How to approach a patient with suspected PH

First line tool: transthoracic echocardiogram

Right heart dilatation and/or raised RVSP identified

PHT Evaluation Protocol

Gold standard for diagnosis: RHC !!!

Exclude secondary causes: +/- CMR

Adult Congenital Heart Disease
Valvular Heart Disease
LV Systolic/Diastolic Dysfunction

Pressure/volume overload

Criterion:
- RV >1/2 LV from PLAX
- TR V_{MAX} >2.6 m/s
- RVOT AT <105 ms
- TAPSE < 1.6 cm
- RV IRT > 75 ms
- IVC > 20 mm & <50% inspiratory ↓
Latest ESC guidelines on pulmonary hypertension (2015) indicated high risk echocardiographic markers...

“RV function is an important prognostic marker in patients with pulmonary hypertension”

“Speckle tracking is a very promising modality”

2015 ESC/ERS guidelines on pulmonary hypertension

The main ambition....

Endpoint previously: functional outcome
Now: death

“Honeymoon period” Symptoms but not yet RH remodeling

New imaging indices

Prognostic indices

Early detection of pulmonary hypertension & right heart remodeling

Early treatment (WHO class I or II)
Right ventricular failure due to chronic pressure load: What have we learned in animal models since the NIH working group statement?

Heart Fail Rev (2015) 20:475–491

- Pathophysiology of the pressure-loaded RV.
- Progression of pathophysiological changes in the pressure-loaded RV.
- Typical pressure–volume (PV) loops from compensation to failure.

Differences between PAH - CTEPH

**Pulmonary arterial hypertension**
- Gradual increase of PVR, RVSP
- RV hypertrophy & impairment
- Significant tricuspid annular dilatation and TR
- Pressure & volume loading

**CTEPH**
- Bouts of sudden increase PVR, RVSP
- RV impairment > hypertrophy
- Acute tricuspid annular dilatation and TR
- Pressure loading
- Less common volume loading

www.escardio.org/EACVI
Characterization of right ventricular remodeling in pulmonary hypertension associated with patient outcomes by 3-dimensional wall motion tracking echocardiography.  

Ryo O et al. Circ Cardiovasc Imaging. 2015 Jun;8(6)

RV adverse - remodeled patients (ESVi, ≥ 114 mL/m\(^2\)) had worse short-term outcome than the RV adapted - remodeled patients: hazard ratio, 2.42; 95% confidence interval, 0.91 to 5.39; P = 0.04.

Endpoint: PH related hospitalization, death, or lung surgery (lung transplantation or pulmonary endarterectomy) during 6 months.

Contractile reserve

- Echocardiographic estimates of RV and pulmonary vascular function are feasible during exercise and identify pathology with reasonable accuracy.
- They represent valid screening tools for the identification of pulmonary vascular disease in routine clinical practice.
- An exercise-induced increase .30 mmHg was a strong predictor of exercise capacity and survival, the inference being that if RV contractile reserve remains good, then a pressure response to exercise can be successfully mounted despite increased afterload.

Claessen G et al. JACC Cardiovasc Imaging. 2015 Oct 16
Quantitative assessment
Indexing for HR and BSA

Indexing for heart rate:
1. RVOT acceleration time
2. RV myocardial performance index
3. S wave – TDI RV free wall

That is why for example:
You CANNOT label as “pulmonary hypertension” a 90 yrs old woman with RVSP 40 mmHg

BSA (m²) = 0.20247 x Height(m)⁰.⁷²⁵ x Weight(kg)⁰.⁴²⁵

Patients with BMI > 30 kg/m²
RVSP > 40 mmHg (TR V₂.₈ m/sec)

McQuillan BM, Picard MH et al. Circulation 2001;104:2797-802

Right ventricular Systolic Pressure

Bernoulli equation: RVSP = 4(TR Vₘₐₓ)² + RAP
TR Vₘₐₓ cut off < 2.7 m/s

Except:
• When PS is present
• Free flow TR

Diagnostic – NOT prognostic

RVSP (mmHg) : PHT Grade:
35 – 49 Mild
50 – 80 Moderate
>80 Severe

RVSP is not the same with the severity of the tricuspid regurgitant jet!!!!
Even if there is no obvious TR, please put the CW across the tricuspid valve

Circulation 70:657-662, 1984

Diagnostic – NOT prognostic
RVOT acceleration time

- Pulsed wave Doppler
- Sample volume positioned at the pulmonary valve in the parasternal short-axis view
- < 105 msec: suggestive of pulmonary hypertension
- Pulmonary systolic notch

Be careful !!!
- Error in pulmonary stenosis
- Heart rate indexed


Right atrial size (volume & area)

Volume = 0.85 (A)^2/L

- RAV Index:  
  - male: < 34 ml/m²  
  - female: < 27 ml/m²

- Prognostic in RVF

Wang, Y et al, Chest 86:595-601, 1984
Raymond RJ et al, JACC 2002

RA sphericity index: prognostic  
(Grapsa J et al. EHJ-CVI 2010)

Remember: one of the echo indices suggested by 2015 ESC guidelines!!

