Pulmonary Hypertension in patients with Heart Failure with Preserved Ejection Fraction

Dr. Fayez EL Shaer
Consultant cardiologist
Assistant professor of cardiology
KKUH
Recent evaluation of available data has shown that the normal mean PAP at rest is 14±3 mmHg with an upper limit of normal of ~20 mmHg.

The significance between 21 and 24 mmHg is unclear, need further evaluation.

PH has been defined as an increase in mean pulmonary arterial pressure $\geq 25 \text{ mmHg at rest}$ as assessed by RHC.
• The definition of PH on exercise as a mean PAP > 30mmHg as assessed by RHC is not supported by published data. Healthy individuals can reach much higher values thus no definition for PH on exercise as assessed by RHC can be provided presently.
<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near syncope.</td>
</tr>
<tr>
<td>Class II</td>
<td>Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope.</td>
</tr>
<tr>
<td>Class III</td>
<td>Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope.</td>
</tr>
<tr>
<td>Class IV</td>
<td>Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.</td>
</tr>
<tr>
<td>Grade</td>
<td>Systolic</td>
</tr>
<tr>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>Grade 1 (Mild)</td>
<td>30-50</td>
</tr>
<tr>
<td>Grade 2 (Moderate)</td>
<td>50-70</td>
</tr>
<tr>
<td>Grade 3 (Severe)</td>
<td>70-110</td>
</tr>
<tr>
<td>Grade 4 (Systemic or suprasystemic)</td>
<td>&gt;110</td>
</tr>
</tbody>
</table>

*Data from 100 patients of PAH and rheumatic heart disease. Quintile 1 & 2 (Grade 1) quintile 3 & 4 (Grade 2) quintile 5 (Grade 3) top 3% (Grade 4)*
The Continuum of Diastolic HF: from HFP EF to PH HFpEF

**VASCULAR**
- Wall stiffening
- Abnormal vasorelaxation (impaired endothelial function, increased constriction)
↑ load on LV

**CARDIAC**
- Hypertrophy
- Fibrosis
- Impaired coronary reserve
↑ EDPVR

**PULMONARY**
- Lung capillary stress failure
- Capillary/arterial remodeling
↑ LA upstream pressure

Further details and images are included in the diagram.
Pathobiology of Left-Sided PH at Different Hemodynamic Stages

**REACTIVE Pulm. Hypertension**

1. Enlarged and thickened pulmonary venules
2. Arterial medial hypertrophy and intimal fibrosis
3. Interstitial edema
4. Lymphatic vessel dilatation
5. No evidence of plexogenic vasculopathy except for few reported cases of severe mitral stenosis exposed to severe high PVRs.

**OUT of PROPORTION Pulm. Hypertension**

- Initial or intermediate venular and arterial changes.
• Beyond the post-capillary contribution to PH, a reactive increase in pulmonary arterial tone or intrinsic arterial remodeling can result in a superimposed pre-capillary component of pulmonary arterial HTN.
PH with Left Heart Disease

- Pulmonary venous congestion is the primary determinant of increased PAP
- Accurate measurement of LV filling pressure is the most critical aspect of defining the nature of PH
- Passive PH: TPG is normal < 10 mmHg, PVR normal < 1.5 WU
- Mixed PH: PVR or TPG is abnormally increased with increased LV filling pressure, features of both PVH and PAH; The increase PAP reflects both PA vasoconstriction and fixed or non-reactive anatomic pulmonary arteriolar and venous narrowing/remodeling

J Heart Lung Transplant 2012; 31: 913-33
22 optimally-treated pts with stable HFpEF and moderate PH (mean PAP 37.8 mmHg)

PCWP (mmHg)

Pulm. Arteriolar Res. (Wood)

Tranpulmonary Gradient (mmHg)

*: p<0.01 vs baseline

- Baseline
- 6 months
- 1-year
<table>
<thead>
<tr>
<th>Definition</th>
<th>Characteristics</th>
<th>Clinical group(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PH</strong></td>
<td>$P_{pa} \geq 25$ mmHg</td>
<td>All</td>
</tr>
<tr>
<td><strong>Pre-capillary PH</strong></td>
<td>$P_{pa} \geq 25$ mmHg</td>
<td>1. Pulmonary arterial hypertension</td>
</tr>
<tr>
<td></td>
<td>$P_{pcw} \leq 15$ mmHg</td>
<td>3. PH due to lung diseases</td>
</tr>
<tr>
<td></td>
<td>CO normal or reduced$^+$</td>
<td>4. Chronic thromboembolic PH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. PH with unclear and/or multifactorial mechanisms</td>
</tr>
<tr>
<td><strong>Post-capillary PH</strong></td>
<td>$P_{pa} \geq 25$ mmHg</td>
<td>2. PH due to left heart disease</td>
</tr>
<tr>
<td></td>
<td>$P_{pcw} &gt;15$ mmHg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CO normal or reduced$^+$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Passive TPG $\leq 12$ mmHg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reactive (out of proportion) TPG $&gt;12$ mmHg</td>
<td></td>
</tr>
</tbody>
</table>
PH with Left Heart Disease

- Left heart disease and Heart failure is the most common cause of PH
- Variability of PH reflects severity/duration of LHD, degree of hemodynamic decompensation and the pulmonary vascular response to the first two
- PH-LHD is associated with greater disability and decreased survival
- As the severity of HF increases mixed PH is more likely to be present.

