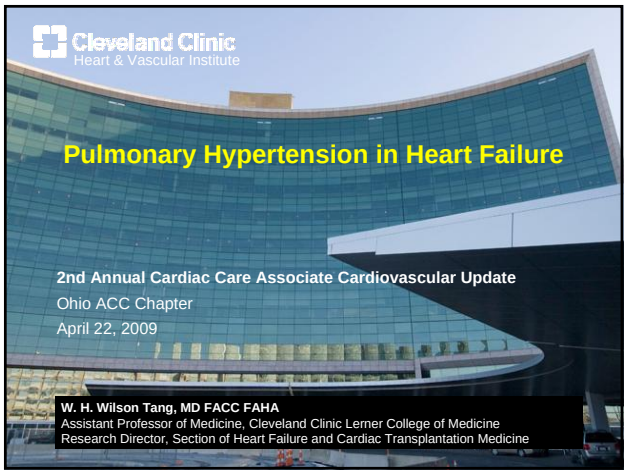


Objectives

- To discuss the relationship between pulmonary venous and arterial hypertension, and potential cardiac causes
- To discuss the impact of pulmonary hypertension in left heart diseases
- To discuss diagnostic and treatment options for pulmonary hypertension in left heart diseases

Pulmonary Hypertension in Heart Failure

- Outline
  - Definition and Epidemiology
  - Diagnostics
    - Cardiac catheterization
    - Echocardiography
  - Pathophysiology
  - Consequences
  - Treatment
  - Future Strategies

Definitions

- **Pulmonary hypertension**: raised mean pulmonary artery pressures (PAP)

$$= \frac{(2 \times PAP_{diastolic} + PAP_{systolic})}{3}$$

– Normal:	7-18 mmHg
– Pulmonary hypertension:	> 25 mmHg at rest
	> 30 mmHg with exercise

- **Heart failure**: Heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.

Focused Update ACC/AHA Guidelines, *Circulation* 2009

Pulmonary Hypertension in Heart Failure

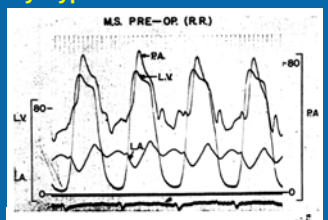
Also known as:

- Pulmonary venous hypertension ("WHO Group 2")
- Post-capillary pulmonary hypertension
- Pulmonary hypertension with left heart disease
  - Systolic heart failure
  - Diastolic heart failure
  - Valvular heart disease
  - Restrictive or constrictive cardiomyopathy
- Secondary pulmonary hypertension in heart failure
  - "Passive" – proportionate to elevated filling pressures
  - "Reactive" – disproportionate to elevated filling pressures
  - "Intrinsic" or "Fixed" – vascular remodeling

Venice Classification of Pulmonary Hypertension

- **Sporadic (IPAH)**
- **Familial (FPAH)**
- **PH Related to:**
  - Collagen vascular diseases
  - Congenital L-to-R shunt
  - Porto-pulmonary HTN
  - HIV (1/200), HHV-8
  - Drugs / toxins (e.g.anorexic drugs, cocaine/amphetamines)
  - Others
- **Pulmonary venous occlusive disease**
- **Pulmonary venous HTN**
  - Left heart disease
  - Valvular dysfunction
- **Hypoxia-induced PH**
  - COPD
  - Interstitial lung disease
  - Sleep-disordered breathing
  - High altitude
- **Arterial obstruction**
  - Thromboembolic / PE (lupus)
  - Sickle-cell
- **Miscellaneous**
  - Sarcoidosis
  - Histiocytosis X
  - Lymphangiomatosis
  - External compression

Pulmonary Hypertension in Mitral Stenosis



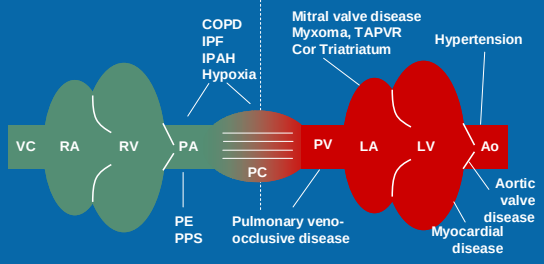
		P.C. m	P.A. s/d/m	R.V. s/d	R.A. m	B.A. s/d/m	L.V. s/d	L.A. m	L.A.-L.V. Diast. Gra
Pre-op	R	20	50/26,34	50/2	2	121/66,89			
	Ex.		87/49,61	86/5		135/73,93			
	C.S.		44/27,32	45/2			100/8	23	16
	Ex.		73/43,55				112/9	38	24
Post-op	R		27/12,17	27/3	2	118/66,86			
	Ex.		36/19,25	38/3		130/70,95			
	C.S.		31/13,21				114/13	14	3
	Ex.		38/20,26				125/13	14	6

