

Pulmonary Hypertension Associated with Diastolic Heart Failure

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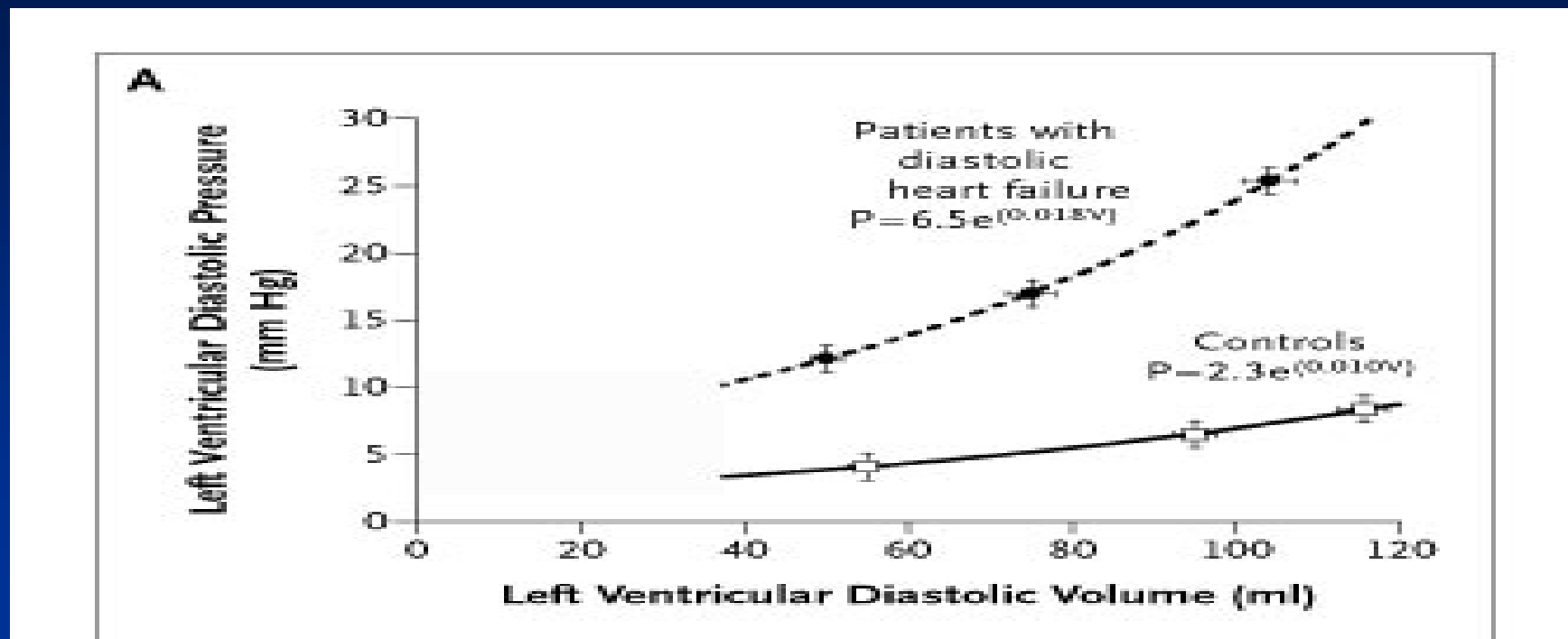


Diastolic Heart Failure (DHF)

- DHF is a clinical syndrome characterized by the symptoms and signs of heart failure, a preserved ejection fraction, and abnormal diastolic function
- These abnormalities are caused by a decrease in ventricular relaxation and/or an increase in ventricular stiffness (reduced compliance)



Diastolic Pressure-Volume Relation in Patients with DHF



Patients with DHF sustain their normal cardiac output via a compensatory elevation of left ventricular filling pressures

- Over 50% of persons 65 years and older who have heart failure are diagnosed as having DHF
- Patients with DHF are generally elderly with a predominance among women
- Risk factors for DHF include hypertension, coronary artery disease, diabetes and obesity

- Clinical signs and symptoms include dyspnea with effort and eventually RV failure with edema, similar to category 1 PAH
- Important and distinctive symptoms are orthopnea and paroxysmal nocturnal dyspnea, which are not features of PAH