Butler. JACC 1999; 34:1802-06; Khush. Am Heart J; 2009; 157: 1026-34
## Suggested Definitions for PH-LHD

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>Description</th>
<th>Physiologic definition</th>
<th>Hemodynamic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passive PH</td>
<td>PH with elevated left cardiac filling pressure</td>
<td>Post-capillary (passive congestion) eg. pulmonary venous hypertension</td>
<td>Mean PAP $\geq 25$ mm Hg and PCW, LAP, LVEDP $&gt; 15$ mm Hg and TPG $\leq 15$ mm Hg or PVR $= 3.0$ WU</td>
</tr>
<tr>
<td>Mixed PH</td>
<td>PH with elevated left cardiac filling pressure and increased pulmonary vascular resistance</td>
<td>Pre- and post-capillary (passive congestion with excessive arterial vasoconstriction = vascular remodeling), eg. pulmonary arterial and venous hypertension</td>
<td>Mean PAP $\geq 25$ mm Hg and PCW, LAP, LVEDP $&gt; 15$ mm Hg and TPG $&gt; 15$ mm Hg or PVR $&gt; 3.0$ WU</td>
</tr>
<tr>
<td>Reactive PH</td>
<td>Component of mixed PH that is acutely or chronically responsive to pharmacologic (diuretics, vasodilators, inotropes) and/or mechanical circulatory support device therapies</td>
<td>With vasodilators and/or inotropes: TPG $\leq 15$ mm Hg or PVR $\leq 3.0$ WU</td>
<td></td>
</tr>
<tr>
<td>Non-reactive PH</td>
<td>Component of mixed PH that is not responsive to above strategies</td>
<td>Despite vasodilators and/or inotropes: TPG $&gt; 15$ mm Hg or PVR $&gt; 3.0$ WU</td>
<td></td>
</tr>
</tbody>
</table>

J Heart Lung Transplant 2012; 31: 913-33
ABNORMAL LV RELAXATION and STIFFNESS

LVDP+IMPAIRED VOLUME REGULATION

↑LA AND LV DIASTOLIC PRESSURE

↑PCWP (PULMONARY CONGESTION)

↑PA PRESSURE

↑RV+RA PRESSURE

RV FAILURE

SYSTEMIC CONGESTION (JVD, edema)

Alveolar Edema

Volume redistribution in pulm. vascular bed + Interstitial Edema

Mitral Regurgitation

- Hydrostatic Pressure
- Alveolar-capillary membrane integrity
- Permeability
- Lymphatic drainage capacity

ABNORMAL LV RELAXATION and STIFFNESS
Right heart involvement in PH with HFPEF

Adjusted $p^* < 0.05$ vs HFpEF; $p^# < 0.05$ vs PAH
Prognostic impact of RV dysfunction in HFpEF-PH

In addition to haemodynamic load, RVD (FAC<35%) in HFpEF was associated with male sex, AF, CAD, and greater ventricular interdependence.

RVD was the strongest predictor of death (HR: 2.4, 95% CI: 1.6–2.6; P, 0.0001)

Melenovsky Eur Heart J 2014
Differential diagnosis of heart failure with preserved left ventricular ejection fraction

<table>
<thead>
<tr>
<th>Diastolic heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive heart disease</td>
</tr>
<tr>
<td>Restrictive cardiomyopathy</td>
</tr>
<tr>
<td>Infiltrative cardiomyopathies</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Noncompaction cardiomyopathy</td>
</tr>
<tr>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>Miscellaneous factors: diabetes mellitus, chronic kidney disease, aging</td>
</tr>
<tr>
<td>Valvular heart disease</td>
</tr>
<tr>
<td>Valvular stenosis</td>
</tr>
<tr>
<td>Valvular regurgitation</td>
</tr>
<tr>
<td>Right heart failure</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Right ventricular infarction</td>
</tr>
<tr>
<td>Arrhythmogenic right ventricular cardiomyopathy</td>
</tr>
<tr>
<td>Pericardial disease</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
</tr>
<tr>
<td>Constrictive pericarditis</td>
</tr>
<tr>
<td>Effusive-constrictive pericardial disease</td>
</tr>
<tr>
<td>Intracardiac mass</td>
</tr>
<tr>
<td>Atrial myxoma</td>
</tr>
<tr>
<td>Congenital heart disease</td>
</tr>
<tr>
<td>High-output heart failure</td>
</tr>
<tr>
<td>Episodic or reversible LV systolic dysfunction</td>
</tr>
<tr>
<td>Pulmonary vein stenosis</td>
</tr>
</tbody>
</table>

Suspected pulmonary hypertension

Echocardiogram suggestive of pulmonary hypertension

- Yes: Significant left heart disease, adequate to explain pulmonary hypertension
  - Yes: Group 2 PH
  - No: Underlying cause of pulmonary hypertension identified?
    - Yes: Group 1 PAH, Group 3 PH, Group 4 PH, or Group 5 PH
    - No: Idiopathic pulmonary arterial hypertension
      - Confirm with right heart catheterization

- No: Low clinical suspicion for pulmonary hypertension?
  - Yes: Seek alternative causes of symptoms
  - No: Exercise echocardiogram OR Right heart catheterization
Symptoms/signs of HF

LVEF > 50% and LVEDVI < 97 ml/m²

Evidence of abnormal LV relaxation, filling, diastolic distensibility, and diastolic stiffness

Invasive measurements
- mPCWP > 12 mmHg
- LVEDP > 16 mmHg
- τ > 48 ms
- b > 0.27

Echo TDI
- E/E′ > 15
- 8 < E/E′ < 15

Natriuretic peptides
- NT-proBNP > 220 pg/ml
- BNP > 200 pg/ml

Natriuretic peptides
- NT-proBNP > 220 pg/ml
- BNP > 200 pg/ml
- E/A ↓, DCT ↑
- abnormal pulmonary venous flow
- left atrial dilation
- LVH
- atrial fibrillation
- TDI E/E′ > 8

