The Scourge of Pulmonary Hypertension in Acute Heart Failure

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What's a Scourge?

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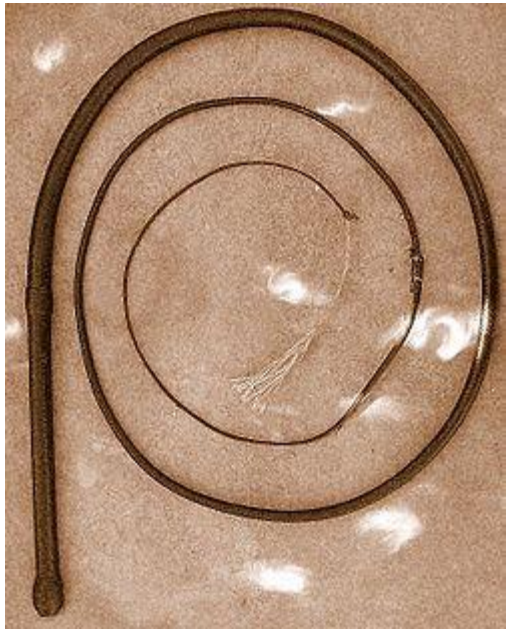
- שוט
- פרגול
- יסור

- Whip
- Punishment
- Agony
- Torment
- Suffering

IS IT ??



Pulmonary Hypertension Predicts Mortality and Morbidity in Patients with Dilated Cardiomyopathy

Abramson SV et al.

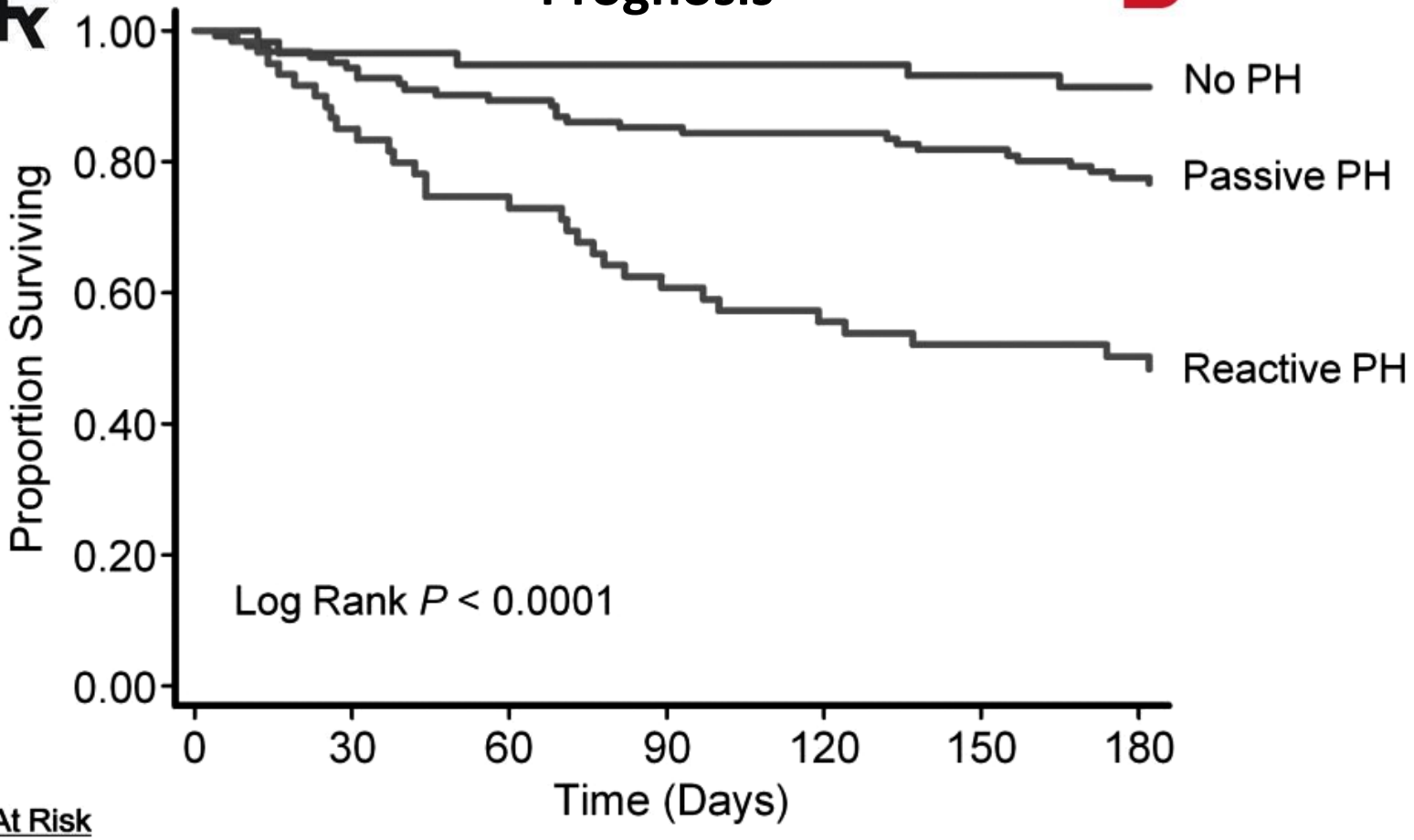
- *Objective:* ***To ascertain whether pulmonary hypertension,*** as assessed noninvasively by continuous wave Doppler of tricuspid regurgitation**, can be an important independent factor in the prognosis of patients with ischemic or idiopathic dilated cardiomyopathy.**
- *Patients: Consecutive sample of 108 patients who* presented for a scheduled office visit during a 15- month period.
- *Results: Twenty-eight patients had a high velocity of* and 80 patients had a low velocity. After **28 months of follow-up**, the mortality rate was 57% in patients with a high velocity *TR* (> 2.5 m/s) compared with 17% in patients with a low velocity ….

  …….
- *Conclusion****: Noninvasive assessment of pulmonary*** **hypertension using continuous-wave Doppler of TR can predict morbidity and mortality in patients with ischemic or idiopathic dilated cardiomyopathy.**

Annals of Internal Medicine. 1992;116:888-895.

Why???

Pulmonary HTN and HF: Prognosis



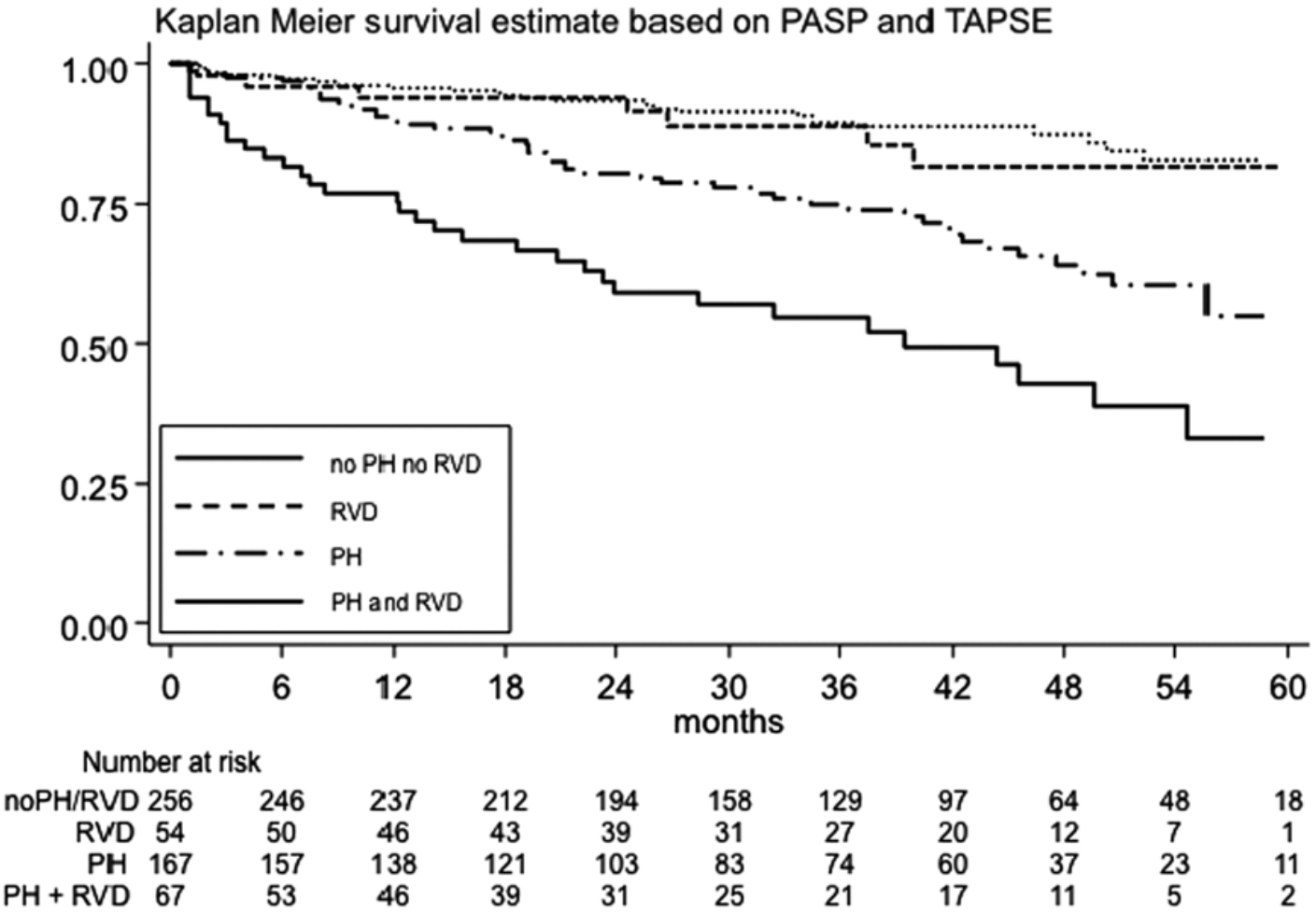
No. At Risk

No PH:	58	56	55	55	55	54	53
Passive PH:	124	116	107	102	100	96	91
Reactive PH :	60	51	43	35	32	29	28

Six-month survival among patients hospitalized with acute heart failure according to their post-treatment pulmonary hypertension profile.

