




**Pulmonary Hypertension:
Guideline and Research
Update**

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MHI Grand Rounds
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The bottom right corner of the slide features the Minneapolis Heart Institute logo, which includes a white heart icon and the text "MINNEAPOLIS HEART INSTITUTE" in a white, serif, all-caps font.

Disclosures

No financial disclosures or conflicts of interest



Objectives

1. Review updated pulmonary hypertension (PH) definition.
2. Differentiate Group 1 (PAH) versus Groups 2-5 PH.
3. Describe patterns of PH in rural Minnesota.
4. Examine PH post-TAVR.



What is Pulmonary Hypertension?

- Pressure in pulmonary vasculature
- Progressive RV failure & subsequent death
- Why it matters → PAH 85%-91% 1 yr survival -- 58% 5-yr survival
- Median 2.7 years from symptoms to diagnosis

Benza RL et al. *Circ*, 2010; 122:164-172.

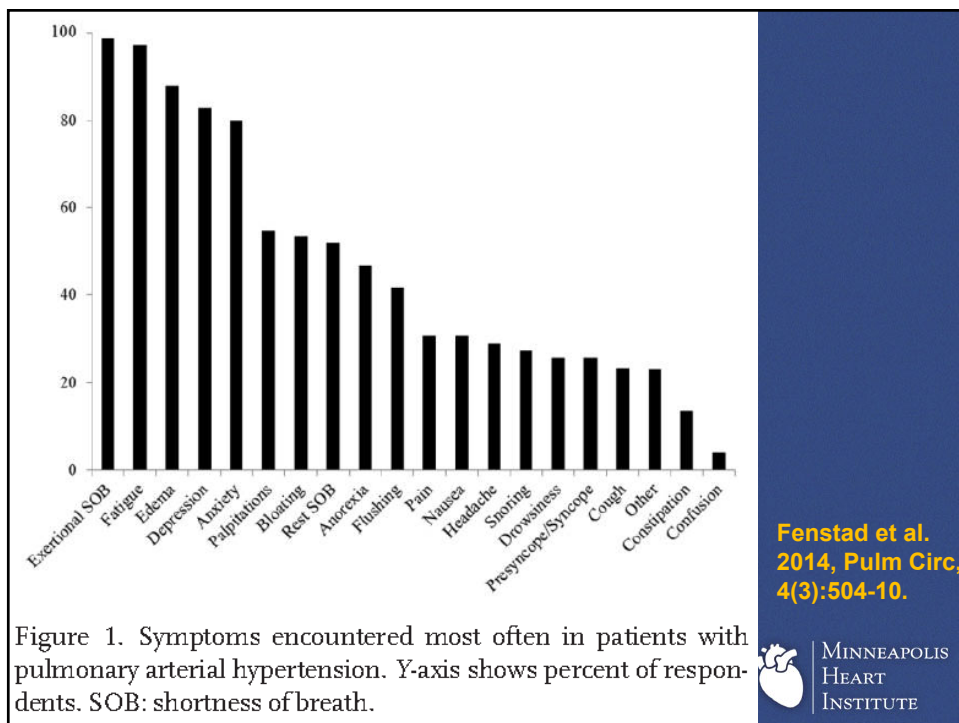


Figure 1. Symptoms encountered most often in patients with pulmonary arterial hypertension. Y-axis shows percent of respondents. SOB: shortness of breath.