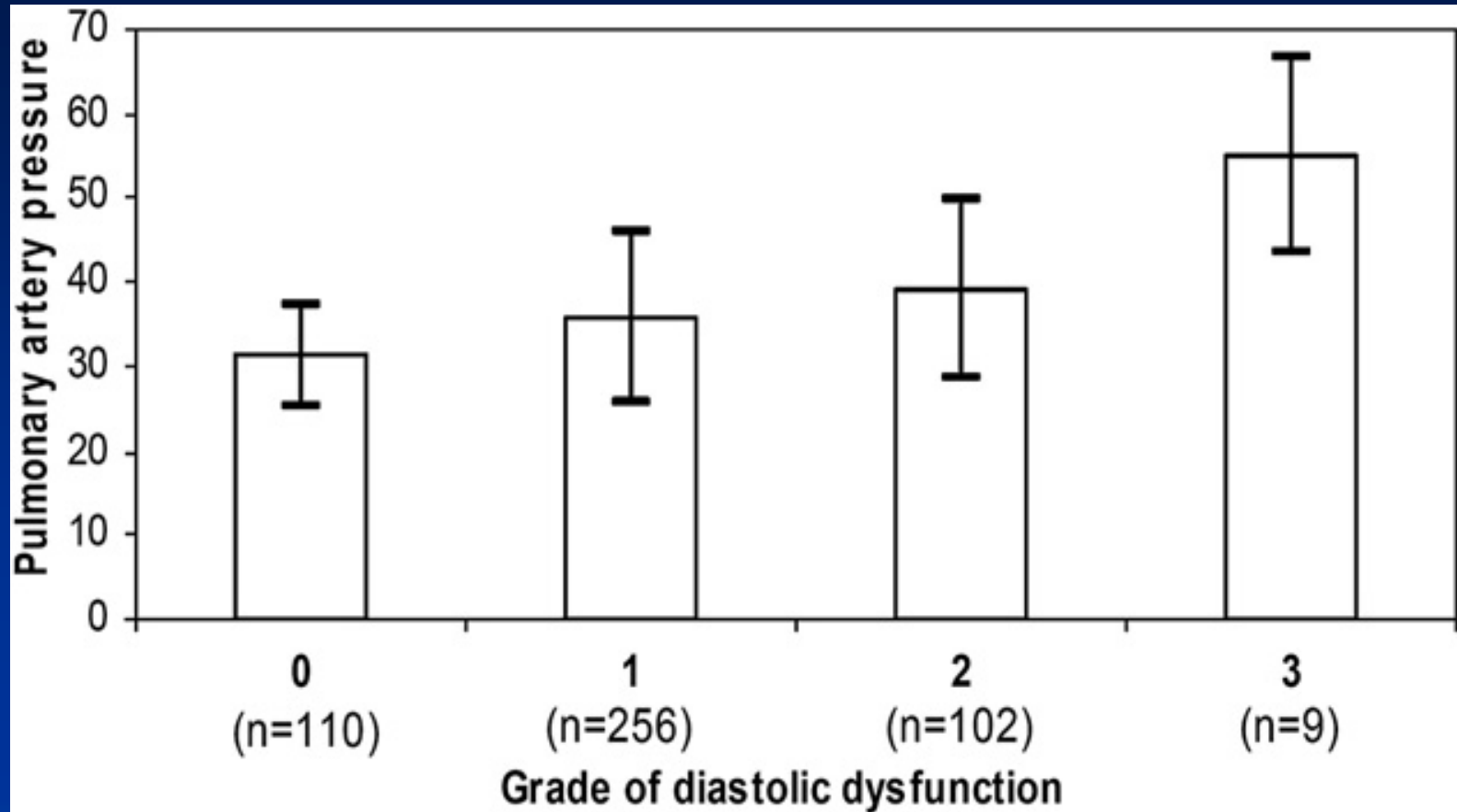
The diagnosis of DHF requires the following three conditions:

- Signs and symptoms of HF
- Normal or mildly abnormal LV systolic function
- Evidence of LV diastolic dysfunction via noninvasive (echocardiography) or invasive (RHC) methods



- Although early case reports described severe PH in patients with DHF, the prevalence of PH and its severity remain poorly defined.
- Klapholz et al reported an average RVSP of 47 mmHg using doppler echocardiography in a large series of patients with DHF