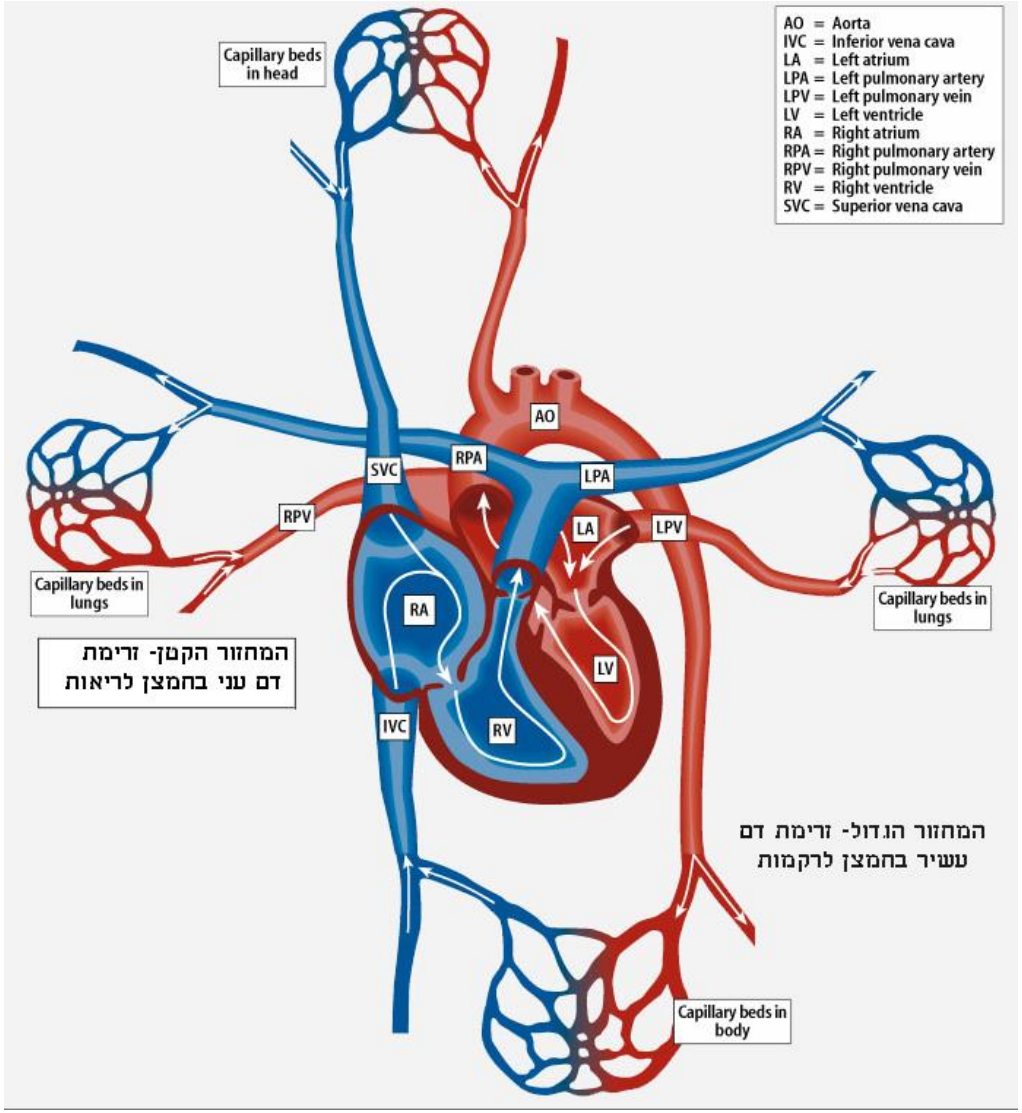
Aronson et al. *Circ Heart Fail. 2011;4:644–650.*

Pulmonary HTN and HF: Prognosis

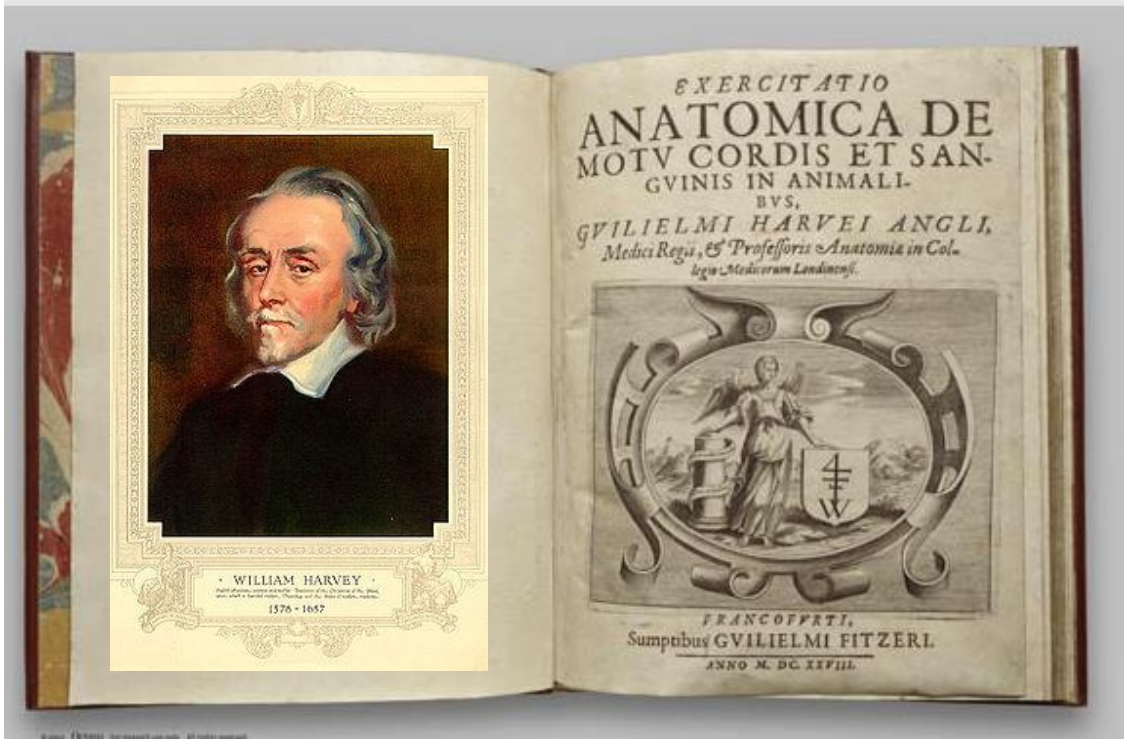


Prognostic relevance of a non-invasive evaluation of RV function and pulmonary artery pressure in patients with chronic HF . **Ghio S et al. Europ J of Heart Failure 2014; 15**:408-414

Cardiac cycle



"The Right ventricle may be said to be made for the sake of transmitting blood through the lungs, not for nourishing them."