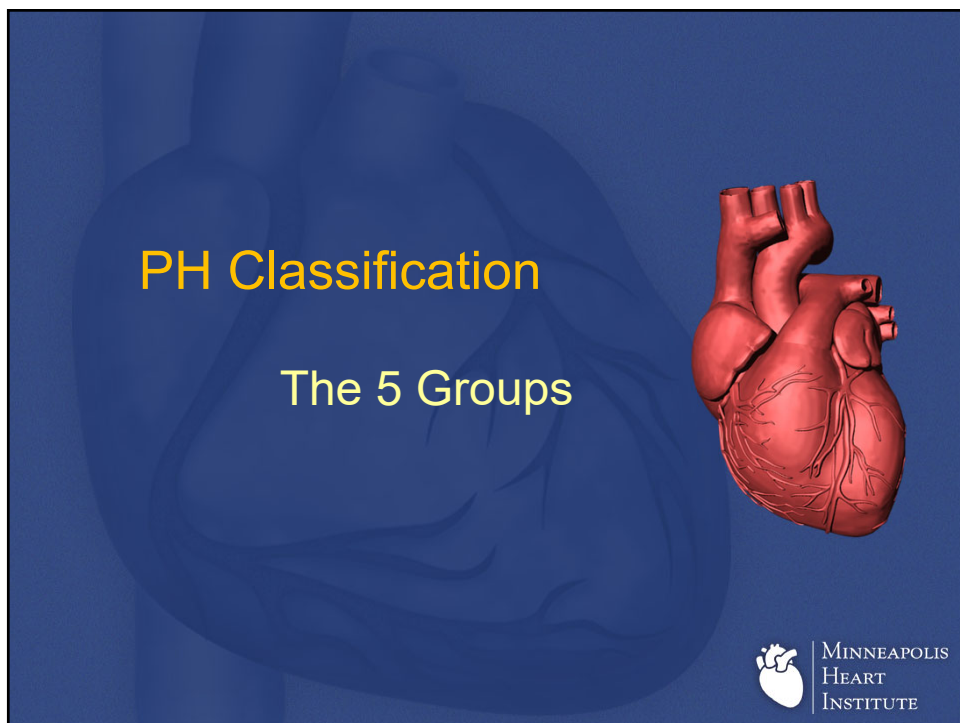
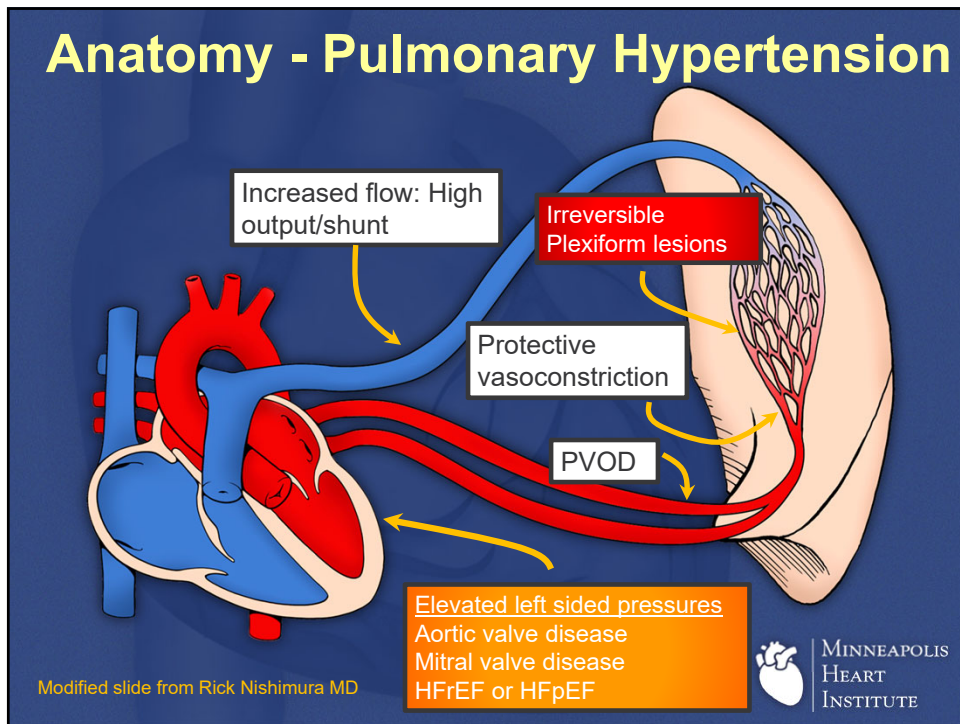


Table 1 Updated Classification of Pulmonary Hypertension*	
<ol style="list-style-type: none"> 1. Pulmonary arterial hypertension <ol style="list-style-type: none"> 1.1 Idiopathic PAH 1.2 Heritable PAH <ol style="list-style-type: none"> 1.2.1 BMPR2 1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3 1.2.3 Unknown 1.3 Drug and toxin induced 1.4 Associated with: <ol style="list-style-type: none"> 1.4.1 Connective tissue disease 1.4.2 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart diseases 1.4.5 Schistosomiasis 1' Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis 1'' Persistent pulmonary hypertension of the newborn (PPHN) 2. Pulmonary hypertension due to left heart disease <ol style="list-style-type: none"> 2.1 Left ventricular systolic dysfunction 2.2 Left ventricular diastolic dysfunction 2.3 Valvular disease 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies 3. Pulmonary hypertension due to lung diseases and/or hypoxia <ol style="list-style-type: none"> 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 lung diseases 	<p style="text-align: center;">PAH</p> <p style="text-align: center;">Left Heart</p> <p style="text-align: center;">Lungs</p>
<p>1998 – 2nd World Symposium</p> <p>2008 – 4th World Symposium (Dana Point)</p> <p>2013 – 5th World Symposium (Nice, France)</p> <p>2018 – 6th World Symposium – updated PH definition</p> <p>Simonneau G. JACC 2013, 62(25S).</p>	