The correlation between diastolic dysfunction and PH



- Patients with advanced diastolic dysfunction have significantly higher PH
- No difference between low and high grade diastolic dysfunction regarding: age, gender, HTN or CAD

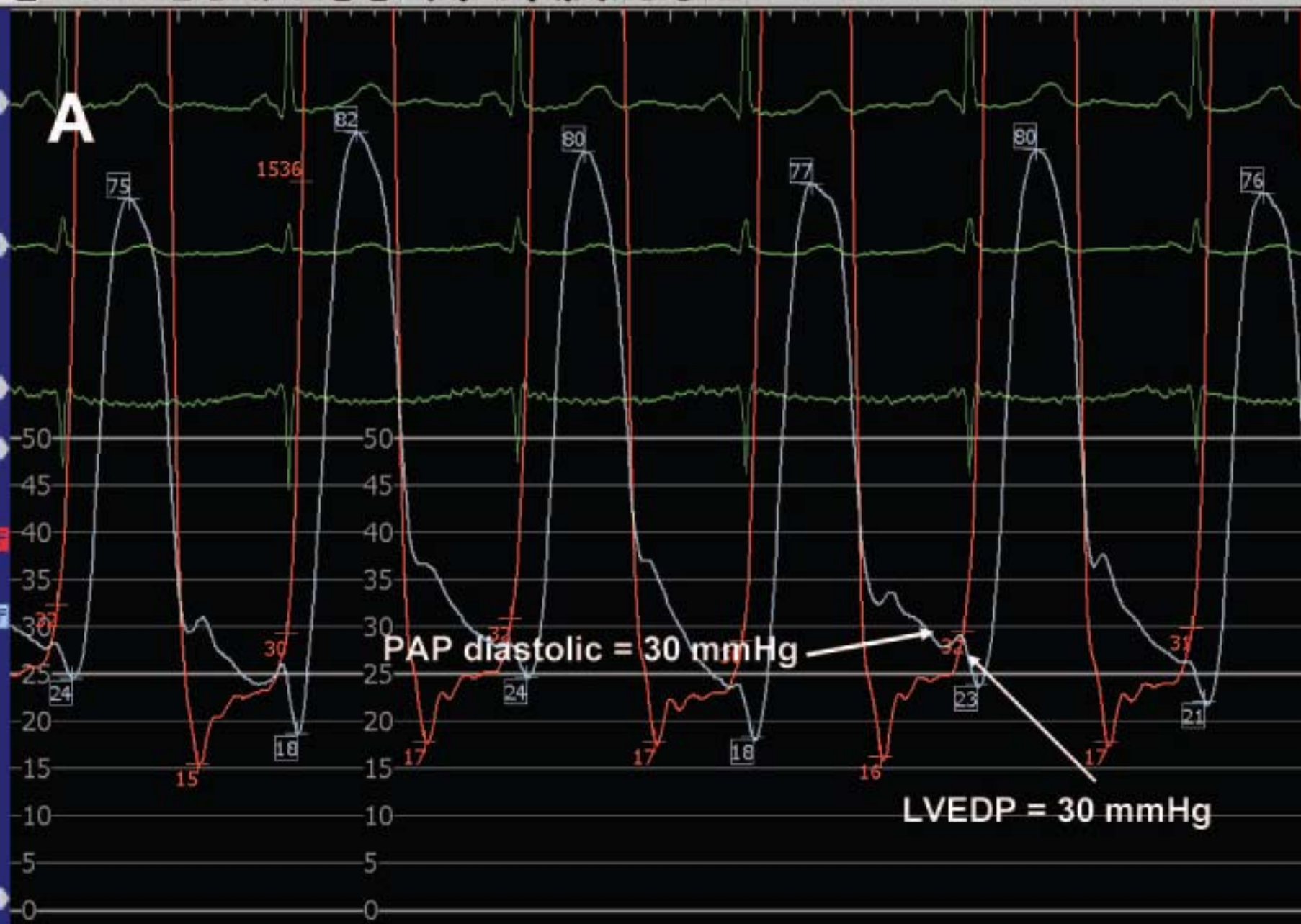


Two hemodynamic profiles are common in these patients:

- Most patients will have an elevation in PAP with only a minimal increase in the TPG, (<12 mmHg), due to the passive increase in PAP
- The preserved RV must generate high systolic pressures to ensure adequate forward blood flow in these patients, and thus moderate degrees of PH are not only characteristic but also favorable