Samet et al, *Chest* 1958

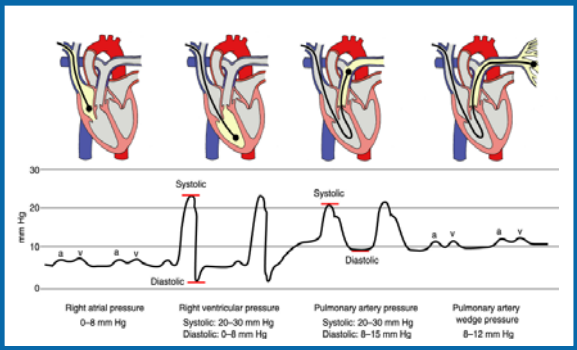
Determine the "Lesion" in Pulmonary Hypertension

"Pre-capillary" PH
(Normal PCWP, ↑ PVR, ↑ TPG)

"Post-capillary" PH
(↑ PCWP, Normal PVR, ↑ TPG)



Diagnosis: Right Heart Catheterization



Pulmonary Vascular Resistance

"Ohm's Law": Δ Pressure = Flow x Resistance
(TPG) (CO) (PVR)

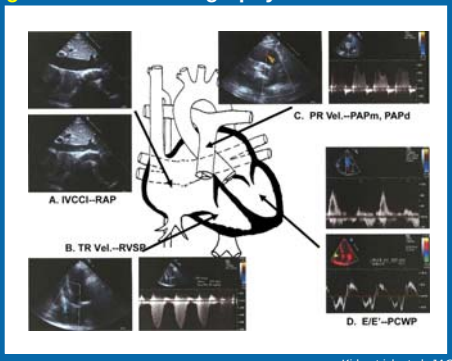
Trans-Pulmonary Gradient (TPG)
= PA_{mean} – $PCWP_{mean}$

Normal: <12 mmHg

Pulmonary vascular resistance (PVR)
= TPG / Cardiac output (CO) in Woods units
(or x80 in dynes-sec-cm^5)

Normal:	<1.5 Wood units
Pulmonary hypertension:	> 3 Wood units (or >250 dynes-sec-cm^5)

Diagnosis: Echocardiography



Kirkpatrick et al, *JACC* 2007

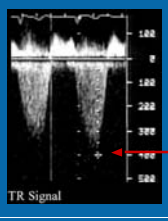
Hemodynamic Definitions of Pulmonary Hypertension

	Normal	Mild PH	Moderate PH	Severe PH
Hemodynamics				
Mean PA (mmHg)	9-24	25-40	41-55	>55
TPG (mmHg)	2-10	10-15		>15
PVR (Woods)	0.5-2	2-5		>5
Doppler Echocardiography				
TR Velocity (m/s)	<3.4	2.8-3.3	3.4-4.2	>4.2
Estimated RVSP (mmHg)	15-57	36-50	50-75	>75

* assumes RAP=5 mmHg

Important Caveats for Echocardiographic Estimates

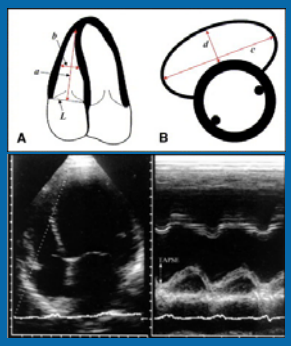
- RV systolic pressure (RVSP) does not necessarily reflect severity of TR
- RVSP can overestimate mPAP in non-PAH pts while underestimate in PAH pts
- Always look for intracardiac shunting ("bubble study")



TR Vel = 4 m/s

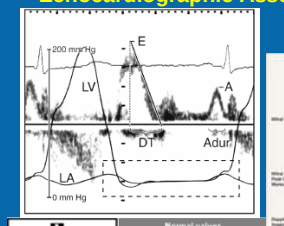
RVSP = RAP + $4v^2$
= 10 + 4 x $(4)^2$
= 74 mmHg

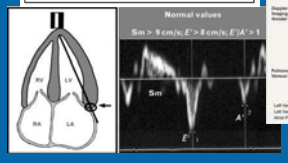
Other Echocardiographic Parameters in PH

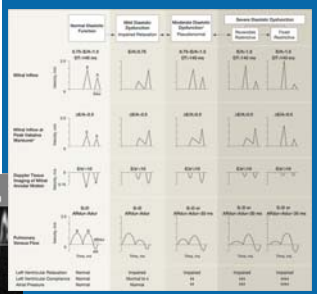


- Pulse Wave at RVOT for Peak Systolic Pulmonary Acceleration Velocities
- Ventricular interdependence
- RV volumes
- Right atrial area or volume index
- Diastolic eccentricity index *(c/d)*
- Mean right ventricular fractional area change
- Tricuspid annular plane systolic excursion (TAPSE)
- Right Myocardial Performance ("Tei") index
- RV Peak Systolic Strain