HFNEF
Most ECG signs are specific but not sensitive for the detection of right ventricular disease. ECG changes do not correlate with disease severity or prognosis.
Left ventricular diastolic dysfunction is a predictor of outcome after a myocardial infarction

Pulsed Doppler recordings of transmitral filling (panel A) and color M-mode Doppler echocardiography (panel B) are methods for evaluating left ventricular (LV) diastolic function. In a normal filling pattern, the mitral E-wave deceleration time (DT) is 140 to 240 ms and the M-mode flow propagation velocity (Vp) is ≥45 cm/s). In diastolic dysfunction with impaired relaxation the DT is prolonged ≥ 240 ms and Vp is normal or reduced (<45 cm/s). In a pseudonormal filling pattern the DT may be normal or prolonged, but the Vp is <45 cm/s. In diastolic dysfunction with a restrictive filling, the DT is <140 ms and the Vp is normal or <45 cm/s. Patients with a myocardial infarction who have a restrictive or pseudonormal pattern have an increased incidence of left ventricular dilation and cardiac death.

Data from Moller JE, Sondergaard E, Poulsen SH, Egstrup K. J Am Coll Cardiol 2000; 36:1841. Reprinted with permission from the American College of Cardiology.
The effect of LV filling patterns on survival

Among patients with a first myocardial infarction, mortality was significantly higher in patients with impaired relaxation (p = 0.02), pseudonormal filling (p <0.00005) or restrictive filling (p <0.00005) than in patients with a normal filling pattern. With a Cox analysis, a pseudonormal and restrictive filling pattern were independent predictors of mortality.

PH was associated with left atrial volume index, diastolic function grade, and left ventricular filling pressures (E/e’), confirming that patients included had type II PH according to the WHO.
## Echo Features Distinguishing PH-LHD and PAH

<table>
<thead>
<tr>
<th>Echo parameter</th>
<th>Echo finding</th>
<th>Likelihood of PH-LHD</th>
<th>Likelihood of PAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction</td>
<td>&lt;50%</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Left atrial size</td>
<td>LAD &gt; 40 mm</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>LAVI &gt; 28 mm/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV wall thickness</td>
<td>&gt;11 mm</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Transmitral Doppler</td>
<td>Grade II/III diastolic dysfunction</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>Severity &gt; 1+</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>RV size</td>
<td>RV-to-LV area &gt; 1.0</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Interventricular septum</td>
<td>Systolic flattening Lateral-septal TDI disparity</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Interatrial septum</td>
<td>Bowing into LA</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>RV systolic function</td>
<td>TAPSE &lt; 1.5 cm</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>RVOT Doppler</td>
<td>Notching</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

*J Heart Lung Transplant 2012; 31: 913-33*
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number Available</th>
<th>AUC (Mean ± SE)</th>
<th>p Value</th>
<th>Optimal Cutoff</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASP, mm Hg</td>
<td>673</td>
<td>0.91 ± 0.02</td>
<td>&lt;0.001</td>
<td>35</td>
<td>83</td>
<td>92</td>
</tr>
<tr>
<td>E/e' ratio</td>
<td>808</td>
<td>0.83 ± 0.02</td>
<td>&lt;0.001</td>
<td>12.5</td>
<td>70</td>
<td>85</td>
</tr>
<tr>
<td>Left atrial volume/BSA, ml/m²</td>
<td>848</td>
<td>0.75 ± 0.02</td>
<td>&lt;0.001</td>
<td>29</td>
<td>66</td>
<td>74</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>759</td>
<td>0.60 ± 0.03</td>
<td>&lt;0.001</td>
<td>0.39</td>
<td>80</td>
<td>36</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>756</td>
<td>0.52 ± 0.03</td>
<td>0.497</td>
<td>105</td>
<td>42</td>
<td>68</td>
</tr>
</tbody>
</table>
Echo Algorithm to Assess PH and LHD

PH suspected by history and exam

PH on echocardiography

1) Age > 60 years?
2) Comorbidities (DM, HTN, CAD, obesity)
3) Valvular heart disease?
4) LV systolic dysfunction?
5) Echo abnormalities (LAE, LVH, or significant DD)
6) BNP markedly elevated?

All no ↓ 1-2 yes ↓ ≥3 yes
PAH  ↓ Probable PH from LHD  ↓ PH from LHD
Required ↓ Consider ↓ Consider

Catheterization to confirm diagnosis

J Heart Lung Transplant 2012; 31: 913-33
55 patients with exercise Dyspnoea, normal BNP assay; normal resting haemodynamics and euvolemic

- PCWP > 25 mmHg at peak exercise as main Criteria for PH Diagnosis

RIGHT and LEFT HEART catheterisation during supine exercise
PASP = 58 mmHg
Mean PAP = 40 mmHg
PCWP = 11 mmHg
TPG = 34 mmHg

mmHg
Mean PAP = 42 mmHg
PCWP = 21 mmHg
TPG = 25 mmHg
| Recommendations for right heart catheterisation (RHC; A) and vasoreactivity testing (B) |
|---------------------------------|---|---|
| **A.**                         |   |   |
| RHC is indicated in all patients with PAH to confirm the diagnosis, to evaluate the severity and when PAH specific drug therapy is considered | I | C |
| RHC should be performed for confirmation of efficacy of PAH-specific drug therapy | IIa | C |
| RHC should be performed for confirmation of clinical deterioration and as baseline for the evaluation of the effect of treatment escalation and/or combination therapy | IIa | C |
Catheterization Algorithm to Assess PH and LAD

PH suspected by history and exam

PH at catheterization

1) LVEDP > 15 mmHg?
2) PCW > 15 mmHg?
3) LAP > 15 mmHg?

no

1) Exercise
2) Leg lift
3) Volume challenge
4) Nitric oxide

LVEDP
1) < 15 mmHg
2) 15-24 mmHg
3) > 24 mmHg

PAH
Intermediate Group
PH from LHD

yes

 Consider
Vasodilator challenge

PH from LHD

J Heart Lung Transplant 2012; 31: 913-33
Figure: Approach to patients with pulmonary hypertension and heart failure. PH = pulmonary hypertension; HF = heart failure; R = right; L = left; HC = heart catheterization; mPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; Rx = medications; VAD = ventricular assist device; PAH = pulmonary arterial hypertension.
• When PH is felt to be out of proportion to the HF, initial efforts are again focused on the HF.