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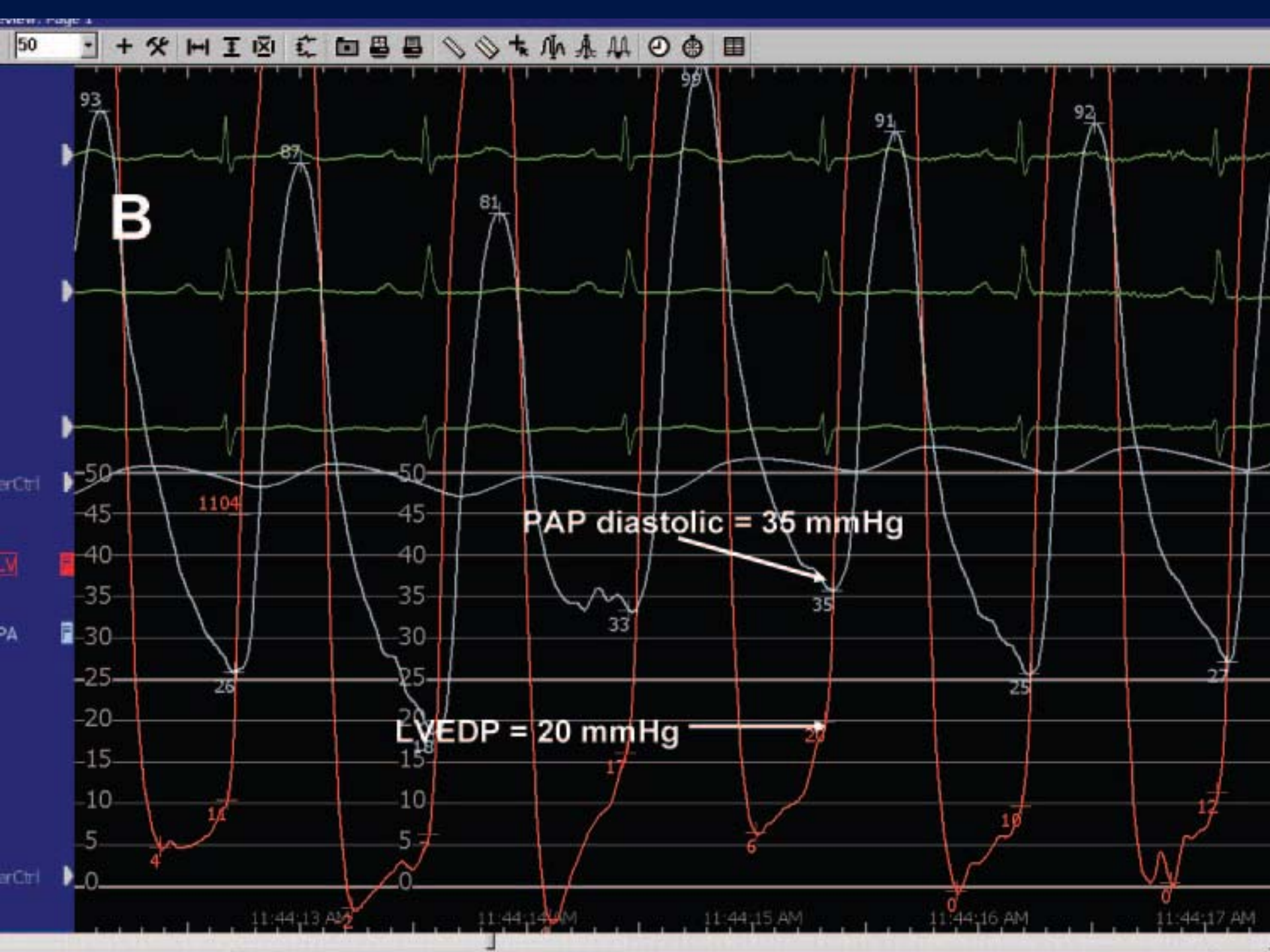
PAP diastolic = 30 mmHg

LVEDP = 30 mmHg

- A subset of patients have marked elevations in PAP beyond that which is necessary to maintain cardiac output.
- In these patients there is a marked elevation in pulmonary arterial diastolic pressure with increased TPG

($TPG = MPAP - PCWP > 12 \text{ mmHg}$) -

out of proportion PH



B

PAP diastolic = 35 mmHg

LVEDP = 20 mmHg

What are the factors which lead to the development of out of proportion PH in patients with chronic HF ?