Echocardiographic Assessment of Diastology



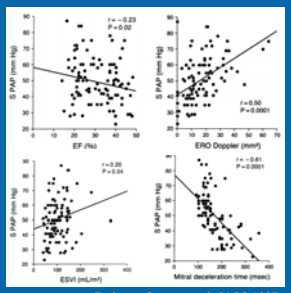




Redfield MM et al, *JAMA* 2003

Determinants of Pulmonary Hypertension

- 102 consecutive patients with LVEF <50%
- Multivariate analysis suggested 3 strongest determinants of systolic PA pressures were:
  - Patient age
  - Diastolic dysfunction
    mitral decel time <150 ms
  - Mitral regurgitation
    effective regurg orifice >20 mm²

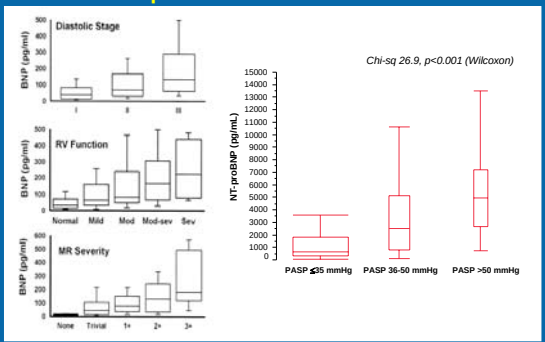


Enriquez-Sarano et al, *JACC* 1997

Other Diagnostic Considerations for PH in HF

- **Left Heart Catheterization**
  - Useful in direct measurement of LV end-diastolic pressure to confirm or rule out pulmonary venous hypertension (elevated LA pressure)
  - Simultaneous LV-RV measurements to assess constriction vs restriction, determine valvular dysfunction
  - Determine vasoreactivity
- **Cardiopulmonary Exercise Testing**
  - Characterize and quantify functional limitations
  - Risk stratification and serial monitoring
- **Cardiac CT**
  - Especially after PV ablation for AF to r/o PV stenosis

Natriuretic Peptides in Left Heart Failure: ADEPT



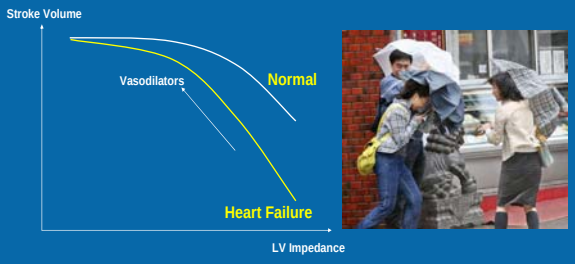
Troughton et al, *JACC* 2004

Tang et al (unpublished) 2009

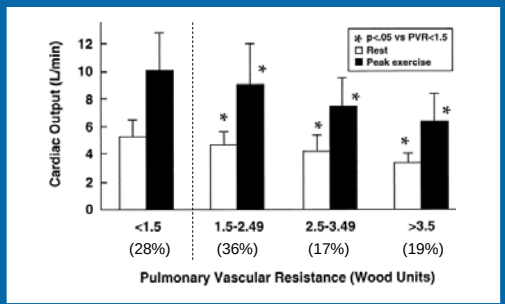
Definition, Epidemiology, & Diagnostics: Summary

- Common: over two thirds of patients with chronic systolic heart failure or symptomatic valvular stenosis have associated PH
- Degree of PH often correlates with symptoms (e.g. mitral stenosis)
- Presence of PH is independent predictor of mortality in systolic heart failure, post-MI, or post-transplant
  - Some challenged the presence of RV systolic dysfunction as major determinant of prognosis rather than RVSP
- Persistent or "Fixed" PH is a contraindication for transplantation
  - TPG and PVR are important determinants

Pathophysiology: LV Impedance ("Afterload")