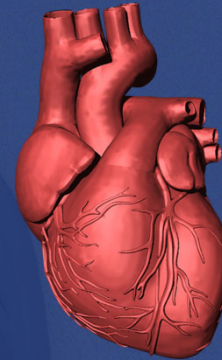


<ol style="list-style-type: none"> 4. Chronic thromboembolic pulmonary hypertension (CTEPH) 5. Pulmonary hypertension with unclear multifactorial mechanisms <ol style="list-style-type: none"> 5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH 	<p style="text-align: center;">VTE</p> <p style="text-align: center;">Misc</p>
<p>*5th WSPH Nice 2013. Main modifications to the previous Dana Point classification are in bold.</p> <p>BMPR = bone morphogenic protein receptor type II; CAV1 = caveolin-1; ENG = endoglin; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension.</p>	

Simonneau G. JACC 2013, 62(25S).

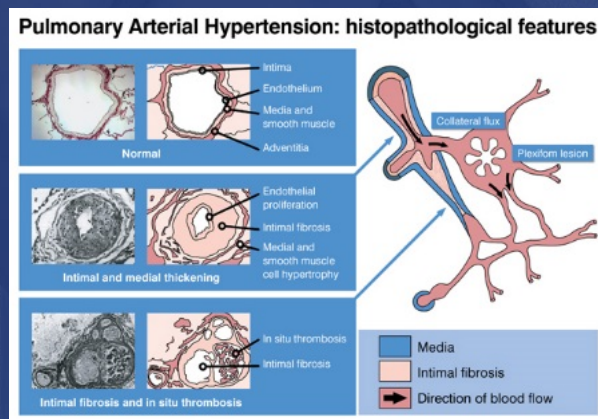


PH Epidemiology



PAH Epidemiology

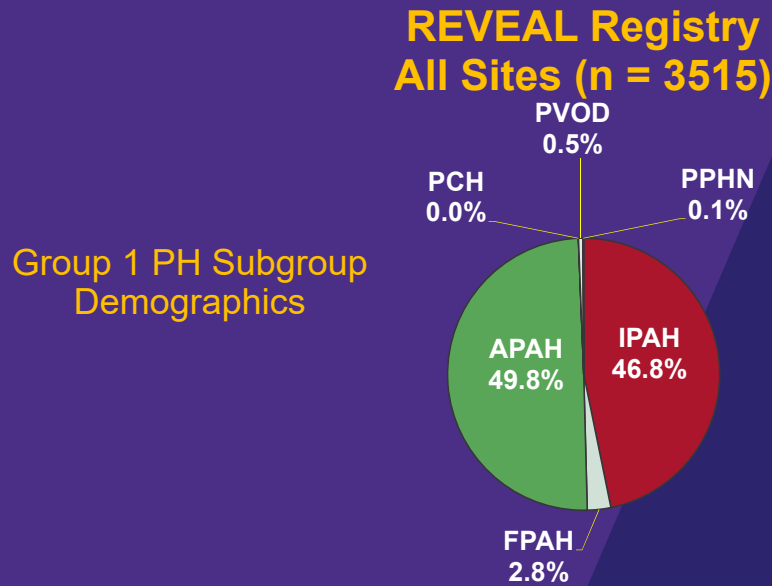
- PAH has a female dominant distribution → 4.8:1 (REVEAL Registry)