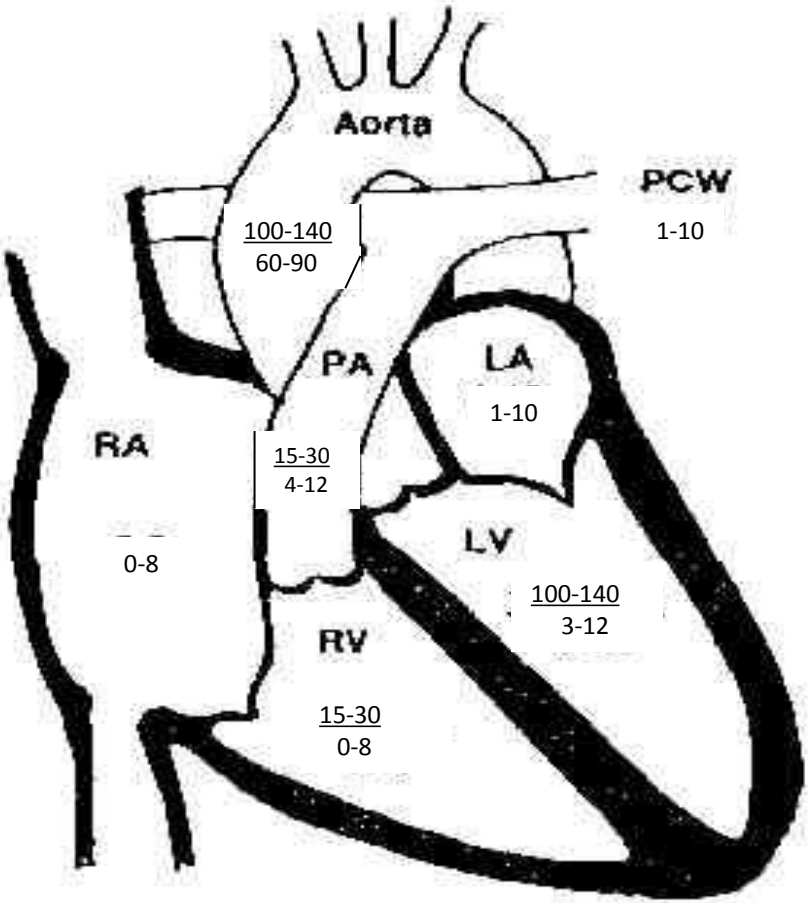


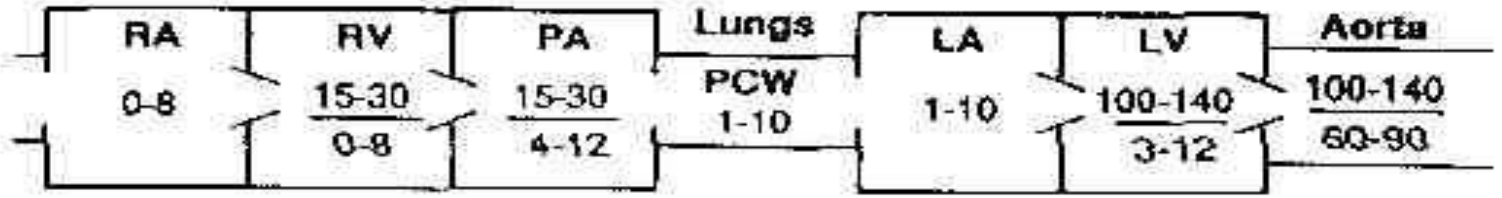
William Harvey, Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus,1628

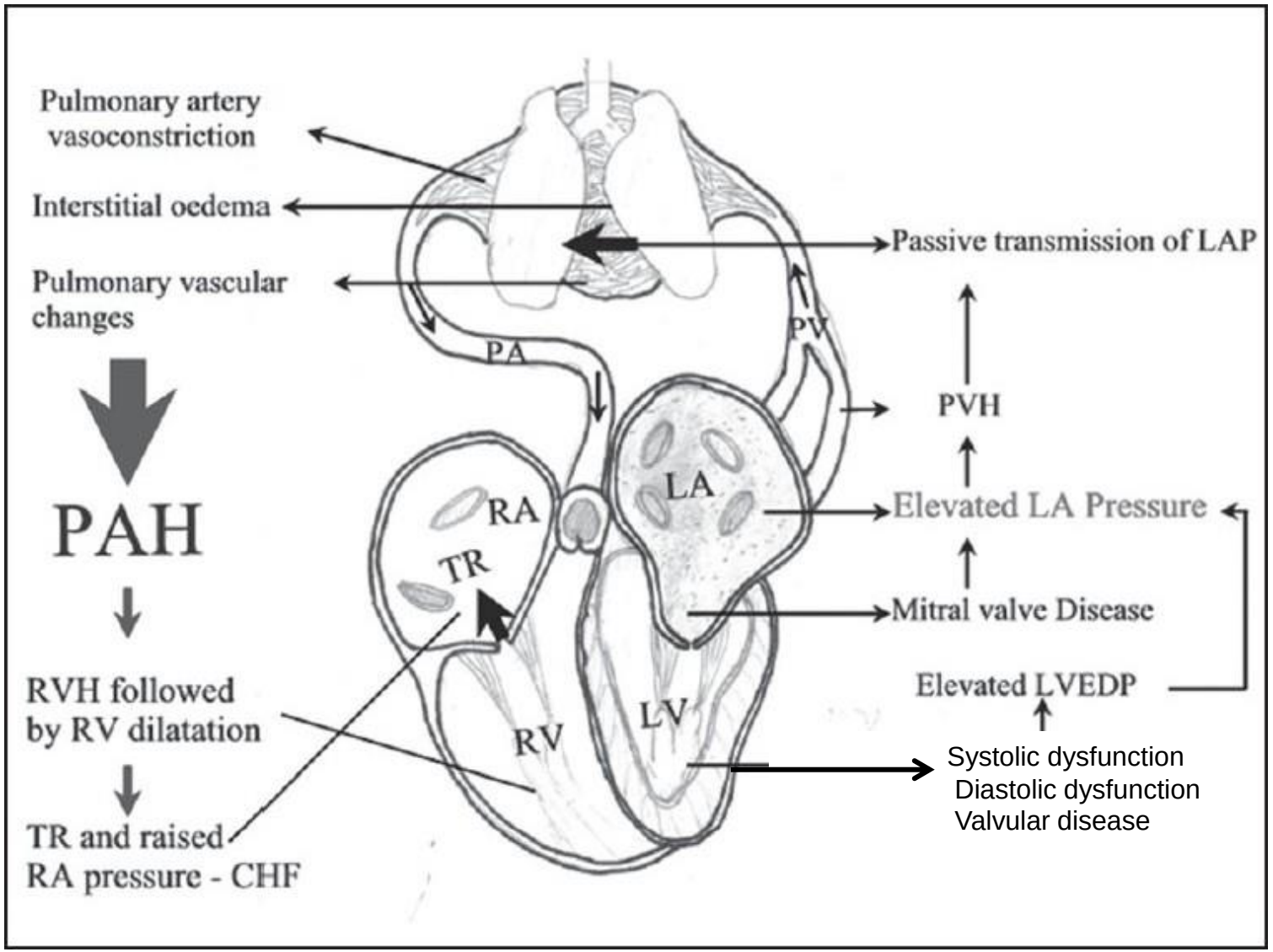
Right Heart Failure

- 1. Preload: Fluid overload
- 2. Right ventricular failure
- 3. Afterload: Pulmonary Hypertension

Normal pressures






Pulmonary artery vasoconstriction
Interstitial oedema
Pulmonary vascular changes
PAH
RVH followed by RV dilatation
TR and raised RA pressure - CHF
Passive transmission of LAP
PVH
Elevated LA Pressure
Mitral valve Disease
Elevated LVEDP
Systolic dysfunction
Diastolic dysfunction
Valvular disease
PA
PV
RA
TR
LA
RV
LV

Pulmonary Hypertension in Acute Heart Failure:

Content

- Prevalence
- Definition
- Pathophysiology
- Clinical significance
- Therapy

Medical therapy in HF

ACE inh,
BB
MRA

Improved prognosis & **delayed** disease progression

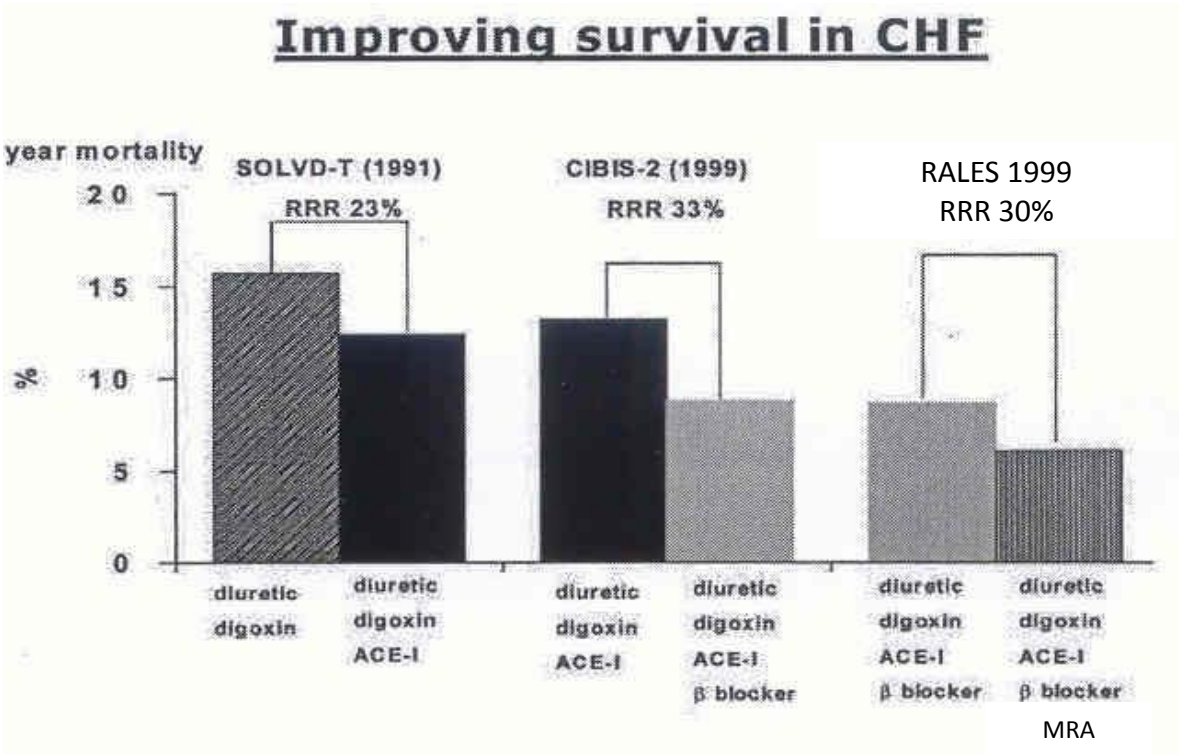


Figure 5. Cumulative benefits of incremental neurohumoral inhibition in CHF. Abbreviations as in Figures 1 through 3.

