-up: 14±13 months

**Hypothesis:** Heart rate lowering is central to improving LV function

- **Uptitration**
  - ACEi/ARB
  - Spironolactone
  - Carvedilol

3-month stable medication doses

- Pacing at high rate (80 ppm)
- Pacing at low rate (60 ppm)

Clinical assessment

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Heart rate lowering in heart failure is beneficial

49 pacemaker-dependent patients with LVSD, LVEF < 40%, paced after 3 months of optimal treatment

**Changes in LV ejection fraction (%)**

- Pacing at 80 bpm
- Pacing at 60 bpm

**Changes in LVEDV and LVESV (mL)**

- LVEDV +8, -65
- LVESV +23, -61

Changes after 3 months of optimal treatment

Effect of change in heart rate and achieved heart rate on clinical outcomes in HF

Meta-regression of beta-blocker trials n=19,537

Correlation of change in heart rate (bpm) with relative risk reduction (RRR) in all-cause mortality

\[ r^2 = 0.41 \]

Correlation of final achieved heart rate (bpm) with annualized mortality in 9 beta-blocker trials in 19,537 patients

\[ r^2 = 0.53 \]


Relation between magnitude of HR reduction and outcomes in heart failure patients

Meta-regression of 23 beta-blocker HF trials involving 19,209 patients

Pooled mortality hazard ratio was 0.76 for an average HR reduction of 12 bpm

Beta-blocker therapy

- Pooled data from 25 RCTs (6511 patients and 810 deaths)
- Compared with placebo, beta-blockers reduced odds of death by 36%
  - (95% CI 25% to 45%)
- No evidence of heterogeneity between trial results
- Benefit is additional to that of ACE inhibitors

Mortality in HFrEF remains high despite the introduction of new therapies that improve survival

- Survival rates in chronic HF have improved with the introduction of new therapies
  - Survival rates: 16% (14.0% HR, 95% CI 0.5 to 3.7 months, SOLVD)
  - 34% (8.2% HR, 95% CI 0.3 to 1.8 weeks, CIBIS-II)
  - 30% (3.3% HR, 95% CI 0.5 to 2.2 months, RALES)
  - 17% (7.5% HR, 95% CI 0.7 to 1.2 years, CHARM-Alternative)

- However, significant mortality remains — ~50% of patients die within 5 years of diagnosis
Insufficient heart rate control in majority of patients with heart failure

HF registries: more than 50% of patients have HR ≥ 70 bpm

Heart rate and β-blocker therapy in European surveys

PHARMACOLOGICAL HEART RATE SLOWING STRATEGIES

DRUGS

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Other CV Effects

- ↓ blood pressure
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- Peripheral vasoconstriction
- ↑ coronary resistance

Limitations

- Bronchospasm
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Primary composite end point

A 3-year, randomized, double-blind, placebo-controlled, phase III study in heart failure, n=6 505

Cumulative frequency (%)

PEP: cardiovascular death & hosp for heart failure

Hospitalization for heart failure

A 3-year, randomized, double-blind, placebo-controlled, phase III study in heart failure, n=6505

Cumulative frequency (%)

- 26%

Death from heart failure

A 3-year, randomized, double-blind, placebo-controlled, phase III study in heart failure, n=6505

Death from HF (%)

- 26%
Reduces the risk of death and rehospitalization in whatever the etiology of heart failure


In patients with HFP EF, HR reduction with ivabradine did not improve outcomes. These findings do not support the use of ivabradine in HFP EF.
2016 ESC Guideline Treatment Algorithm

Step 1: Establish Dx of HFrEF; assess volume; initiate GDMT

Step 2: Consider the following patient scenarios

Step 3: Implement indicated GDMT.

Choices are not mutually exclusive, and no order is inferred

Step 4: Reassess symptoms

Step 5: Consider additional therapy

HFrEF NYHA class I–IV (Stage C)

ACEI or ARB AND GDMT beta blocker; diuretics as needed (COR I)

NYHA class II–IV, provided est. CrCl > 30 mL/min and K+ < 5.0 mEq/L

NYHA class II–III HF. Adequate BP on ACEI or ARB*; no C/I to ARB or sacubitril

NYHA class III–IV, in black patients

NYHA class II–III, LVEF ≤ 35%; (caveat: > 1 y survival, > 40 d post MI)

NYHA class II–III, NSR, heart rate ≥ 70 bpm on maximally tolerated dose beta blocker

Hydral-Nitrates†‡ (COR I)

ICD‡ (COR I)

CRT or CRT-D (COR I)

Ivabradine (COR IIa)

Refractory NYHA class III–IV (Stage D)

Symptoms improved

Transplant‡ (COR I)

LVAD‡ (COR IIa)

Palliative care‡ (COR I)

Investigational studies§

Continue GDMT with serial reassessment and optimized dosing/adherence

2017 ACC/AHA/HFSA guideline recommendations for the treatment of patients with HFrEF

Step 1: Establish Dx of HFrEF; assess volume; initiate GDMT

Step 2: Consider the following patient scenarios

Step 3: Implement indicated GDMT.

Choices are not mutually exclusive, and no order is implied

Step 4: Reassess symptoms

Step 5: Consider additional therapy

Follow-up care (COR I)

Investigational studies§

Continued GDMT with serial reassessment and optimized dosing/adherence

Notes:

*New publication time for important treatment directions. †Hydral-Nitrates green box: the combination of ISDN and HYD with ARNI has not been robustly tested. BP response should be carefully monitored; ‡Hydral-Nitrates green box: the combination of ISDN/HYD with ARNI has not been robustly tested. BP response should be carefully monitored; §Participation in investigational studies is also appropriate for Stage C, NYHA class II and III HF.
• The ACC/AHA/HFSA have released a focused update on pharmacological therapy for HF that includes ARNI (sacubitril/valsartan) and a sinoatrial node modulator (ivabradine) recently approved in the US
• These guidelines recommend sacubitril/valsartan as standard of care for HFrEF for replacement of ACEi/ARBs in HF patients tolerating ACEi/ARBs who remain symptomatic (mild to moderate symptoms NYHA Class II-III)
• Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF ≤35%) who are receiving GDEM, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest
• These new drugs complement established pharmacological and device-based therapies and represent a milestone in the evolution of care for patients with HF

Take Home Message

➤ HR is a primary determinant of cardiac work, myocardial oxygen consumption and myocardial contractility.

➤ HR can be modulated with drugs in most cardiac disease states, pharmacological HR slowing minimizes pathophysiology.

➤ When HR is reduced with drugs in patients with HF, cardiac function is enhanced and survival improved.
“We’re all born with a certain number of heart beats; I don’t want to waste mine on exercise.”

ANDREW GLENN MORROW, M.D.,
some time before 1971