Two dimensional assessment

3 dimensional assessment

Black N, Grapsa J, Rudski L
ASE Dynamic Echocardiography. Right atrial assessment - 2015

RA Pressure (IVC Size)

- IVC Diameter at End-diastole & End-expiration
- Measure perpendicular to IVC long axis
- 1.0 – 2.0 cm from junction with RA

<table>
<thead>
<tr>
<th>Mean RAP (mmHg)</th>
<th>IVC Ø (mm)</th>
<th>Inspiratory Collapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 5</td>
<td>&lt; 15</td>
<td>Complete</td>
</tr>
<tr>
<td>5 – 10</td>
<td>15 – 25</td>
<td>&gt; 50%</td>
</tr>
<tr>
<td>10 – 15</td>
<td>15 – 25</td>
<td>&lt; 50 %</td>
</tr>
<tr>
<td>15 – 20</td>
<td>&gt; 25</td>
<td>&lt; 50 %</td>
</tr>
<tr>
<td>&gt; 20</td>
<td>&gt;25</td>
<td>No change</td>
</tr>
</tbody>
</table>

RV Function: MPI:
- Normal < 0.32
- Mild 0.32 – 0.49
- Moderate 0.50 – 0.75
- Severe > 0.75

**RV Myocardial Performance Index**

- S wave < 12 cm/sec: bad prognosis
- IVRT: > 110 msec: suggestive of PH

- Independent of chamber geometry
- Prognostic
- HR and load dependent

Song ZZ et al. Am J Cardiol. 2007

---

**How about TAPSE?**

- Good correlation with RVEF
- Simple
- Reproducible
- But load dependent

31 years old IPAH: Severely impaired RV systolic function
Pressure loaded

TAPSE : 10 mm

In certain cases diagnostic – definitely NOT prognostic!!

Kaul S et al. Am Heart J 1984

28 years old sinus venosus defect: Mildly impaired RV systolic function
Volume loaded

TAPSE : 30 mm
Aim: Prognostic value of echocardiographic and hemodynamic measures in a large cohort of patients with precapillary pulmonary hypertension before and after initiation of treatment

Endpoint: RH CARDIAC RELATED DEATH

The study cohort comprised 777 patients (514 women) with precapillary pulmonary hypertension. A total of 195 (25%) died

### Variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>86 ± 12</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>132.8 ± 14.6</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>72.4 ± 11.9</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>86.2 ± 19.5</td>
</tr>
<tr>
<td>Mean pulmonary arterial systolic pressure, mm Hg</td>
<td>78.2 ± 21.7</td>
</tr>
<tr>
<td>Mean pulmonary capillary wedge pressure, mm Hg</td>
<td>7.3 ± 2.6</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, Wood units</td>
<td>16.8 ± 7.6</td>
</tr>
<tr>
<td>Mean right atrial pressure, mm Hg</td>
<td>12.6 ± 3.3</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>3.35 ± 1.54</td>
</tr>
</tbody>
</table>

### Results:

In multivariable analysis:

- **Moderate or severe tricuspid regurgitation (HR, 26.537)**
- **RV myocardial performance index (HR, 3.42)**
- **Pericardial effusion (HR, 1.38)**

High PVR and RAP by invasive hemodynamic measurements were independent predictors of mortality
Stratification of risk of death
- Severity of tricuspid regurgitation
- RV MPI
- Pericardial effusion
- Pulmonary vascular resistance
- Cardiac index
- Right atrial pressure

Kaplan Meier for the 6 top prognostic indices and for the survival PAH vs CTEPH


Advanced echocardiographic modalities

The value of:
- 3D RV echocardiography
- 2D speckle tracking
- 3D RV strain
Acquisition

Apical 4 chamber view

Tip: more lateral

3D-dataset

Tip: don’t forget RV apex!!
Adjust depth and width

Full volume dataset
  • 4-7 consecutive beats

Tip: ↑ cardiac cycles, ↑ temporal resolution
Avoid stitching artifact

Save raw data

Step 1

Step 2

Step 3

Analysis

Endocardial mapping:
  1. RVOT excluded
  2. Trabeculations included to the blood pool

Epicardial mapping

Short axis from base to apex (Simpson’s rule)
  7 mm slices

Myocardial volume

Multiplied with myocardial density (1.05 g/dl) > myocardial mass

Step 1

Step 2

Step 3
Right heart in pulmonary hypertension: echocardiography strikes back?