Endothelial Dysfunction

- Basal pulmonary artery NO production is relatively deficient in patients with HF and secondary PH
- The loss of NO-dependent vasodilatation may contribute to the development of PH
- Patients with severe HF have significantly elevated plasma ET-1 levels that are correlated with PAP and PVR suggesting that ET-1 may be a mediator or marker for reactive PH in patients with LV failure

Moraes et al; *Circulation*. 2000

Stewart et al; *Ann Intern Med* 1991

- ET-1 may be involved in mediating angiotensin-stimulated vascular hypertrophy and may increase local concentrations of catecholamines
- Activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system contribute to vasoconstriction and reduced NO production

Guarda et al; Cardiovasc Res. 1993
Moreau et al; Circulation. 1997

Genetic susceptibility

- The variability in the response of the pulmonary arterial circulation to the elevated venous pressure indicates that genetic factors may dictate the potential reversibility of the disease
- Hansmann et al reported that insulin resistance, frequently observed in association with impaired LV diastolic function, is independently linked to the development of PH

Pathology

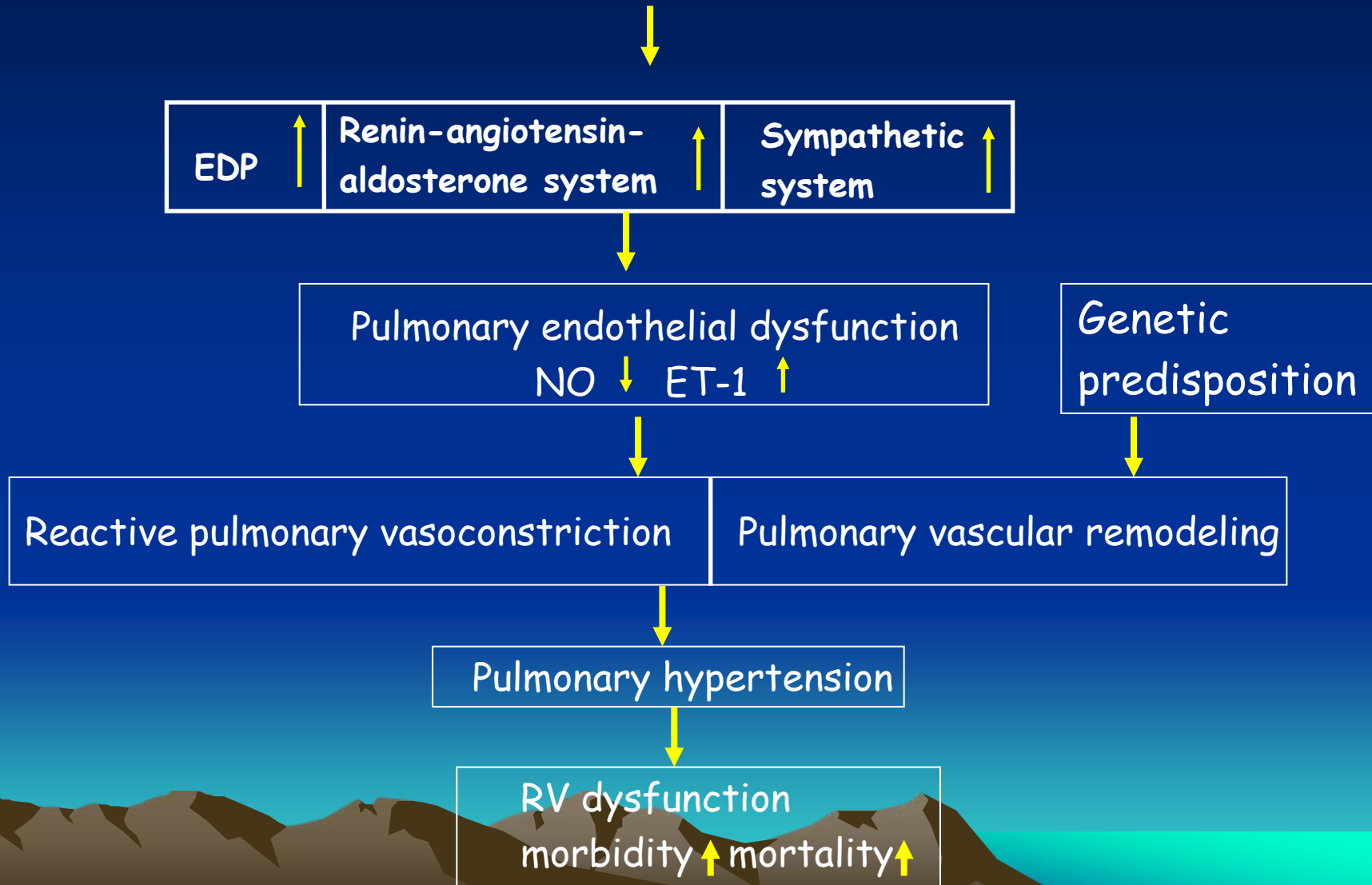
Abnormal thickening of the veins together with intimal fibrosis, abnormalities of elastic fibers and medial hypertrophy of the pulmonary arteries result in vascular stiffness and reduced vasodilator responsiveness