The New HF Patient's clinical characteristics

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Co-morbidities:	DM with end organ involvement
	PVD: Ischemic ulcers,
	CRF, Liver function Abnormalities
Low BP (100/60):	Low CO state
Cardiac Cachexia:	Catabolic metabolism

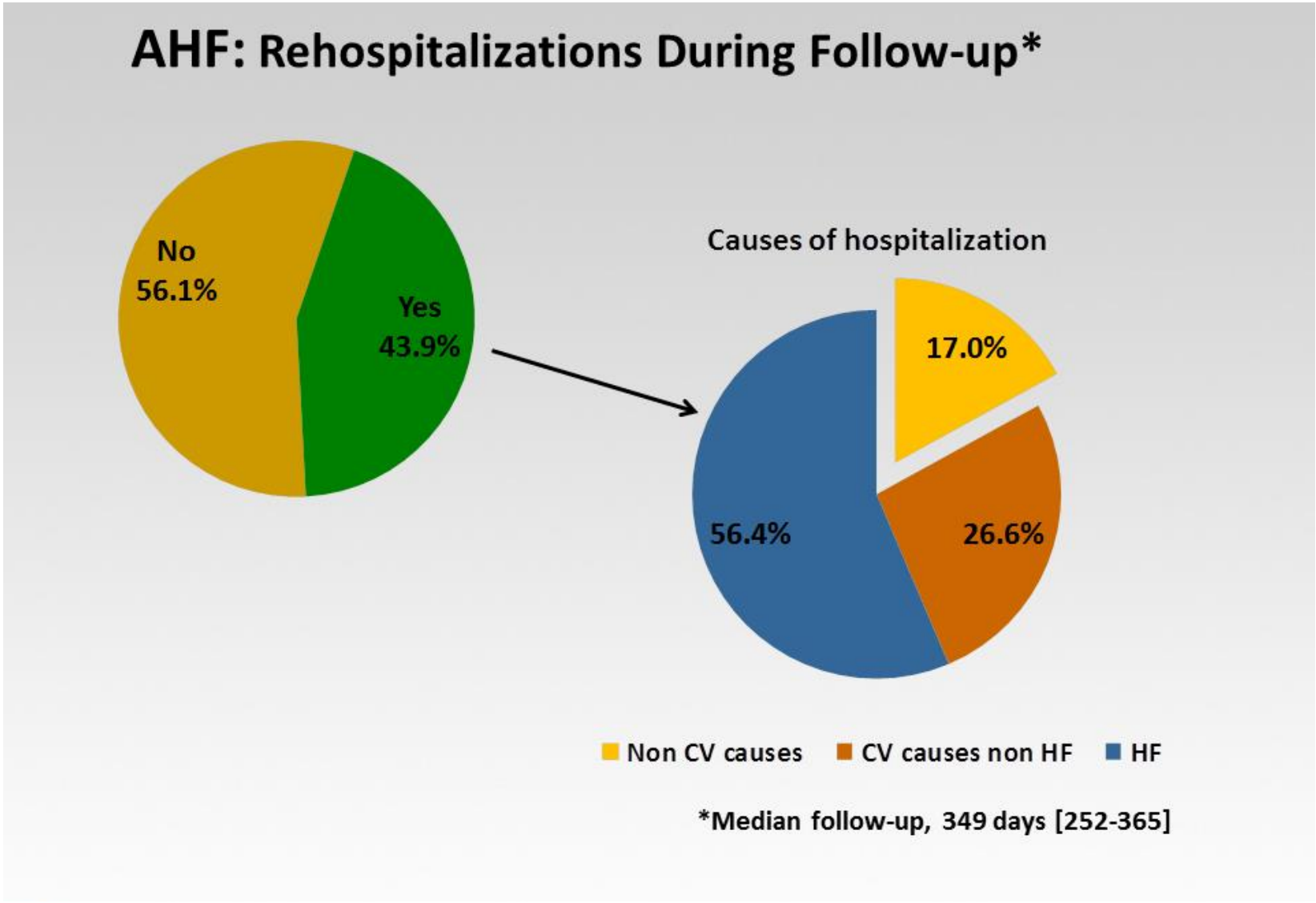
Coagulopathy.

Anemia (Fe. Def.)…

Pulmonary HTN

Prevalence of Pulmonary Hypertension in Patients With Acute Heart Failure

Kjaergaard 2007	388	LVEF 33%	RVSP ≥39 mm Hg	**50%**
			RVSP ≥50 mm Hg	**25%**
Khush 2009	171	LVEF ≤30%	RHC mPAP ≥25 mm Hg; PCWP >15 mm Hg; PVR ≥3 WU:	**47%**
Aronson 2011	242	LVEF 25±13%	RHC mPAP >25 mm Hg	**76.0%**
			PVR ≤3 WU (passive)	**51.2%**
			PVR >3 WU (reactive)	**24.8%**



Maggioni AP et al, Eur J Heart Fail, 2013;15(7):808-817

Heart Failure: Gradual disease progression

- Elevation of pulmonary pressures
- Gradual worsening of RV function
- Combination of low perfusion & congestion
- Low cardiac output: Low BP, intolerance to drugs
- Malabsorption: Cardiac cachexia
- Multi-organ failure
- Extreme agonizing weakness
- Death

Classification of PH

(Dana point 2008)

1. PAH

- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2
  - 1.2.2 ALK-1, endoglin (with or without hereditary haemorrhagic telangiectasia)
  - 1.2.3 Unknown
- 1.3 Drugs and toxins induced
- 1.4 Associated with (APAH)
  - 1.4.1 Connective tissue diseases
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
  - 1.4.6 Chronic haemolytic anaemia
- 1.5 Persistent pulmonary hypertension of the newborn

1'. Pulmonary veno-occlusive disease and/or pulmonary and/or capillary haemangiomatosis

2. PH due to left heart disease

- 2.1 Systolic dysfunction
- 2.2 Diastolic dysfunction
- 2.3 Valvular disease

3. Pulmonary hypertension due to lung diseases and/or hypoxia

- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental abnormalities

4. Chronic thromboembolic pulmonary hypertension

5. PH with unclear and/or multifactorial mechanisms

- 5.1 Haematological disorders: myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Simonneau G et al. *Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009;54:S43-S54.*

Definition

PCWP > 15 mm Hg

mean PAP > 25 mm Hg by PA catheter

PAsP >35-45 mm Hg by echo velocity of TR.

Mild: 35-45 mm Hg

Moderate: 46 to 60 mm Hg,

Severe > 60 mm Hg.

2. PH due to left heart disease

2.1 Systolic dysfunction

2.2 Diastolic dysfunction

2.3 Valvular disease

Pathophysiology

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Hydrostatic or Passive component:

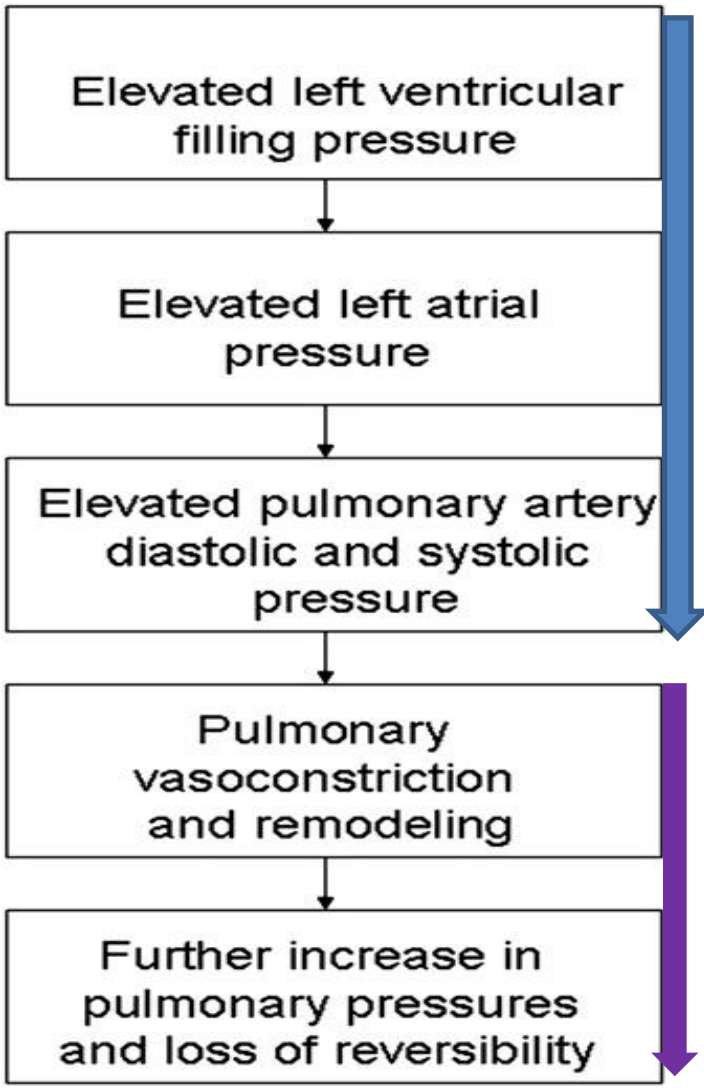
Backward transmission of elevated

LVEDP.