Promising imaging modalities that have demonstrated effectiveness in relation to functional outcome and needing more studies associated with death

Currently proved:

1) Area strain is prognostic for PH
   Smith BC et al. JACC 2014 (4)
   Ryo O et al. Circ CV Imaging. 2015 Jun

2) RV free wall strain is more prognostic than RV global strain
   Giusca S et al. Echocardiography 2015 Nov
   Park JH et al. Korean Circ J. 2015 Sep
   Cameli M et al. Transplant Proc. 2015 Sep

Emerging… the prognostic value of RA strain

Landmark manuscript: Orientation of tricuspid annulus

Considerable tricuspid dilatation can be present even in the absence of substantial TR. Tricuspid dilatation is an ongoing disease process that will, with time, lead to severe TR


Nature Reviews Cardiology 10, 190-203 (April 2013)
One step further…

Three-dimensional dynamic assessment of tricuspid and mitral annuli using cardiovascular magnetic resonance.

Left: the anatomical reciprocal position of the aortic, mitral, pulmonary and tricuspid valves as seen from the atria (top), and an example of the reconstructed models on a normal subject (bottom). Right: mitral (top) and tricuspid (bottom) annuli and the bounding box used to calculate annular diameters and height. Solid, dotted, and dashed lines represent different annular regions. AL-PM, anterolateral-posteromedial; AP, antero-posterior; SM, septal-medial.


---

3D reconstruction of tricuspid leaflets and annulus

Different PH etiology > different RV remodeling > different TV mobility

- CTEPH: most restricted mobility
- LHD: closer to normal mobility

Different RV remodelling depends on different etiology

<table>
<thead>
<tr>
<th>Indices</th>
<th>PAH</th>
<th>Chronic thromboembolic disease</th>
<th>Post-capillary PH</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV volumes</td>
<td>↑↑</td>
<td>↑</td>
<td>↑ or ~</td>
</tr>
<tr>
<td>RV ejection fraction</td>
<td>↓↓</td>
<td></td>
<td>↓ or ~</td>
</tr>
<tr>
<td>RV mass</td>
<td>↑↑ (end-stage: ↓)</td>
<td>↑</td>
<td>↑ or ~</td>
</tr>
<tr>
<td>Tricuspid mobility</td>
<td>↓↓</td>
<td></td>
<td>↓ or ~</td>
</tr>
<tr>
<td>Tricuspid annular diameter</td>
<td>↑↑</td>
<td>↑</td>
<td>↑ or ~</td>
</tr>
<tr>
<td>RVSP</td>
<td>↑↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>PVR (RHC)</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>PCWP (RHC)</td>
<td>&lt; 15 mmHg</td>
<td>&lt; 15 mmHg</td>
<td>≥ 15 mmHg</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD.

* Significantly different between groups (analysis of variance and Bonferroni test, p <0.01).
Cardiac magnetic resonance

Specific differences of the RV compared with LV

**Anatomy and morphology**
- Irregular shape with no axis of symmetry
- Moderator band and other trabeculae
- Lack of tricuspid-pulmonary continuity
- Peristaltic contraction pattern

**Quantitative analysis**
- Muscle mass < LV
- Volume: 10---20% > LV
- Ejection fraction < LV
- Stroke volume = LV

**Pathophysiology**
- More resistant to ischemia
- Lower O2 consumption
- Pulmonary resistance = 1/10 systemic
- More compliant
- Better adaptation to volume overload
- More respiratory variation
When we should consider CMR?

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Define our CMR anatomy

www.escardio.org/EACVI
Principle 1: Difference in mass and size

B-SSFP sequence:
• This is usually accomplished by refocusing the phase-encoding gradient in each repetition interval in order to keep the phase integral (or gradient moment) constant.
• Fully balanced SSFP MRI sequences achieve a phase of zero by refocusing all imaging gradients.

Principle 2a: Anatomical delineation: RVOT

Slight oblique angle through pulmonary artery on transverse view (1). Biarect pulmonary outflow tract on right ventricular inflow view (2).
**Principle 2b: Anatomical delineation: RV inflow**

- Accuracy
- Reproducibility
- Correct anatomy
- Late gadolinium enhancement for fibrotic segments

**Example: RVOT in arrhythmogenic cardiomyopathy (ARVC)**
Principle 3: Gold standard for volumes and mass

? To include trabeculation in the blood pool?