Septal veins with nearly occluded lumens by fibrous intimal thickening

Wagenvoort et al; Pathology of Pulmonary Hypertension 1997
Pietra et al, J Am Coll Cardiol. 2004

LV DYSFUNCTION

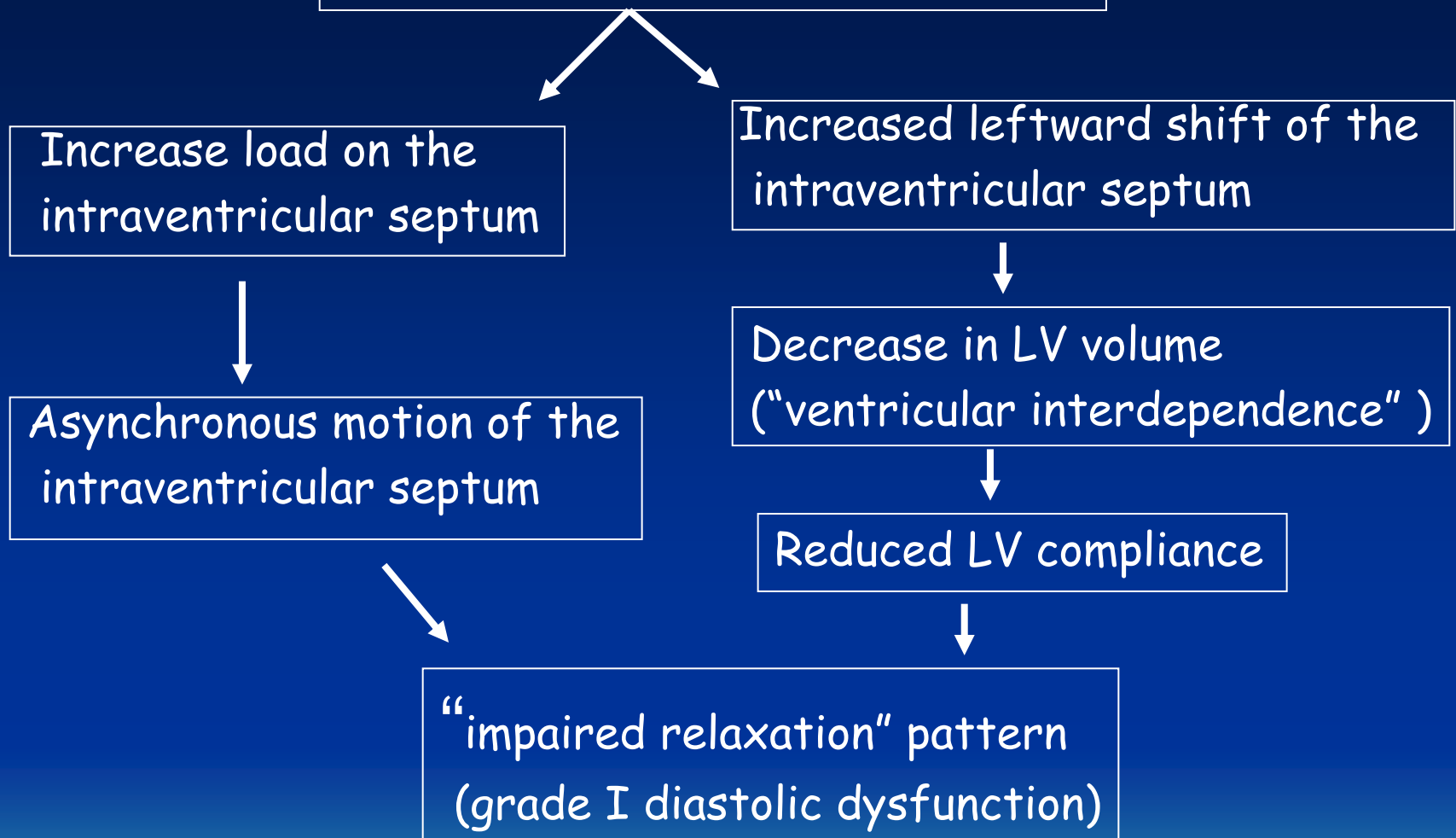


Distinguishing between
DHF with secondary PH
and

IPAH with secondary diastolic dysfunction
can be quite challenging



Chronic RV pressure overload



Clinical studies suggest that while LV diastolic function is altered in IPAH, it is not perturbed enough to result in elevated PCWP

- A normal PCWP at rest may still be present in patients with DHF and PH
- Echocardiography may be helpful:
 - Evidence of LVH, LAE and advanced diastolic dysfunction (grades II-IV) support the diagnosis of DHF
 - Not all patients with DHF have echocardiographic evidence of LVH and may have only grade I diastolic dysfunction

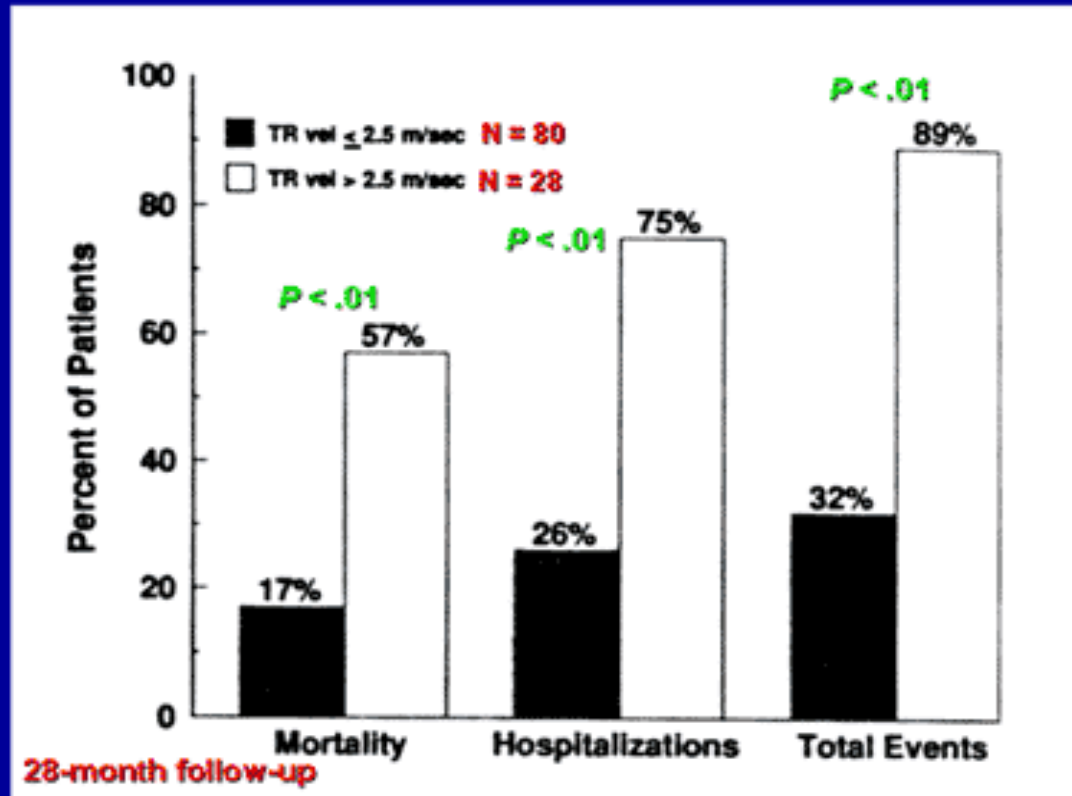


- Using exercise, a vasodilator challenge or an inotropic challenge at the time of RHC to increase the cardiac output may be helpful.
- If a significant increase in cardiac output is accompanied by an increase in PCWP, the patient likely has DHF
- Large V wave in the PCWP tracing which reflects reduced atrial compliance also supports the diagnosis of DHF