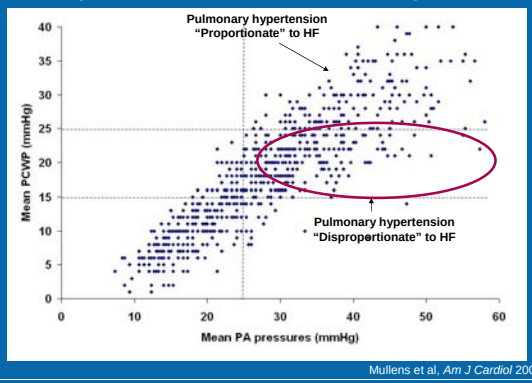


Pulmonary Hypertension and Exercise Capacity



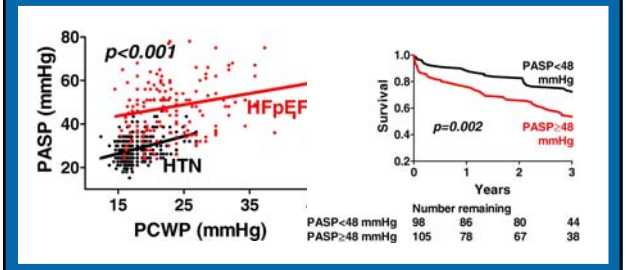
Butler et al, *J Am Coll Cardiol* 1999

Hemodynamic Correlates for Ambulatory CHF



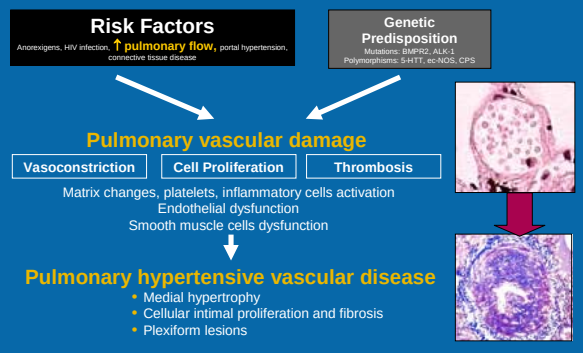
Mullens et al, *Am J Cardiol* 2008

Pulmonary Hypertension in Diastolic HF



Lam et al, *Circulation* 2009

Pathophysiology of Pulmonary Hypertension



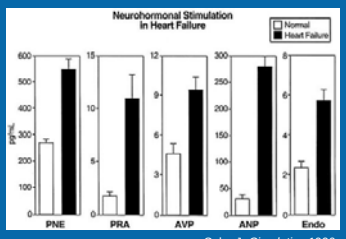
Pathophysiology: Vasoconstrictor Excess

Vasoconstrictors

- Norepinephrine
- Angiotensin II
- Aldosterone
- Vasopressin
- Endothelin
- Cytokines

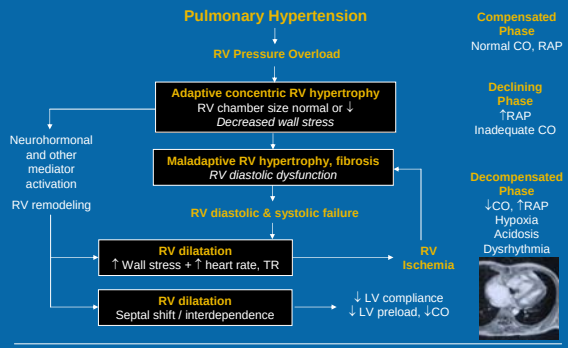
Vasodilators

- Natriuretic peptides



Cohn J, *Circulation* 1996

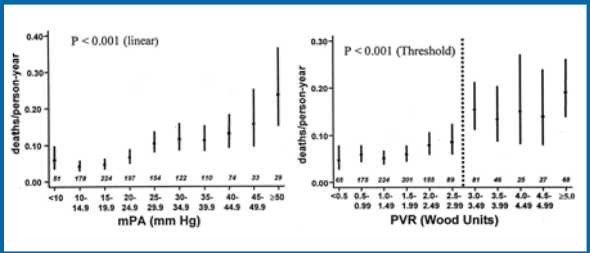
Pathophysiology of Right Heart Failure and *Cor Pulmonale* in Pulmonary Hypertension



Pathophysiology: Summary

- Mechanical complication of disturbed left ventricular filling
  - ↑ Hydrostatic pressure from:
    - **Passive** "backward" transmission of elevated intracardiac pressures
    - **Reactive** response due to endothelial dysfunction and structural abnormalities in pulmonary microcirculation
    - **Damage** *? Surfactant Protein Type B*
  - Progressive pulmonary vascular remodeling similar to PAH
- Chronic hypoxia or high pulmonary artery flow
  - Cyanotic congenital heart defects or shunts
  - *? Sleep apnea*

Prognosis of PH Related to Left Heart Disease



Cappola et al, *Circ* 2002

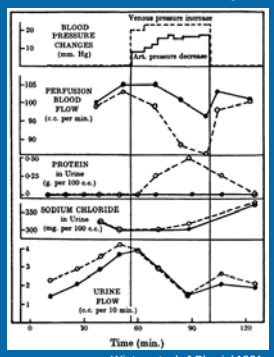
Consequences: Independent Predictors of Adverse Events in Patients with Advanced Heart Failure