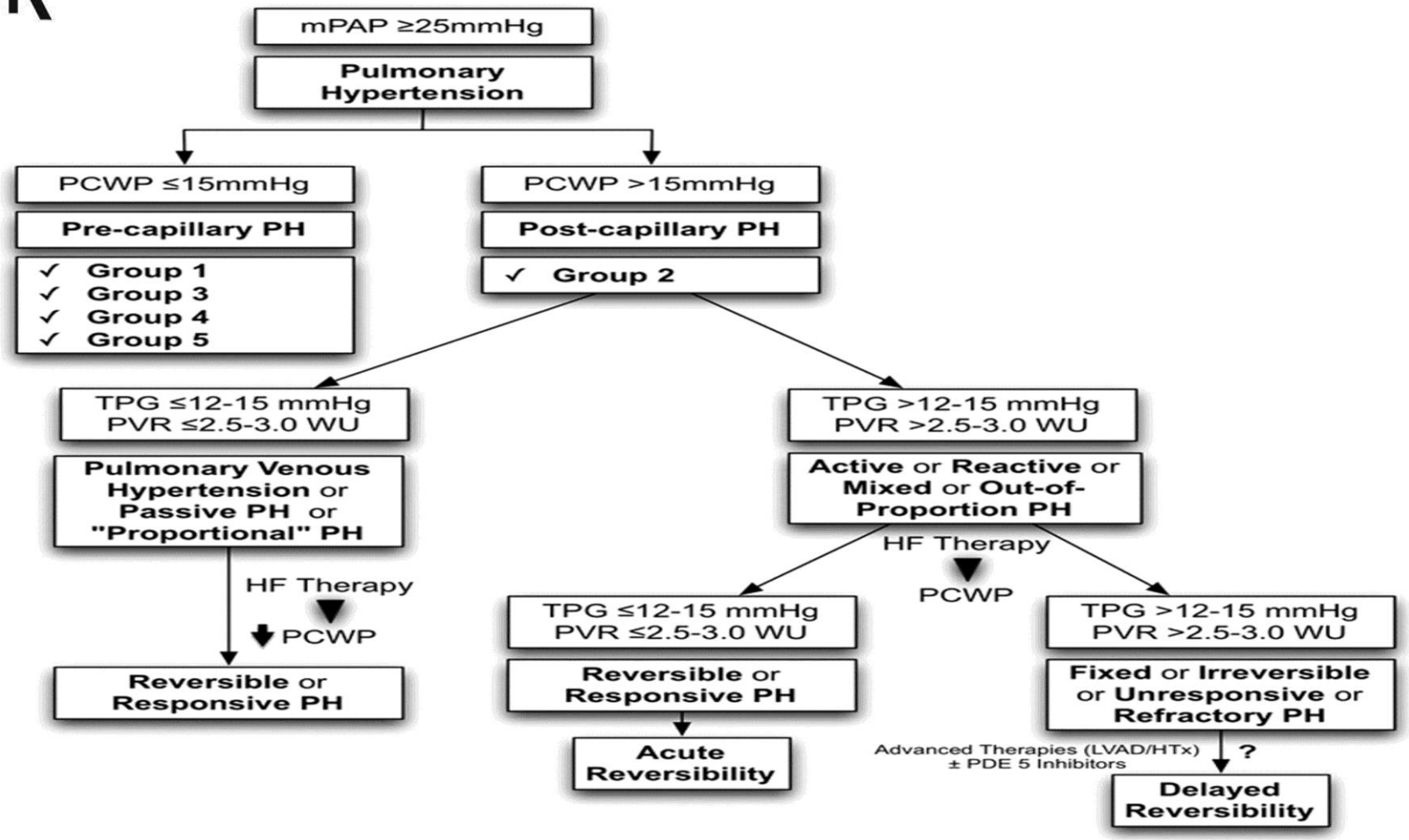
PAsP correlates with PCWP: Low TPG

Vaso-reactive or Reactive or Fixed

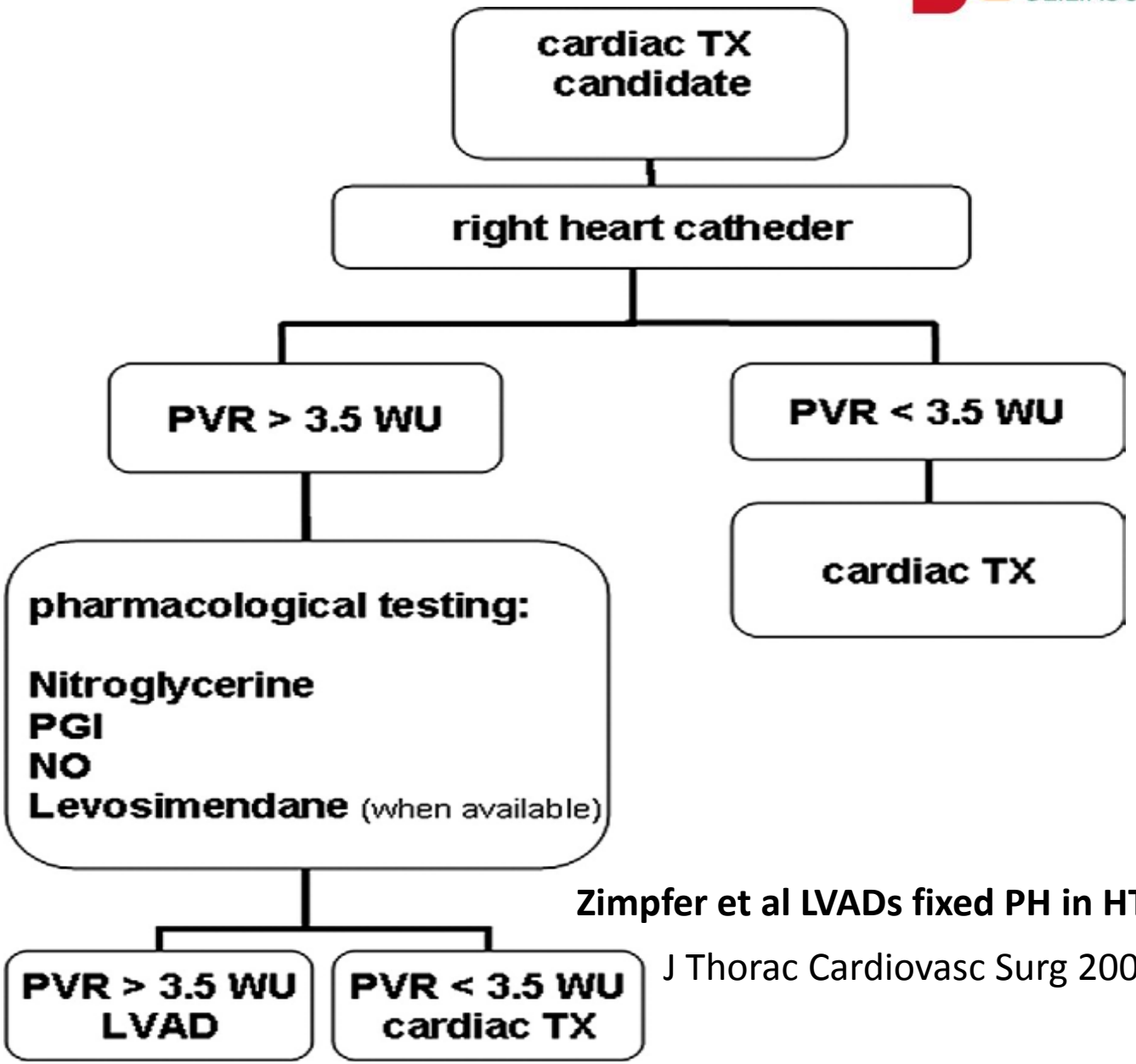
Vasoconstriction & remodeling: High TPG



Types of pulmonary hypertension in Patients with heart failure.



Georgiopoulou V V et al. Left Ventricular Dysfunction With Pulmonary Hypertension
***Circ Heart Fail*. 2013;6:344-354**