• If the PH persists, and the PCWP is maintained in an acceptable range, the use of PAH-specific therapies may be considered.

• Caution must be used, however, because these agents may precipitate fluid retention and pulmonary edema in patients with HF.
• 455 HFpEF patients studied
• mPAP determined by right heart cath.

N=239 PH
 mean PAP= 34 mmHg

N=219 no PH
 mean PAP= 20 mmHg
The Prevalence, Clinical Characteristics, and Prognosis of Diastolic Heart Failure: A Clinical Study in Elderly Saudi Patients With Up to 5 Years Follow-Up

Fayez ElShaer MD¹, Walid Hassan MD¹, Mohamed E Fawzy MD¹, Marilyn Lockyer BSHS¹, Suliman Kharabsheh MD¹, Nathem Akhras PharmD², Maie Shahid MD¹, Hassan ElWidaa MD¹, Naser ElKum PhD³ and Charles Canver PhD¹

Article first published online: 13 FEB 2009
DOI: 10.1111/j.1751-7133.2008.00043.x

© 2009 Wiley Periodicals, Inc.
Risk factors for HF in all patients

- Patients equal to or >65 yrs old
  - HTN: 81.30%
  - DM: 46.10%
  - Hyperlipid: 34.50%
  - IHD: 33.00%
  - Smoker: 5.40%
Primary Outcome: Def. of PH prevalence and severity in HFpEF due to hypertensive heart disease
• Secondary Outcome: Mortality rate according to PASP

n=619
CONTROL Group
LVEF>50%
No CV disease
BMI<30

719
HTN without HFpEF
>50%
Hypertension
No HF

n=244
HTN with HFpEF
LVEF>50%
HF signs/sympt.
no valve disease
Prevalence of PH (PASP ≥ 35 mmHg):
2% in CON; 8% in HTN; 83% in HFpEF

Lam C et al.
JACC 2009;53:1119-1126. PASP in HFPEF
Prevalence, Predictors and Outcome of Pulmonary Hypertension in Elderly Patients with Heart Failure and Preserved Ejection Fraction Versus Heart Failure and Reduced Ejection Fraction

Fayez AlShaera, MD1; Khalid AlHabib, MD2; Hanan AlBackr, MD2; Ahmad Hersia, MD1 and Abdelfatah Elasfar, MD1,4
1National Heart Institute, Cairo; 2King Fahad Cardiac Center, King Khalid University Hospital, College of Medicine, King Saud University; 3Prince Salman Heart Center, King Fahd Medical City, Riyadh, Saudi Arabia and 4Cardiology Department, Tanta University, Cairo.

Background
Pulmonary hypertension (PH) is prevalent among patients with heart failure and remained a strong predictor of cardiovascular mortality even after adjusting for diastolic function.

Objective
We aimed to assess the prevalence, predictors and outcome of pulmonary hypertension in elderly patients with heart failure and preserved ejection fraction (HFPEF) in comparison to patients with heart failure and reduced ejection fraction (HREF).

Methods
A prospective nonrandomized single center study of 529 consecutive patients above the age 65 years admitted with congestive heart failure (CHF). We assessed ejection fraction (EF), the prevalence of hypertension, diabetes mellitus (DM), atrial fibrillation (AF) and coronary artery disease (CAD). We also assessed the prevalence, risk factors and outcome of pulmonary hypertension in those elderly patients with congestive heart failure both with preserved and reduced ejection fraction. Detailed echocardiographic studies for the LV systolic and diastolic parameters and pulmonary artery pressures were performed.

Results
Patients were divided into two groups according to the ejection fraction: 350(66.1%) patients with preserved left ventricular (LV) systolic function with EF ≥50% (group P) and 179(34.9%) patients with reduced LV function with EF <50% (group R). The distribution of risk factors for heart failure included hypertension (81%), followed by DM (46%), and CAD (33%). Compared to HREF, HFPEF was more predominant in, elderly female (38% vs. 26%, P = 0.007), elderly hypertensive (86% vs. 72%, P = 0.0001), LV hypertrophy (67% vs. 45%, P= 0.001), while male (62% vs. 74%, P = 0.001) ischemic heart disease (22% vs. 30.5%, P= 0.001) were more predominant in HREF. Regardless of the level of PAP, Mild PH, less than 50mmHg, was present in 55(10.5%) patients of the entire population (43 in group P and 12 in group R, P value = 0.0001), and 74(14%) patients had moderate PH. (283 in group P and 17 in group R, P value <0.0001), and 74(14%) patients had severe PH (24 in group P and 50 in group R, P value <0.0001). Mild and moderate PH was higher in group P while severe PH was higher in group R. There was statistically significant difference in mortality only in patients with moderate PH (4.2% in group P and 9.4% in group R, P= 0.04). 24-Holter monitoring revealed higher average and maximum heart rates (92.7±8.102 vs. 76.4±6.793bpm, P value <0.05), (125±14.366 vs. 129.30±18.607bpm, P value <0.05), (1.236±1.363bpm vs. 26.8±5.653 vs. 8.7±9.26851, P value <0.05) respectively, longer duration of sinus tachycardia (3.81009±1.53825 versus 1.236±1.363bpm, P value <0.05) and more PVC count (26.8±5.653 vs. 8.7±9.26851, P value <0.05) in Qot chewers.