Predictor	Hazard Ratio	95% Confidence Interval	p Value
All-cause mortality			
CI	0.46	0.299–0.707	<0.001
MPA	1.021	1.001–1.004	0.04
Mitral valve regurgitation	1.3	1.116–1.514	0.001
Creatinine	2.032	1.461–2.827	<0.001
Age	1.024	1.005–1.044	0.014
Cardiac transplantation			
CI	0.431	0.278–0.668	<0.001
MPA	1.075	1.033–1.078	<0.001
Mitral valve regurgitation	1.273	1.121–1.457	0.001
Heart failure hospitalization			
CI	0.702	0.518–0.951	0.023
MPA	1.027	1.007–1.044	0.007
Mitral valve regurgitation	1.19	1.077–1.316	0.001

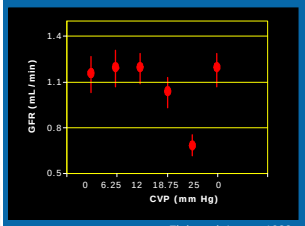
CI = cardiac index; MPA = mean PA pressure

Mullens et al, *Am J Cardiol* 2008

Arterial and venous pressure in blood and urine flow



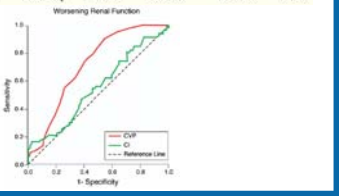
Winton et. al. *J Physiol* 1931



Firth et al, *Lancet* 1988

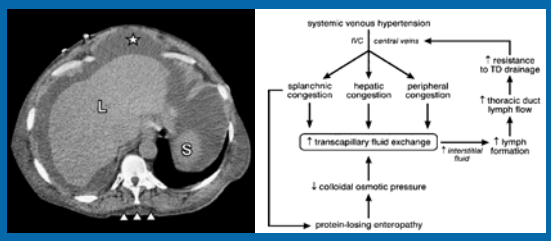
Pulmonary Hypertension and Worsening Renal Function in Advanced Heart Failure

	Patients With WRF (n = 56)			Patients Without WRF (n = 87)		
	Baseline	Follow-Up	p Value	Baseline	Follow-Up	p Value
HR (beats/min)	86 ± 22*	90 ± 16*	NS	89 ± 46	88 ± 19	NS
SBP (mm Hg)	111 ± 21*	110 ± 25*	NS	108 ± 15	109 ± 15	NS
CVP (mm Hg)	18 ± 7†	11 ± 8‡	<0.001	12 ± 6	8 ± 5	<0.001
SPA (mm Hg)	57 ± 13*	49 ± 15*	<0.001	54 ± 16	46 ± 12	<0.001
PCWP (mm Hg)	25 ± 7*	19 ± 5*	<0.001	24 ± 7	18 ± 5	<0.001
CI (l/min/m²)	2.0 ± 0.8§	2.7 ± 0.7‖	<0.001	1.8 ± 0.4	2.4 ± 0.5	<0.001



Mullens et al., *J Am Coll Cardiol* 2009

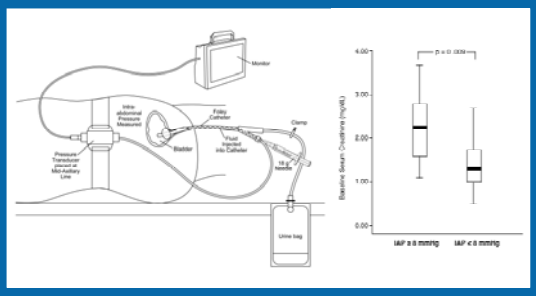
Consequences: Hepatic Congestion



- ↓ serum albumin and protein-losing enteropathy
- ↑ serum cobalamin (vitamin B_{12}), and liver function tests (e.g. bilirubin)
- Lymphocytopenia and anemia

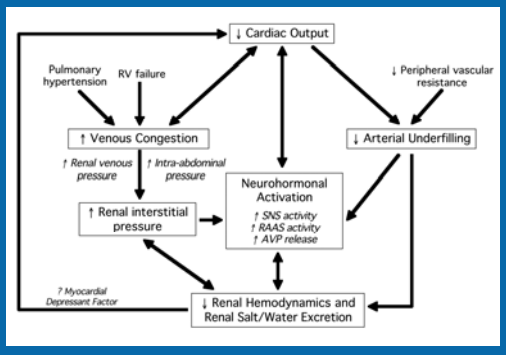
Paulus et al, *Am J Med Sci* 2008

Visceral Edema: Raised Intra-Abdominal Pressure



Mullens et al., *J Am Coll Cardiol* 2008

Consequences: Summary



Tang et al., *Heart* 2009 (in press)

Management: ACC/AHA Guideline Updates

2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults

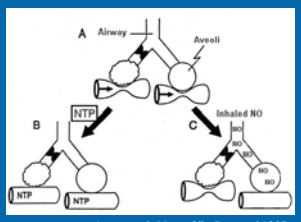
ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension

"Reversibility Testing" in Left Heart Disease

- **Determination of heart transplant candidacy**
  - **Acute**: vasoreactivity testing in cath lab
  - **Sub-acute**: Sodium nitroprusside challenge in ICU
  - **Chronic**: LVAD implantation
- **Determination of treatment strategy**
  - Identify reversible causes (valve surgery, heart failure Rx)
  - Add-on vasodilator therapy:
    - **Acute**: nitroprusside, nesiritide, nitroglycerin
    - **Chronic**: isosrbide dinitrate, hydralazine
    - **Inodilators**: milrinone/dobutamine in low-output states

Inhaled Nitric Oxide in Left Heart Disease

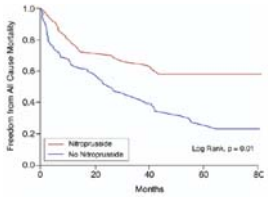
- Selective vasodilatory effects on pulmonary vasculature
- Currently used for PH due to RV dysfunction (post-op or MI)
- *Advantage*: Only reaches ventilated alveoli, without worsening V/Q mismatch
- *Disadvantage*: May lead to pulmonary edema in the setting of raised LA pressure as increased flow in the absence of decrease in LVEDP



Lunn et al, *Mayo Clin Proceed* 1995

Sodium nitroprusside in Left Heart Disease

	No Nitroprusside (n = 49)			Nitroprusside (n = 60)		
	Admission	Discharge	p Value	Admission	Discharge	p Value
MAP (mm Hg)	82 ± 12	74 ± 8	<0.001	87 ± 12	74 ± 11	<0.001
Systolic PAP (mm Hg)	55 ± 14	41 ± 13	<0.001	65 ± 13	42 ± 12	<0.001
Diastolic PAP (mm Hg)	28 ± 8	20 ± 7	<0.001	33 ± 7	19 ± 6	<0.001
CI (L/min/m²)	1.6 ± 0.2	2.4 ± 0.5	<0.001	1.6 ± 0.2	2.6 ± 0.5	<0.001

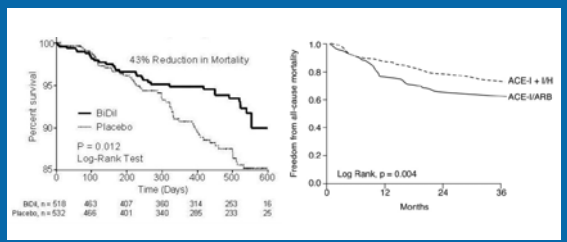


Mullens et al, *J Am Coll Cardiol* 2008

Add-on Oral vasodilators in Advanced Heart Failure

A-HeFT
(African-Americans)

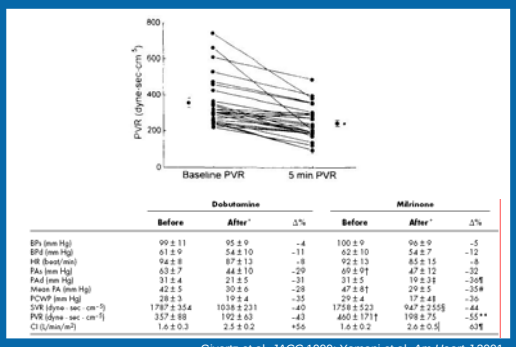
Cleveland Clinic
(low-output HF)