Clinical Implications of Secondary PH In Systolic HF

Figure 2



TRV > 3.0 m/s

Reproduced with permission; Abramson SV, et al. Ann Intern Med. 1992;116:888-895.

Death and hospitalization for heart failure were increased
in patients with PH

DHF and PH- clinical experience

- 13 cases with severe symptoms of effort dyspnea and signs of right heart failure were referred to our clinic.
- Their average age was 76 ± 7 year old and 11/13 were females. The average BMI was 29.9 ± 5
- On echocardiogram all had good LV function with $EF > 55\%$, diastolic dysfunction grade I-II and $SPAP > 55$ mmHg.
- All had Negative work-up for other causes of PH

- Ten patients (77%) had **resting hypoxemia** and five had **obstructive sleep apnea**. All were treated with CPAP.
- Eight patients (62%) had **CAD** and a history of previous CABG or interventional heart catheterizations.
- **Atrial fibrillation** was present in 11(85%) of the patients and **diabetes mellitus** and **hypertension** in 6 (46%) and 9 (69%) of the patients respectively.



- On RHC {mmHg}:
 - Mean RAP - 14 ± 6
 - Mean PAP - 53 ± 7
 - Mean capillary wedge pressure - 24 ± 5
 - TPG - 26 ± 5 .
 - PVR - 7.6 ± 3 Wood unit
 - SVR - 22 ± 6 Wood units
 - Mean cardiac index was 2.3 ± 0.6 L/Minute/M².
 - Only two patients (15%) had positive pulmonary vaso-reactive response to NO inhalation.

All have DHF with out of proportion PH
(TPG > 12 mmHg and PVR > 3 Wood unit)

Treatment

- Treatment of DHF can be framed in 2 steps:
 - Decreasing pulmonary venous pressure at rest and during exertion.
 - Treatment of the disease that contributes to the diastolic dysfunction such as hypertension or CAD
- When successful, the pulmonary arterial pressure will also fall, and the cardiac output will increase

Pulmonary vasodilator therapy ?

- The main concern is that by decreasing the PVR, there is an associated increase in the cardiac output and venous return to the LV.
- In the presence of a noncompliant LV, it would trigger further failure by increasing an already elevated left heart filling pressure and may result in pulmonary edema

However, Several studies have tested the effects of specific pulmonary vasodilators in patients with coexisting **LV systolic failure** and PH

Table 2. Major Trials With Pulmonary Vasodilators in Patients With Heart Failure

Study ^{Ref}	Agent	Condition	N patients randomized	Clinical Improvement	Hemodynamic improvement	Effect on Mortality
FIRST ²⁹	Epoprostenol	Advanced HF	471	Yes	Yes	Worsen
RITZ-5 ³⁶	Tezosentan	Pulmonary edema	84	Yes	N/a	N/a
VERITAS ³⁷	Tezosentan	ADHF	1300	Similar to placebo	+/-	None
REACH-1 ³⁹	Bosentan	Severe HF	377	Worse than placebo, then similar	N/a	None
ENABLE ⁴⁰	Bosentan	Severe HF	1613	Probable worse than placebo	N/a	None

ADHF: Acute decompensated heart failure; HF: heart failure.

Clinical and echocardiographic evidences of DHF and PH

RT(\pm L) HC

PH out of proportion to DHF

Optimize therapy for HF and risk factors

Persistent symptoms?

Yes ↓

Repeat RHC

↓ No

Continue RX for HF

Persistent PH, high TPG and PCWP $<$ 20

Should specific PAH therapy be consider?

Suggested approach to patients with PH and DHF

PHARMACOLOGY



AGE 0-4
AMOXICILLIN

4-12
RITALIN

12-18
APPETITE
SUPPRESSANTS

18-24
NO-DOZ

24-38
PROZAC

38-65
VIAGRA

65 —
EVERYTHING
ELSE