Conclusions
Mild and moderate pulmonary hypertension was more prevalent in patient with HFPEF while higher degrees were more prevalent in patients with HREF. In the subgroup of patients with
Systolic PA Pressure

HFpEF
- <50 mmHg: 12.00%
- 50-70 mmHg: 81.00%
- >70 mmHg: 7.00%

HFrEF
- <50 mmHg: 12.00%
- 50-70 mmHg: 65.00%
- >70 mmHg: 27%
• *Mild and moderate* pulmonary hypertension was more prevalent in patients with *HFpEF* while *higher degree* was more prevalent in patients with *HFrEF*. 
• HFpEF is common and more prevalent in elderly hypertensive female patients, while HFrEF is common in elderly ischemic male patients.
• LVEF didn't vary significantly by PA systolic pressures; moreover, the effect of PH on outcome was similar both for patients with HFrEF and HFpEF.
KM curves according to median PASP

<table>
<thead>
<tr>
<th>Number remaining</th>
<th>PASP&lt;48 mmHg</th>
<th>PASP≥48 mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 yrs</td>
<td>98</td>
<td>105</td>
</tr>
<tr>
<td>1 yrs</td>
<td>86</td>
<td>78</td>
</tr>
<tr>
<td>2 yrs</td>
<td>80</td>
<td>67</td>
</tr>
<tr>
<td>3 yrs</td>
<td>44</td>
<td>38</td>
</tr>
</tbody>
</table>

$P = 0.002$

Multivariate predictors of Death

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Hazard Ratio</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASP, mm Hg</td>
<td>136</td>
<td>1.20 per 10 mm Hg</td>
<td>0.028</td>
</tr>
<tr>
<td>E/e' ratio</td>
<td>136</td>
<td>0.98 per U</td>
<td>0.199</td>
</tr>
<tr>
<td>Left atrial volume/BSA, ml/m²</td>
<td>136</td>
<td>1.12 per 10 ml/m²</td>
<td>0.237</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>136</td>
<td>1.26 per 0.1 U</td>
<td>0.121</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>136</td>
<td>0.96 per 10 g/m²</td>
<td>0.383</td>
</tr>
</tbody>
</table>
Differences in HF-PH mortality

HFpEF-PH had higher 5-year mortality (52% vs 42% p=0.024).
<table>
<thead>
<tr>
<th>Better prognosis</th>
<th>Determinants of prognosis</th>
<th>Worse prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Clinical evidence of RV failure</td>
<td>Yes</td>
</tr>
<tr>
<td>Slow</td>
<td>Rate of progression of symptoms</td>
<td>Rapid</td>
</tr>
<tr>
<td>No</td>
<td>Syncope</td>
<td>Yes</td>
</tr>
<tr>
<td>I, II</td>
<td>WHO-FC</td>
<td>IV</td>
</tr>
<tr>
<td>Longer (&gt;500 m)*</td>
<td>6-MWT</td>
<td>Shorter (&lt;300 m)</td>
</tr>
<tr>
<td>Peak $O_2$ consumption $&gt;15$ mL·min$^{-1}$·kg$^{-1}$</td>
<td>Cardiopulmonary exercise testing</td>
<td>Peak $O_2$ consumption $&lt;12$ mL·min$^{-1}$·kg$^{-1}$</td>
</tr>
<tr>
<td>Normal or near-normal</td>
<td>BNP/NT-proBNP plasma levels</td>
<td>Very elevated and rising</td>
</tr>
<tr>
<td>No pericardial effusion TAPSE$^\dagger$ $&gt;2.0$ cm</td>
<td>Echocardiographic findings$^\dagger$</td>
<td>Pericardial effusion TAPSE$^\dagger$ $&lt;1.5$ cm</td>
</tr>
<tr>
<td>RAP $&lt;8$ mmHg and CI $&gt;2.5$ L·min$^{-1}$·m$^{-2}$</td>
<td>Haemodynamics</td>
<td>RAP $&gt;15$ mmHg or CI $\leq 2.0$ L·min$^{-1}$·m$^{-2}$</td>
</tr>
<tr>
<td>Test</td>
<td>At baseline (prior to therapy)</td>
<td>Every 3–6 months‡</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>--------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Clinical assessment WHO-FC</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>ECG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-MWT§</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cardiopulmonary exercise testing$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP/NT-proBNP</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>RHC</td>
<td>✓‡</td>
<td></td>
</tr>
</tbody>
</table>
# Management of patients with diastolic heart failure

## Control edema
- Low salt diet (e.g., <2 g sodium per day)
- Diuretic (e.g., furosemide or hydrochlorothiazide)
- ACE inhibitor* (e.g., enalapril or lisinopril)
- Angiotensin II receptor blocker* (e.g., candesartan, valsartan, or losartan)
- Aldosterone antagonist* (e.g., spironolactone)

## Rate control
- Calcium channel blocker (e.g., diltiazem or verapamil)
- Beta blocker (e.g., atenolol, metoprolol)
- Radiofrequency modification of atrioventricular node and pacing

## Maintain and restore atrial contraction
- Cardioversion
- Radiofrequency ablation
- Antiarrhythmic therapy

## Manage myocardial ischemia
- Medical management
  - Nitrates (e.g., isosorbide dinitrate or isosorbide mononitrate)
  - Beta blocker (e.g., atenolol or metoprolol)
  - Calcium channel blocker (e.g., diltiazem or verapamil)
- Percutaneous coronary intervention
- Coronary artery bypass surgery

## Control arterial hypertension
- Diuretic (e.g., chlorothalidone or hydrochlorothiazide)
- Beta blocker (e.g., atenolol or metoprolol)
- Calcium channel blocker (e.g., amlodipine or felodipine)
- Angiotensin converting enzyme inhibitor (e.g., enalapril or lisinopril)
- Angiotensin II receptor blocker (e.g., candesartan, valsartan, or losartan)

*The renin-angiotensin-aldosterone system is inhibited by angiotensin converting enzyme inhibitor, angiotensin II receptor blocker, and aldosterone antagonist and thus these agents have a theoretical benefit in promoting regression of left ventricular hypertrophy and preventing myocardial fibrosis. However more data are required to demonstrate whether they improve outcomes in patients with diastolic heart failure. Two of these three agents may be combined in some patients with proper monitoring but use of all three is generally not recommended.