Taylor et al, *NEJM* 2004

Mullens et al, *AJC* 2009

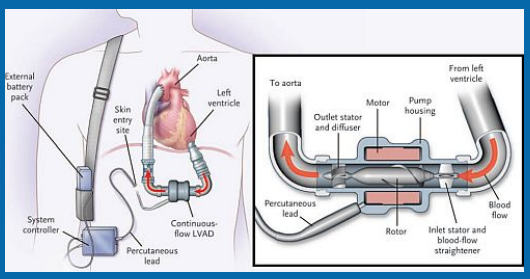
Milrinone and Hemodynamic Improvement



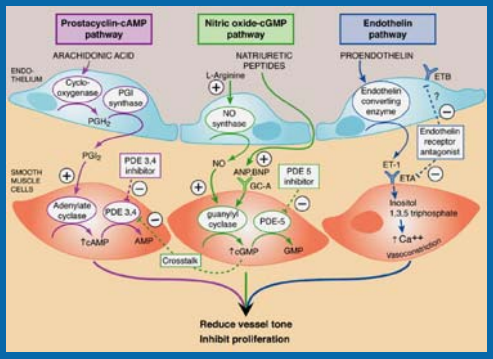
	Dobutamine			Milrinone		
	Before	After*	Δ%	Before	After*	Δ%
BPs (mm Hg)	99 ± 11	95 ± 9	−4	100 ± 9	96 ± 9	−5
BPd (mm Hg)	61 ± 9	54 ± 10	−11	62 ± 10	54 ± 7	−12
HR (beat/min)	94 ± 8	87 ± 13	−8	92 ± 13	85 ± 15	−8
PAs (mm Hg)	63 ± 7	44 ± 10	−29	69 ± 9†	47 ± 12	−32
PAd (mm Hg)	31 ± 4	21 ± 5	−31	31 ± 5	19 ± 3‡	−36¶
Mean PA (mm Hg)	42 ± 5	30 ± 6	−28	47 ± 8†	29 ± 5	−35#
PCWP (mm Hg)	28 ± 3	19 ± 4	−35	29 ± 4	17 ± 4‖	−36
SVR (dyne · sec · cm⁻⁵)	1787 ± 354	1038 ± 231	−40	1758 ± 523	947 ± 255§	−44
PVR (dyne · sec · cm⁻⁵)	357 ± 88	192 ± 63	−43	460 ± 171†	198 ± 75	−55**
CI (L/min/m²)	1.6 ± 0.3	2.5 ± 0.2	+56	1.6 ± 0.2	2.6 ± 0.5‖	63¶

Givertz et al, *JACC* 1999; Yamani et al, *Am Heart J* 2001

Mechanical Circulatory Assist Devices

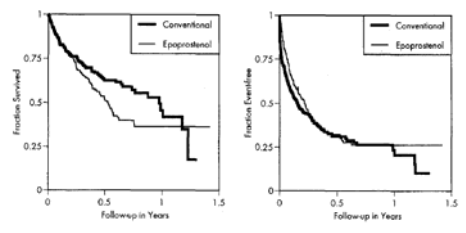


Therapeutic Targets for Pulmonary Hypertension



Benza et al, *J Heart Lung Transplant* 2007

Epoprostenol in Severe Heart Failure: FIRST (n=471)



- NYHA 3b-4, LVEF <25-30%, CI <2.2 l/min/1.73m^2, PCWP >15 mmHg
- Median mPAP 38 mmHg, PCWP 25 mmHg, CI 1.8 l/min/1.73m^2
- Events included death, heart failure hospitalization, IV inotropes, mechanical circulatory assistance, tracheotomy, CPR, MI
- Improved hemodynamics but no impact on functional capacity
- Some case series on inhaled iloprost with hemodynamic benefits

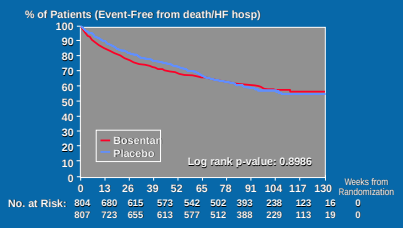
Califf et al, *Am Heart J* 1997

Bosentan Clinical Trials in Chronic Heart Failure

- **REACH-1**: (n=370) Increased incidence of worsening heart failure during 1st month of treatment in CHF patients related to starting dose (125 and 250 mg bid) and speed of up-titration (weekly to 500 mg bid)

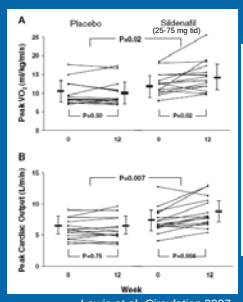
Kalra et al, *Int J Cardiol* 2002

- **ENABLE**: (n=1,613) Bosentan 125 mg bid vs placebo

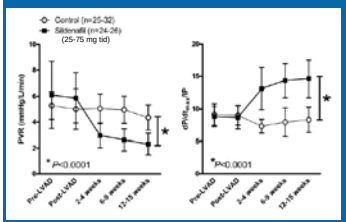


Packer, *ACC Late Breaking Clinical Trials* 2002

Sildenafil in Secondary Pulmonary Hypertension

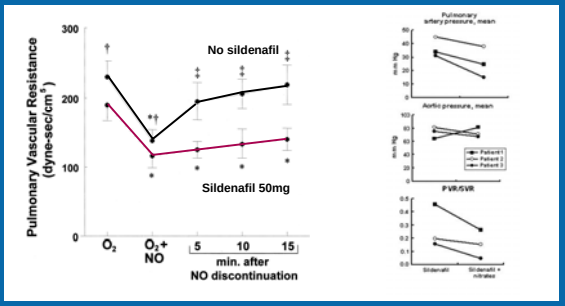


Lewis et al, *Circulation* 2007



Tedford et al, *Circ HF* 2008

Sildenafil combined with nitric oxide/nitrate therapy



Leopore et al, *Chest* 2005

Stehlik et al, *J Card Fail* 2009

Ongoing study: RELAX (sildenafil in diastolic HF, n=190)

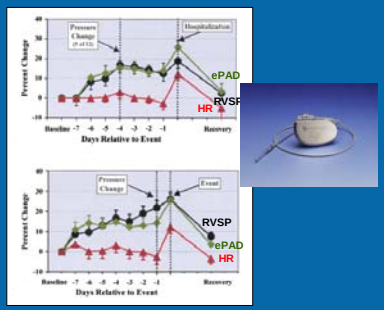
Vasoactive Drugs in Heart Failure: Summary