Zimpfer et al LVADs fixed PH in HTx candidates

J Thorac Cardiovasc Surg 2007;133:689-95

Pharmacologic agents used for testing reversibility of PH

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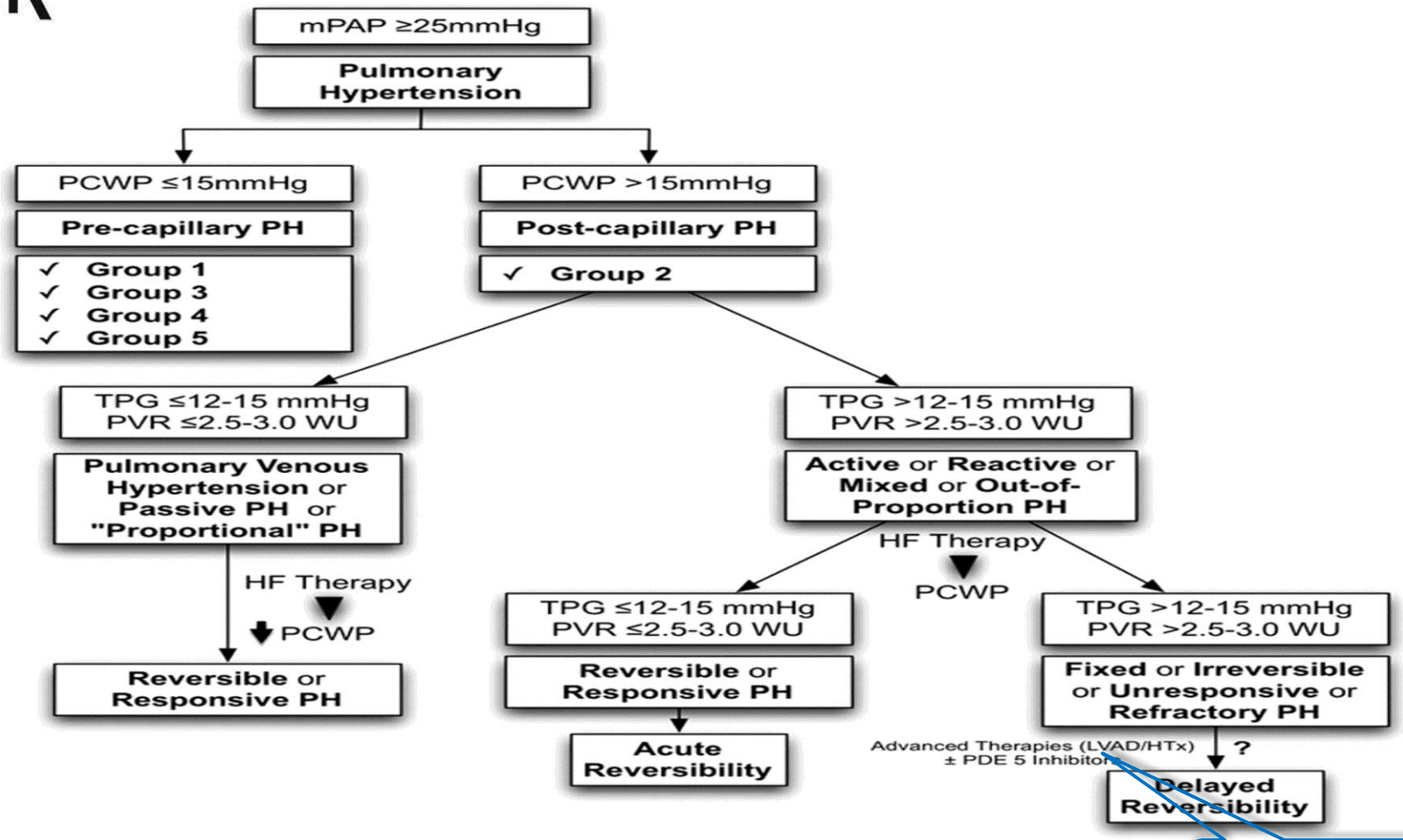
Agent	Dose	Route	Author, Year
Milrinone	50 mcg/kg	IV	Givertz et al 1996,[48] Pamboukian et al 1999,[49] Botha 2009[68]
Enoximone	0.5–2.5 mg/kg	IV	Murali et al 1991[64]
Dobutamine	7.5–15 mcg/kg/min	IV	Murali et al 1991[64]
Sodium nitroprusside	1–1.5 mcg/kg/min to maximally tolerated	IV	Murali et al 1991,[64] Semigran et al 1994,[53] Kieler-Jensen 1994,[51] Pagano et al 1996,[146] Weston et al 2001[60]
Prostaglandin E1	>50 ng/kg/min	IV	von Scheidt et al 2006,[57] Radovancevic 2005[63]
Prostaglandin E1	<50 ng/kg/min	IV	Murali et al 1992,[147] Murali et al 1991,[64] Wasler 1993[148]
Prostacyclin	5–13 ng/kg/min	IV	Kieler-Jensen 1994,[51] Pagano et al 1996,[146] Trautnitz 1999[149]
Prostacyclin	50–1000 mcg	Inhaled	Weston et al 2001,[60] Haraldsson et al 1998,[62] Sablotzki et al 2002[61]
Sildenafil	25–100 mg	PO	Angel Gomez-Sanchez et al 2004,[67] Alaeddini et al 2004,[66] Lepore et al 2005,[83] De Freitas 2009[150]
Sildenafil	0.43 mg/kg	IV	Botha 2009[68]
Sildenafil	0.05 mg/kg	IV	Botha 2009[68]
Nitroglycerin	15–25 mcg/kg/min	IV	Murali et al 1991[64]
Nitric oxide	5–80 parts per million	Inhaled	Kieler-Jensen N 1994,[51] Lepore et al 2005,[54,83] Mahajan et al 2007,[151] Haraldsson et al 1998,[62] Pagano et al 1996,[146] Sablotzki et al 2002,[61] Radovancevic et al 2005,[63] Semigran et al 1994,[53] Fojon 2006,[152] Loh 1994[153]
Dipyridamole	0.2-mg/kg bolus, then infusion of 0.0375 mg/kg/min	IV	Lepore et al 2005[54]
Nesiritide	Bolus 2 mcg/kg then 0.01 mcg/kg/min	IV	O'Dell et al 2005[136]

PO, orally; IV, intravenously.

Types of pulmonary hypertension in Patients with heart failure.



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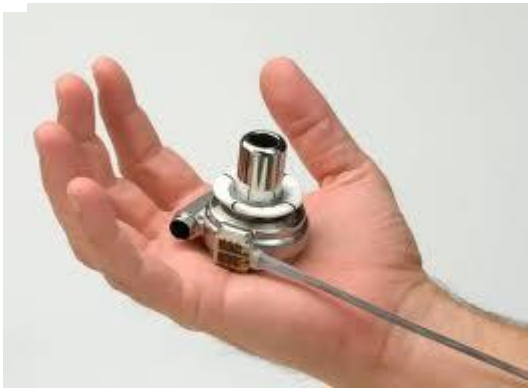

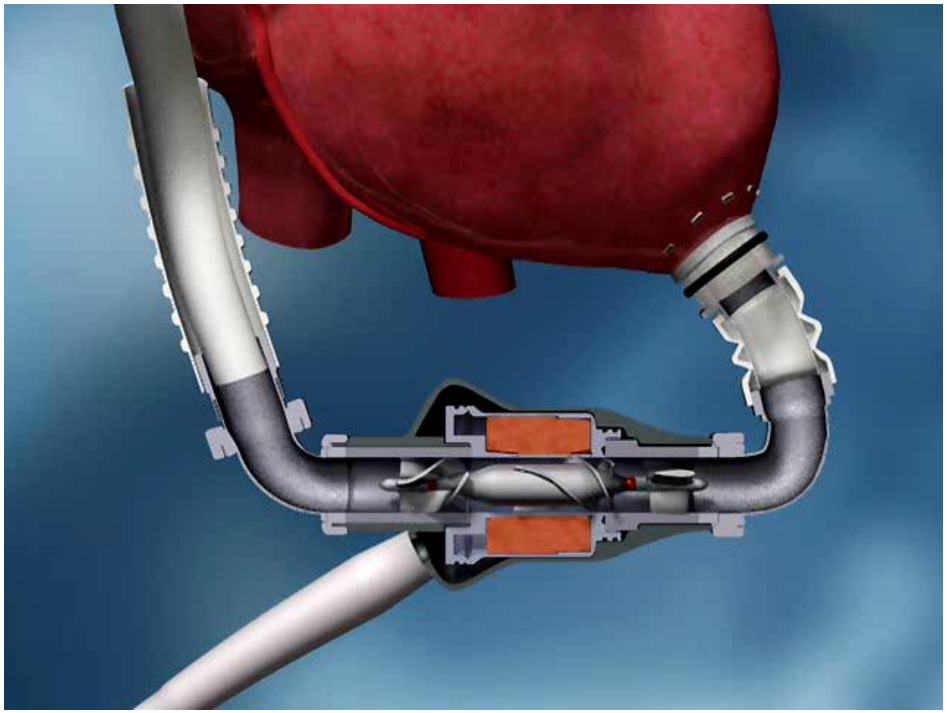

LVAD implantation

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Clinical Parameters predicting post LVAD risk: RV failure

high peri-operative morbidity & mortality.

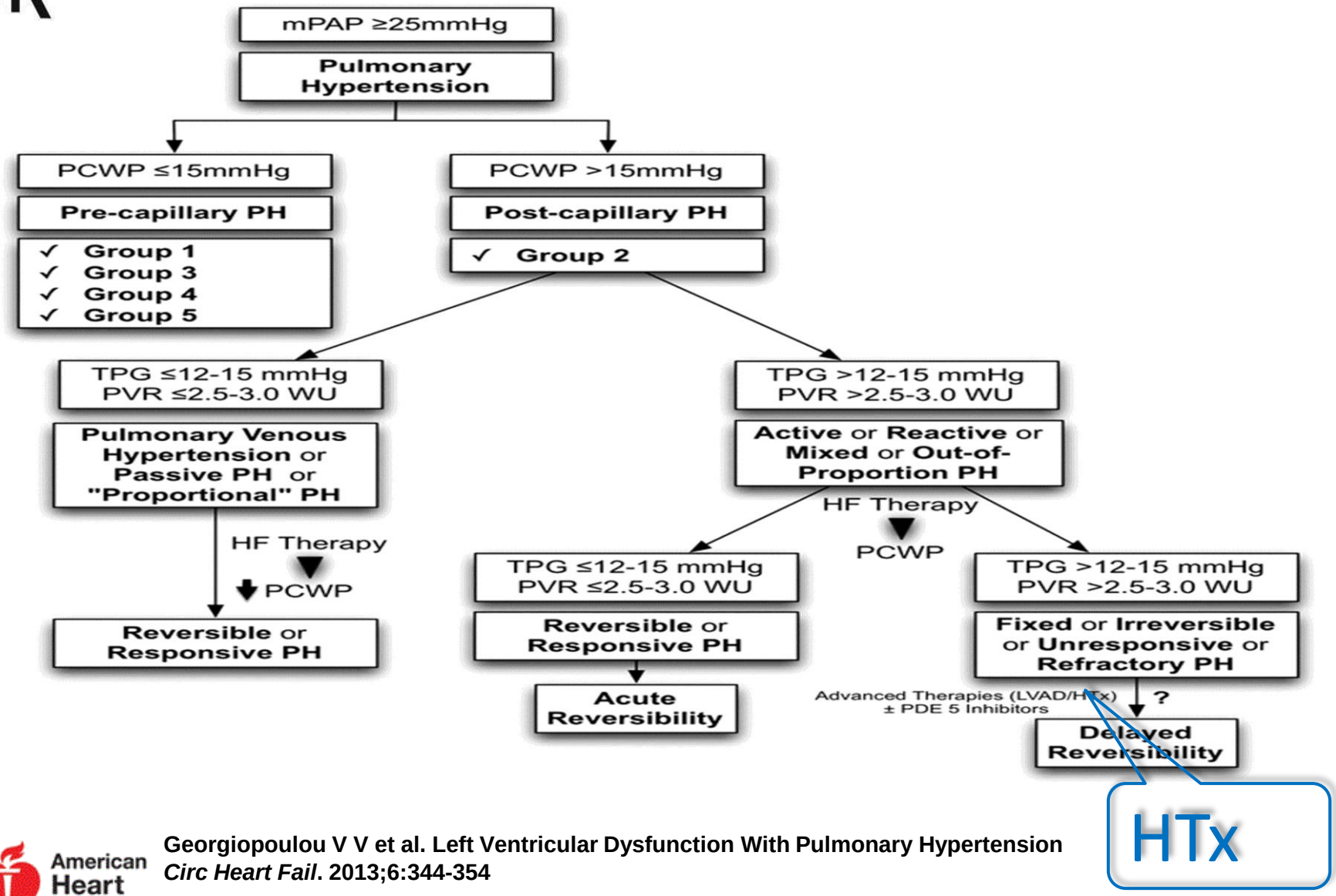
Assessment of pre-operative RV function: Crucial!!