The list of medications is not comprehensive but rather includes examples that are in common clinical use or have been included in studies of patients with diastolic dysfunction or heart failure. A more exhaustive list of antihypertensive agents can be found in the guidelines of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

*Courtesy of Dr. William H. Gaasch.*
HR = 0.83 (0.69 – 0.99)

p = 0.042
Exploratory (post-hoc): Placebo vs. Spiro by region

US, Canada, Argentina, Brazil
HR=0.82 (0.69-0.98)

Russia, Rep Georgia
HR=1.10 (0.79-1.51)

Interaction p=0.122
• Male, 38 years old
• First presentation at ER dept. for incoming dyspnea
• Severe hypertension (210/130 mmHg)
• PO2= 92 mmhg
• NTproBNP=2390 pg/ml
Baseline

2-months post-therapy *
Endothelium

- L-arginine → e-NOS → Nitric Oxide
- Pre-proendothelin → Proendothelin → Endothelin-1
- Arachidonic acid → Prostacyclin synthesis → Prostacyclin

Inhaled NO → Endothelin Receptor Antagonists

- ETα, ETβ

GC stimulators/activators

- Soluble guanylyl cyclase → cGMP
- cGMP-gated ion channels

PDE5-Inhibitors

- PDE5
- PDE3

Prostaglandins

- Adenilate cyclase → cAMP → AMP
- ATP
Treatment of pulmonary arterial hypertension algorithm

- Pulmonary hypertension (NYHA functional class I, II, III, or IV)
  - Conventional therapy (oral anticoagulant ± diuretics ± oxygen)
    - Acute vasodilator response?
      - Yes
        - Oral calcium-channel blockers
          - Sustained response?
            - Yes
              - Continue calcium-channel blockers
            - No
              - Observation Treat contributing factors
      - No
        - Class I
          - Ambrisentan, or Bosentan, or Macitentan, or Sildenafil, or Tadalafil, or Riociguat*
        - Class II
          - Observation Treat contributing factors
          - Ambrisentan, or Bosentan, or Macitentan, or Sildenafil, or Tadalafil, or Riociguat*
          - No improvement or deterioration
            - Consider combination therapy
              - Atrial septostomy or Lung transplantation
          - Preferred: Epoprostenol
            - Acceptable: Treprostinil IV
        - Class III
          - Ambrisentan, or Bosentan, or Macitentan, or Sildenafil, or Tadalafil, or Riociguat*, or Epoprostenol IV*, or Inhaled Iloprost*, or Treprostinil IV, SC*, or INH

NYHA: New York Heart Association; IV: intravenous; SC: subcutaneous; INH: inhaled.
* Riociguat has been best studied in patients with chronic thromboembolic pulmonary hypertension.
- These agents are not approved for this use by regulatory agencies but may be used by some experts for patients with rapid deterioration or progressive disease.

• Whereas initial studies of PAH-specific therapies were discouraging, more recent ones have suggested promise.

• Consensus statements from experts in the field will be forthcoming and should provide guidance.
Novel Paradigm for HFpEF

- Comorbidities and especially obesity induce a systemic proinflammatory state.
- The proinflammatory state causes coronary microvascular endothelial cells to produce reactive oxygen species (ROS) which limits nitric oxide (NO) bioavailability for adjacent cardiomyocytes.
- Limited NO bioavailability decreases protein kinase G (PKG) activity in cardiomyocytes.
- Low PKG activity removes the brake on cardiomyocyte hypertrophy, inducing concentric LV remodeling and stiffens the cardiomyocyte because of hypophosphorylation of the giant cytoskeletal protein titin.

Paulus and Tschope. JACC 2013: 62, 4: 263-71
Transpulmonary release of CGMP in HF with high PVR. Acute effect of sildenafil
Effects of PDE5 Inhibition on RV Contractility in HFpEF

Stroke Volume
ml/beat

Baseline

Stroke Volume
ml/beat

6 months

[Graph showing data points for Placebo and Sildenafil at baseline and 6 months]

- Placebo
- Sildenafil
Effect of Phosphodiesterase-5 Inhibition on Exercise Capacity and Clinical Status in Heart Failure with Preserved Ejection Fraction (RELAX):

A Randomized Clinical Trial
Study Design

Baseline CPXT, 6MWT, Echo-Doppler, MLHFQ, Biomarkers, and CMR (sinus rhythm)

Double-blind; 1 to 1 randomization stratified by site and rhythm (AF)