Drug	Endpoint	Outcome
Epoprostenol	LVEF	Acute increase in LVEF and hemodynamic improvement, but can induce ischemia or pulmonary edema, no long-term outcomes
Nitric oxide	Vasoreactivity	Improve vasoreactivity; sometimes raise PCWP due to inability to reduce LVEDP
Hydralazine/ isosorbide dinitrate	Clinical status	Improved endpoints (primarily from A-HeFT and observational series)
Bosentan	Clinical status	No change, some risk for anemia/edema and hepatotoxicity (not indicated), but did not restrict to pts with PH
Sildenafil	Exercise	Improved exercise, blunted HR, some acute hemodynamic improvement, selective benefits synergistic with nitrates and LVAD

Future: Increased Intra-cardiac Pressures Precede HF Hospitalizations

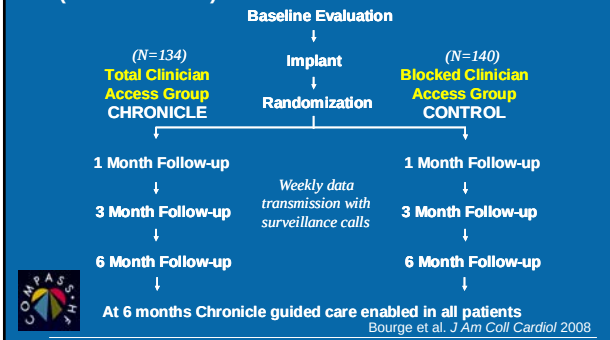
Major exacerbation (hospitalization)

Minor exacerbation



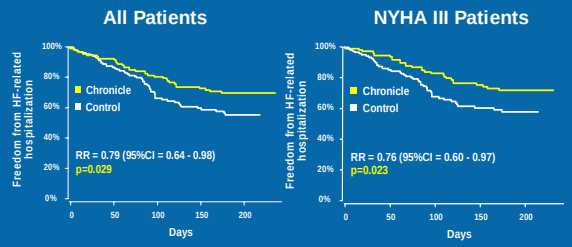
Adamson et al. *J Am Coll Cardiol* 2003

Future: Chronicle® Offers Management to Patients with Advanced Signs & Symptoms of Heart Failure (COMPASS-HF)



Bourge et al. *J Am Coll Cardiol* 2008

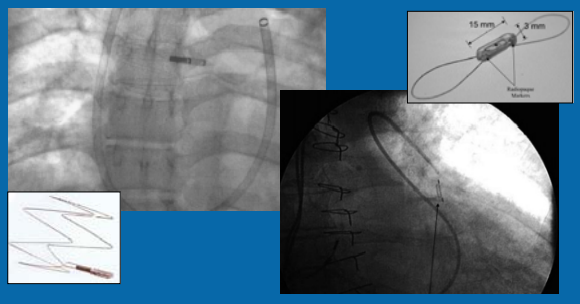
Future: COMPASS-HF HF-related Hospitalization



↓21% First HF-related Hospitalization (p= 0.029)
↓33% Worsening HF by Symptom Score (p= 0.035)

Bourge et al. *J Am Coll Cardiol* 2008

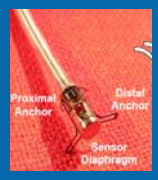
Future: Next-Generation Hemodynamic Sensors

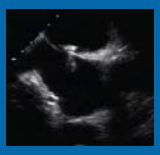


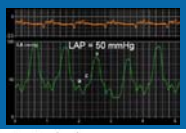
Rozenman et al, *JACC* 2007

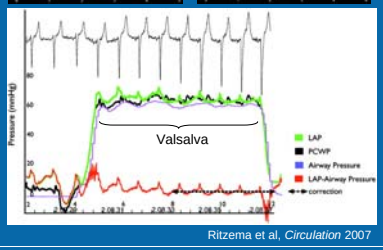
Verdejo et al, *JACC* 2007

Future: Left Atrial Pressure Monitoring









Ritzema et al, *Circulation* 2007

Conclusions

- Pulmonary hypertension is prevalent, clinically significant, but underappreciated in left heart failure
- "Find the lesion" is important: PH in left heart disease can be due to either pulmonary venous or pulmonary arterial hypertension (or both)
- Need to appreciate pros and cons of diagnostic tests
- RV dysfunction may alter pulmonary artery pressures and portends poor prognosis
- Potential interventions include valve surgery, heart failure drug titrations, mechanical assist devices ± transplant
- Limited treatment options, although vasodilators (especially nitric oxide donors) and PDE-V inhibitors are promising; PH drugs are of limited use.