Analysis

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Short axis from base to apex (Simpson's rule)
7 mm slices

Myocardial volume
Multiplied with myocardial density (1.05 g/dl) > myocardial mass
CMR gold standard imaging tool

Accurate assessment of RV volumes, stroke volume, EF and mass
Tadic M. Clin Cardiol. 2015 Aug

The large meta-analysis that included 807 subjects revealed underestimation of RV volumes obtained by 3DE vs CMR

Larger RV volumes were related with underestimation, whereas older patient age was associated with overestimation of RV volumes.
Shimada YJ et al. JASE 2010

Advantage: the precise RVOT identification

Myocardial deformation: CMR derived strain: Easier in RV hypertrophy
The value of RV mass as prognostic index in pulmonary hypertension

30 consecutive patients with newly diagnosed IPAH were recruited and followed with 3DE, strain and CMR 6 monthly for 2 years (longitudinal data).

8 patients (27%) died.

At 6 months, changes in 2D RV global longitudinal strain but not 3D RVEF or RV mass was significant in patients who died compared to patients who were alive.

However at 18 months only changes relative to baseline in RV mass by CMR and not RV strain or LVEF was significant in patients who died.


2D curvature

- Immediate correlation with pressure overload
- Prognostic in PH patients

Dellecrotaglie et al. JCMR 2011
CMR 3D curvature index

3-dimensional CMR interventricular septal curvature on a patient with pulmonary hypertension
Sciancalepore MA et al. Int J CV Imaging 2012

Prognostic value in PH patients with longitudinal data and with the endpoint of death
Grapsa J et al. (submitted)

### Agreement between 3DE and CMR

<table>
<thead>
<tr>
<th>Study</th>
<th>Methodology</th>
<th>Results</th>
</tr>
</thead>
</table>
| Fujimoto S. Int J Card Imaging 1998 | 15 healthy volunteers Comparison 3DE-CMR | RV-EDV: $r = 0.94$, $p<0.001$  
RV-ESC: $r = 0.97$, $p<0.001$, SD of bias: 5% |
| Kjaergaard J. Eur J CV Imaging 2006 | 34 pts (10 healthy, 17 inferior ST changes, 7 Hx PE) | RVEF: $r=0.48$, $p<0.01$  
Compared to CMR, 3DE underestimated RVEF by 5.9%  
RVESV: $r=0.31$, $p<0.01$ |
| Niemann PS JACC 2007      | 30 pts (14 healthy, 16 CHD) | RVEF: $r = 0.91$, $p<0.01$, RVEDV: $r=0.99$, $p<0.01$  
RVESV: $r=0.98$, $p<0.01$ |
| Jenkins C. Chest 2007     | 50 patients with LV RWMA    | Good inter and intra observer agreement  
(ICC=0.8)  
3DE: less test retest variation |
| Gopal AS. JASE 2007       | 71 healthy volunteers      | 3DE test retest variability (ICC = 0.8-0.9) |
| Nesser IU. Echocardiography 2006 | 20 pts (LVD-mixed etiology) | Agreement 3DE-CMR for EF ($r=0.82$) |
| Grapsa J.2009 Eur J CV Imaging       | 60 PAH pts – 20 healthy volunteers | Excellent agreement (ICC: 0.8-0.9)  
Poor EF and Rvmass agreement for healthy volunteers |
| Leibundgut G. JASE 2010    | 100 adult patients with normal or pathological RV | Excellent agreement 3DE-CMR  
($r=0.7-0.9$) |
| Oomah SR, JASE 2011       | 15 half marathon athletes  | Excellent 3DE-CMR agreement |
Learning curve for quantification of RV size and systolic function in PAH: comparison of CMR and 3DE

Jonathan Afilalo, Julia Grapsa, Giuliana Durighel, Declan O'Regan, David Dawson,

Robert A Levine, Petros Nihoyannopoulos SCMR 2012

Conclusion:
Novice observers can achieve high levels of intra and inter observer reliability after interpreting 60 CMR scans and 120 3D echocardiographic scans

<table>
<thead>
<tr>
<th></th>
<th>CMR</th>
<th>3DE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RV end diastolic volume</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limits of agreement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inter-observer ICC</td>
<td>0.88</td>
<td>0.98</td>
</tr>
<tr>
<td>Intra-observer ICC</td>
<td>0.94</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>RV end systolic volume</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limits of agreement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inter-observer ICC</td>
<td>0.92</td>
<td>0.99</td>
</tr>
<tr>
<td>Intra-observer ICC</td>
<td>0.97</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>RV stroke volume</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limits of agreement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inter-observer ICC</td>
<td>0.81</td>
<td>0.90</td>
</tr>
<tr>
<td>Intra-observer ICC</td>
<td>0.87</td>
<td>0.91</td>
</tr>
<tr>
<td><strong>RV ejection fraction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limits of agreement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inter-observer ICC</td>
<td>0.85</td>
<td>0.93</td>
</tr>
<tr>
<td>Intra-observer ICC</td>
<td>0.89</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Tagging of RV myocardium?
What is the future? Fusion imaging...