Placebo 20 mg TID

Sildenafil 20 mg TID

12 week CPXT, 6MWT, MLHFQ

Placebo 60 mg TID

Sildenafil 60 mg TID

24 week CPXT, 6MWT, Echo-Doppler, MLHFQ, Biomarkers and CMR
# Baseline Features

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (N = 103)</th>
<th>Sildenafil (N = 113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction (%)</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>NT-proBNP (pg/ml)</td>
<td>648</td>
<td>757</td>
</tr>
<tr>
<td>Peak VO2 (ml/kg/min) (% predicted)</td>
<td>11.9 (41%)</td>
<td>11.7 (41%)</td>
</tr>
<tr>
<td>Chronotropic incompetence present</td>
<td>78%</td>
<td>76%</td>
</tr>
<tr>
<td>6MWD (m) (% predicted)</td>
<td>305 (68%)</td>
<td>308 (70%)</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²) - (normal &gt; 2.5)</td>
<td>2.48</td>
<td>2.47</td>
</tr>
<tr>
<td>Relative Wall Thickness ≥ 0.42</td>
<td>44%</td>
<td>48%</td>
</tr>
<tr>
<td>E/e’ - (normal ≤ 8)</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>LA volume index (ml/m²) - (normal &lt; 29)</td>
<td>43</td>
<td>44</td>
</tr>
<tr>
<td>PASP (mmHg) - (normal &lt; 30)</td>
<td>41</td>
<td>41</td>
</tr>
</tbody>
</table>

Median values or % shown

All p > 0.05
Results: Primary Endpoint

Change in Peak VO\textsubscript{2}

\[ p = 0.90 \]

Data are median and IQR

Sensitivity analyses for missing data
Multiple imputation: \[ p = 0.98 \]; LOCF: \[ p = 0.98 \]
Results: Secondary Endpoints

Change in 6MWD

-40
-20
0
20
40
60

Sildenafil
n = 90

Placebo
n = 95

p = 0.92

Data are median and IQR
# Results: Safety

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo</th>
<th>Sildenafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (%)</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>CV or cardiorenal hospitalization (%)</td>
<td>13%</td>
<td>13%</td>
</tr>
<tr>
<td>Adverse events (%)</td>
<td>76%</td>
<td>80%</td>
</tr>
<tr>
<td>Serious adverse events (%)</td>
<td>16%</td>
<td>22%</td>
</tr>
<tr>
<td>Withdrew or Unwilling or Unable to complete 24 week CPXT</td>
<td>8%</td>
<td>16%</td>
</tr>
</tbody>
</table>

*All p > 0.05*
## Results: Other endpoints

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo</th>
<th>Sildenafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in LV mass by CMR (g)</td>
<td>0.6</td>
<td>-1.5</td>
</tr>
<tr>
<td>Change in E/e’</td>
<td>-1.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Change in PASP (mmHg)</td>
<td>-2</td>
<td>2</td>
</tr>
<tr>
<td>Change in creatinine (mg/dl)</td>
<td>0.01</td>
<td>0.05*</td>
</tr>
<tr>
<td>Change in cystatin C (mg/L)</td>
<td>0.01</td>
<td>0.05*</td>
</tr>
<tr>
<td>Change in NT-proBNP (pg/ml)</td>
<td>-23</td>
<td>15*</td>
</tr>
<tr>
<td>Change in endothelin-1 (pg/ml)</td>
<td>-0.01</td>
<td>0.38*</td>
</tr>
<tr>
<td>Change in uric acid (mg/dl)</td>
<td>-0.01</td>
<td>0.30*</td>
</tr>
</tbody>
</table>

*p-value < 0.05

Median values shown
• Chronic therapy with the PDE-5 inhibitor sildenafil was not associated with clinical benefit in HFP EF
Continued efforts to identify key pathophysiologic perturbations and novel therapeutic targets in HFpEF are needed.

Fayez elshaer
And Finally

Thank You
Normal Hemodynamics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAP, mm Hg</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>14.0 ± 3.3</td>
</tr>
<tr>
<td>Systolic</td>
<td>20.8 ± 4.4</td>
</tr>
<tr>
<td>Diastolic</td>
<td>8.8 ± 3.0</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>8.0 ± 2.9</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>76 ± 14</td>
</tr>
<tr>
<td>Cardiac index, liters/min/m²</td>
<td>4.1 ± 1.3</td>
</tr>
<tr>
<td>PVR, dynes · sec/cm⁵</td>
<td>74 ± 30 (&lt;1 WU)</td>
</tr>
</tbody>
</table>

PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, peripheral vascular resistance; SD, standard deviation.

N = 882 healthy volunteers.

Adapted from Kovacs et al.³

Can Respir J 2009; 34: 888-94
Treatment Goals for PH-LHD

- Improvement in dyspnea and functional capacity
- Reduction in morbidity and mortality
- Successfully bridging patients to advanced therapies such as heart transplantation and mechanical circulatory support
- The mainstay of current therapy will be diuretics and arterial vasodilators such as ACE inhibitors and hydralazine.
- For HFpEF there are trials underway with PDE-5 inhibitors and soluble guanylate cyclase cyclase stimulators
Novel Paradigm for HFpEF

- In the past decade, several groups obtained myocardial tissue from patients with HFPEF or LV diastolic dysfunction for pathologic analysis.
- Specific alterations in myocardial structure and function relevant to concentric LV remodeling and diastolic dysfunction were observed with HFPEF.
- Structural alterations included cardiomyocyte hypertrophy, interstitial fibrosis; functional changes include incomplete relaxation, increased cardiomyocyte stiffness.
- There was abnormal intramyocardial signaling.

Novel Paradigm for HFP EF (2)

- Stiff cardiomyocytes and increased collagen deposition by myofibroblasts cause diastolic LV dysfunction which is the major cardiac functional deficit in HFP EF.
- The most important non-cardiac comorbidities are overweight/obesity, diabetes mellitus, COPD, anemia and chronic kidney disease.
- All of these have the ability to induce a systemic inflammatory state.