Pre-operative prediction of RV function after LVAD implantation:
important for device selection and patient outcome.

Some of the parameters:

RV after-load: PA pressure
RV Pre-load: RA pressure
RV stroke work index (meanPAP-meanRAP)x CI/HR
TR severity
RV geometry

Types of pulmonary hypertension in Patients with heart failure.



Georgiopoulou V V et al. Left Ventricular Dysfunction With Pulmonary Hypertension
Circ Heart Fail. 2013;6:344-354

HTx

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PH in Heart Transplant Candidates

- Fixed PH increases mortality early and late after HTx.
- **Hemodynamic Parameters** predicting post HTx risk for RV failure and early death:
- Pulmonary HTN, Elevated PVR, Elevated TPG:

  PA Syst.> 50-60 mm Hg

  PVR >3.5-5 WU or TPG > 12-15 mm Hg.
- LVAD implantation as Bridge to transplantability.
- PDE5 inhibitors.

Treatment

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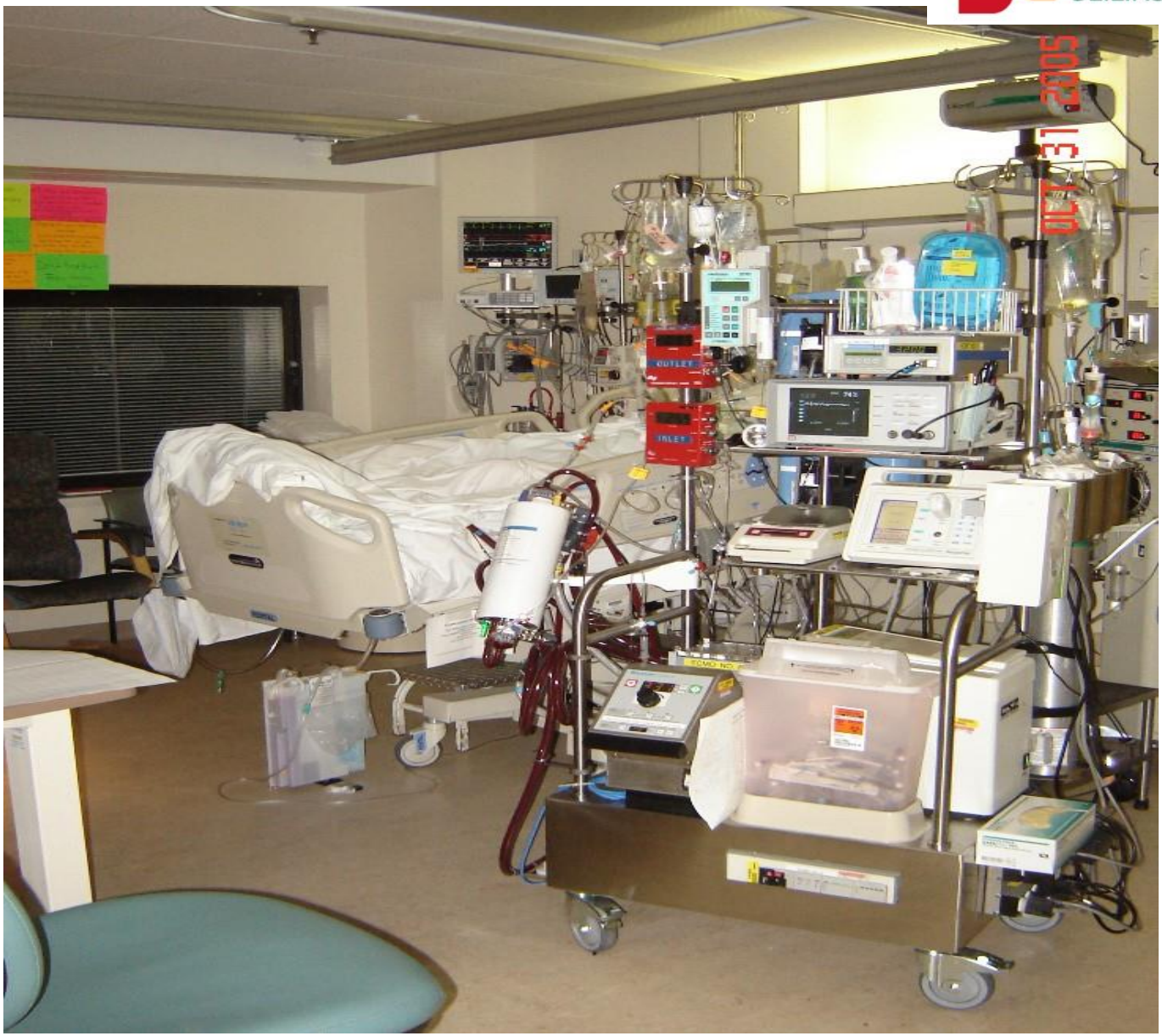
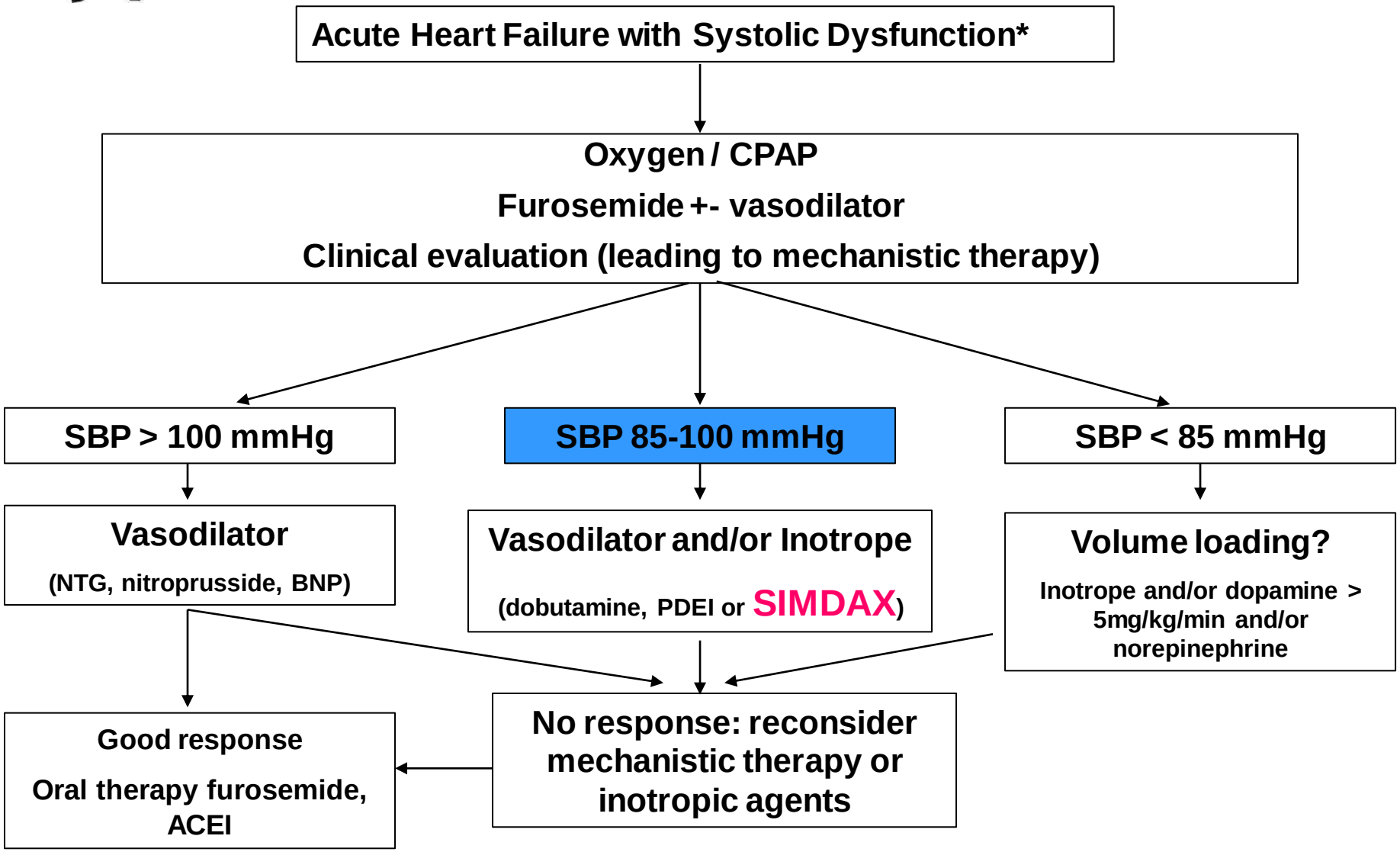


ESC HF-Guidelines



Tailored therapy to hemodynamic goals for advanced heart failure

Stevenson Eur. J. Heart fail.