Paulus and Tschope. JACC 2013: 62, 4: 263-71
Novel Paradigm for HFpEF

Myocardial Remodeling in HFPEF
Importance of Comorbidities

- Overweight/Obesity
- Hypertension
- Diabetes Mellitus
- COPD
- Iron Deficiency

Endothelium

- ROS
- VCAM
- E-selectin
- NO
- ONOO-
- Leukocytes
- TGF-β
- Fibroblasts
- Myofibroblasts
- Collagen

Cardiomyocytes

- sGC
- cGMP
- F_passive
- PKG
- Hypertrophy

Paulus and Tschope. JACC 2013: 62, 4: 263-71
Novel Paradigm for HFpEF

Myocardial Remodeling in HFpEF and HFrEF

HFpEF

- Overweight/Obesity
- Hypertension
- Diabetes Mellitus
- COPD
- Iron Deficiency
- IL-6
- THF-α
- ST2
- Pentraxin 3

ROS

VCAM E-selectin

ONOO^-

NO^-

sGC

cGMP

PKG

F\text{passive} \quad \text{Hypertrrophy}

HFrEF

- Collagen
- Autophagy
- Apoptosis
- Necrosis
- Ischemia
- Infection
- Toxicity

ROS

Paulus and Tschope. JACC 2013: 62, 4: 263-71
Novel Paradigm for HFpEF

Myocardial Remodeling in HFPEF, HFREF and Advanced HFREF

HFPEF
- Overweight/Obesity
- Hypertension
- Diabetes Mellitus
- COPD
- Iron Deficiency
- IL-6
- TNF-α
- sST2
- Pentraxin 3

VCAM E-selectin
ROS
NO↓
TGF-β
Collagen
sGC↓
cGMP↓
PKG↓
F_passive↑
Hypertrophy

HFREF

Advanced HFREF
- IL-6
- TNF-α

VCAM E-selectin
ROS
NO↓
TGF-β
Collagen
sGC↓
cGMP↓
PKG↓
F_passive↑
Hypertrophy
- Necrosis
- Apoptosis
- Autophagy

Ischemia
Infection
Toxicity

Paulus and Tschope. JACC 2013: 62, 4: 263-71
Myocardial Remodeling in HFPEF

Importance of Comorbidities

- Overweight/Obesity
- Hypertension
- Diabetes Mellitus
- COPD
- Iron Deficiency

IL-6
TNF-α
sST2
Pentraxin 3

Endothelium

ONOO
\[ \text{NO} \downarrow \]

ROS
VCAM
E-selectin

Leukocytes
Fibroblasts
Myofibroblasts

Cardiomyocytes

sGC
\[ \text{cGMP} \downarrow \]
\[ \text{PKG} \downarrow \]
Hypertrophy

\[ \text{F}_{\text{passive}} \uparrow \]

Paulus and Tschope. JACC 2013: 62, 4: 263-71
<table>
<thead>
<tr>
<th>SPAP</th>
<th>Groups</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HFrEF</td>
<td></td>
<td>HFpEF</td>
</tr>
<tr>
<td>&lt; 50 mmHg (55)</td>
<td>n = 12</td>
<td>6.7%</td>
<td>n = 43</td>
</tr>
<tr>
<td>50-70 mmHg</td>
<td>n = 117</td>
<td>65.3%</td>
<td>n = 283</td>
</tr>
<tr>
<td>&gt; 70 mmHg</td>
<td>n = 50</td>
<td>27.9%</td>
<td>n = 24</td>
</tr>
</tbody>
</table>
• The pathogenesis of pulmonary hypertension (PH) is complex and likely multifactorial. However, it is clear that overlap exists since vascular remodeling and increased pulmonary vascular resistance are common to all groups.

• Group 1 pulmonary arterial hypertension (PAH) is a proliferative vasculopathy of the small muscular pulmonary arterioles. It is characterized pathologically by medial hypertrophy, intimal hyperplasia as well as by plexiform lesions. The pathophysiology of group 2, 3, 4, or 5 PH is less well understood than group 1 PAH.
The E/e' ratio does not reliably estimate LV filling pressures in normal subjects and patients with mitral valve disease including heavy mitral annular calcification. In patients with mitral valve disease, some studies have shown that the ratio of IVRT to the time interval between the onset of mitral E and annular e' (T(E-e)) can be used to predict pulmonary capillary wedge pressure (PCWP) [25].
• In patients with constrictive pericarditis, an inverse relationship between E/e' and PCWP was observed \([26]\).

• The systolic filling fraction (SFF) is computed as \(S/(S + D)\). It is computed using TVI of the above signals (\textit{figure 3}), though peak velocities may be used. PV flow.

A Vp > 50 cm/s is considered normal. Studies in animals and humans have shown that Vp is inversely related to the time constant of LV relaxation and is not affected by preload.
• A Vp >50 cm/s is considered normal. Studies in animals and humans have shown that Vp is inversely related to the time constant of LV relaxation and is not affected by preload. Therefore, the presence of an abnormally reduced Vp can help distinguish patients with pseudonormal filling from those with normal LV relaxation [31]. Furthermore, the ratio of peak E-wave velocity to Vp (E/Vp) correlates with LV filling pressures, particularly in patients with depressed EF [2,32-34]. In a small study, E/Vp ≥2.5 predicted a PCWP of >15 mmHg with a sensitivity and specificity of 78 and 77 percent in patients with LVEF <50 percent and 71 and 73 percent in patients with LVEF ≥50 percent [33].
Definition of PH by Right Heart Catheterization

- Pulmonary Hypertension
  - mPAP >= 25 mmHg

- Pulmonary Arterial Hypertension
  - mPAP >= 25 mmHg
  - PCWP or LVEDP <= 15 mmHg

- Pulmonary Hypertension due to Left Heart Disease
  - mPAP >= 25 mmHg
  - PCWP > 15 mmHg
  - LVEDP > 18 mmHg

J Heart Lung Transplant 2012; 31: 913-33