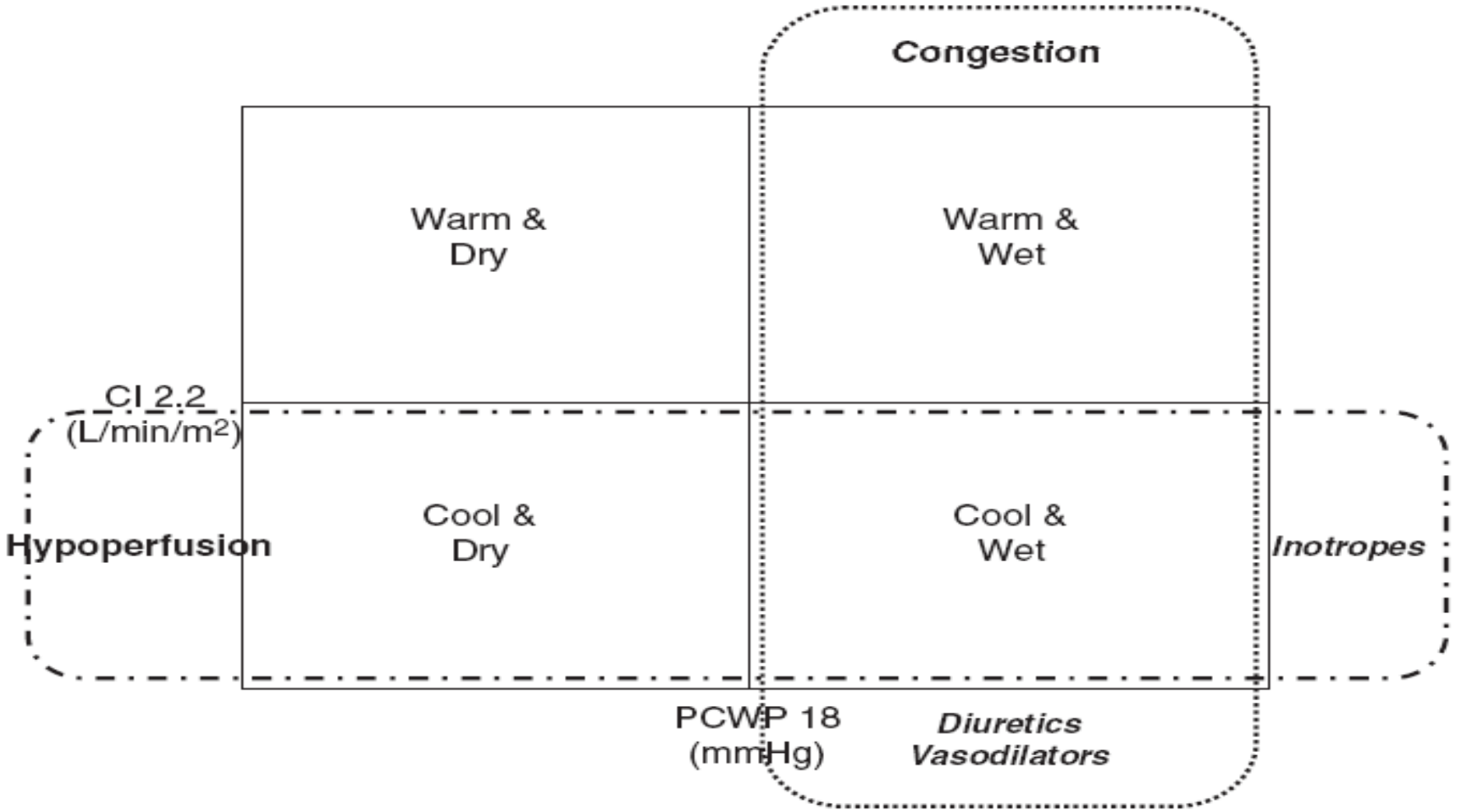


Fig. 1. Hemodynamic subsets in acute heart failure. CI, cardiac index.

Treatment of PH in HF

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- PH should be a therapeutic target in patients with HF.

- No adequately powered trials: decreasing PAP or PVR improves morbidity & mortality in patients with HF.

Concern:

High PVR: a protective adaptation to LV failure.

selective pulmonary arterial vasodilation might worsen left-sided heart congestion and trigger pulmonary edema.

Treatment of PH in HF

- Prostacyclin analogs and endothelin antagonists in chronic and acute HF: Neutral or negative.
- Patient selection inappropriate.
- The effects of PDE5 inh : favorable but small studies.
- PDE5 inh for HF with PH rarely causes pulmonary edema!

Sildenafil Improves Exercise Capacity and Quality of Life in Patients With Systolic Heart Failure and Secondary Pulmonary Hypertension

Gregory D. Lewis, MD; Ravi Shah, MD; Khurram Shahzad, MD; Janice M. Camuso, RN; Paul P. Pappagianopoulos, MEd; Judy Hung, MD; Ahmed Tawakol, MD; Robert E. Gerszten, MD; David M. Systrom, MD; Kenneth D. Bloch, MD; Marc J. Semigran, MD

Background—Patients with systolic heart failure (HF) who develop secondary pulmonary hypertension (PH) have reduced exercise capacity and increased mortality compared with HF patients without PH. We tested the hypothesis that sildenafil, an effective therapy for pulmonary arterial hypertension, would lower pulmonary vascular resistance and improve exercise capacity in patients with HF complicated by PH.

Methods and Results—Thirty-four patients with symptomatic HF and PH were randomized to 12 weeks of treatment with sildenafil (25 to 75 mg orally 3 times daily) or pl[acebo]. Patients underwent cardiopulmonary exercise testing before and after treatment. The change in peak $\dot{V}O_2$ fro[m baseline, the primary end point, was greater in the sildenafil group] (1.8 ± 0.7 mL · kg^{-1} · min^{-1}) than in th[e placebo group (0.27 mL · kg^{-1} · min^{-1}; $P=0.02$)] vascular resistance and increased cardia[c index and stroke volume index and decreased] pulmonary capillary wedge or mean arterial p[ressure. Exercise duration increased with] treatment to augment peak $\dot{V}O_2$ correlated [inversely with baseline pulmonary vascular resistance ($P=0.002$) and indirectly with baseline rest] treatment also was associated with improve[ment in the Minnesota Living With Heart Failure score (–] fewer hospitalizations for HF and a higher i[ncidence of] excess serious adverse events.

Conclusions—Phosphodiesterase 5 inhibition with sildenafil improves exercise capacity and quality of life in patients with systolic HF with secondary PH. (*Circulation*. 2007;116:1555-1562.)

Key Words: exercise ■ heart failure ■ hypertension, pulmonary

34 patients with symptomatic HF and PH were randomized to 12 weeks of treatment with
sildenafil (25 to 75 mg orally 3 times daily) or placebo.

Patients underwent cardiopulmonary exercise testing before and after treatment.

The change in peak VO_2 from baseline, the primary end point, was greater in the sildenafil group (1.80.7 mL · kg^{-1} · min^{-1}) than in the placebo group (0.27 mL · kg^{-1} · min^{-1}; *P=0.02)*

Treatment of PH in Acute HF

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Vasodilators: That unload the LV, improve PAP and PVR without acute increase in LA pressures:
Nitroprusside

Therapeutic interventions with balanced pulmonary and systemic vasodilator effects:
Nitrates, guanylate cyclase stimulators (riociguat)

Inodilators: the combination of positive inotropic and vasodilating therapy:
Milrinone, Calcium Sensitizers

Inotropes and Vasodilators

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lower PVR.

sustained inotropic effect

increase in contractility and CO

Venous and pulmonary vasodilation.

Decrease in right and left heart filling pressures

Decrease in systemic and PVR

New Paradigm

- Prevent /Slow disease progression:
  - Meds.
  - AICD
  - Rehab.
- Disease-exchange therapies:
  - CRT
  - LVAD
  - HTx
- Paliative care:
  - Pulm. HTN Tx
  - Hemo filt. Dialysis
  - Ferric HF
  - Recormon
  - Rec inotorpes
- End of life
  - No Tx
  - Stop AICD

Pulmonary hypertension

Heterogeneous entity.
Different causes.
Increased pressures in the pulmonary circulation.

Frequent consequence of left-sided HF.
Presence of PH is associated with worse HF outcomes.

PH secondary to left heart disease combination of:

- Elevated LV filling pressures,
- Reactive pulmonary arterial vasoconstriction,
- Pulmonary vascular remodeling.

Treatment of PH in AHF

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- Optimize HF Tx: Pre-load & After-load reduction
  - SG catheter??
  - IABP?
  - Impella??

- Inotropes & Vasodilators

- Inodilators

- PDE5 inh. & Prostacycline analogs

- Tx for PH in HF patients rarely causes pulmonary edema!


Thank you for your attention