PAH Epidemiology

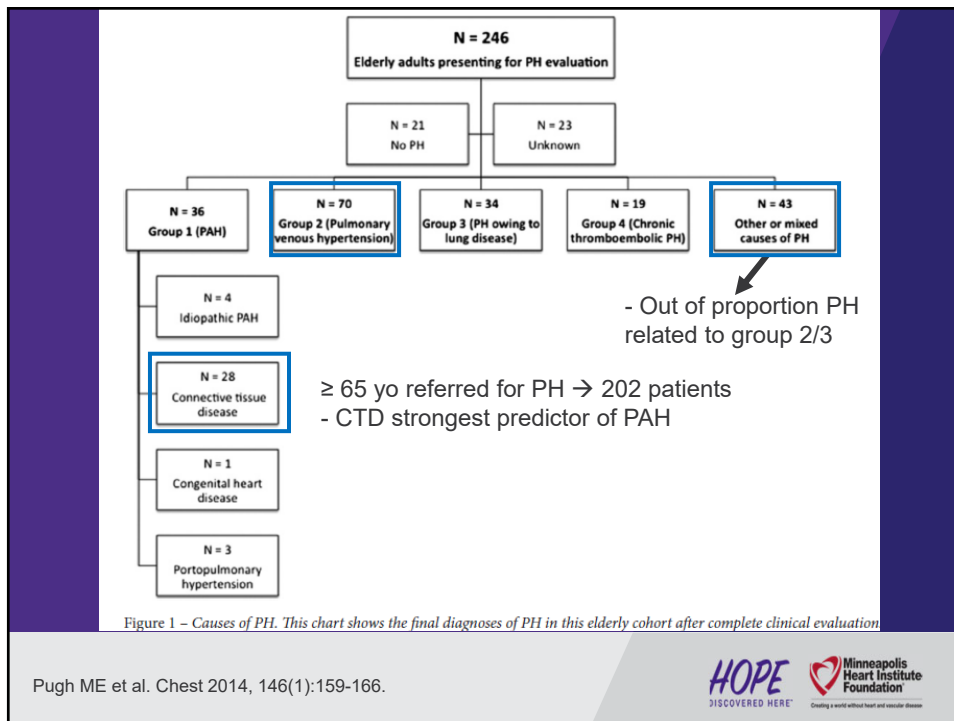
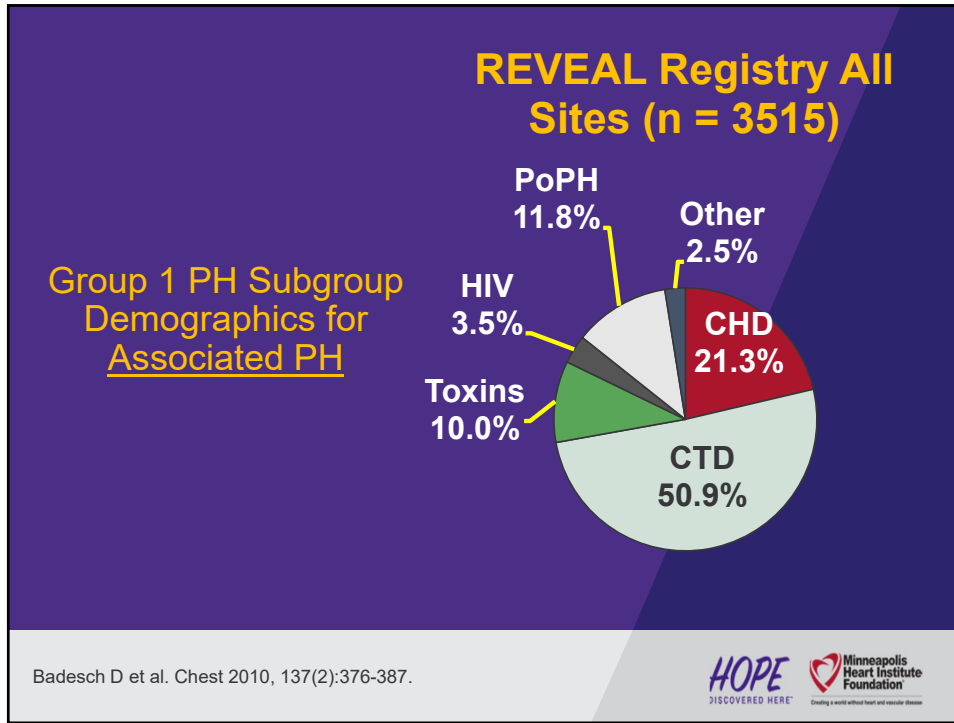
- Idiopathic & heritable PAH incidence: estimated at 5-15 per million
- 10-15% of patients with Scleroderma (most common CTD)
- 3-10% of patients with congenital heart disease (shunts)
- 2-16% of patients with portal hypertension

McGoon MD et al. JACC 2013, 62(25S):D51.



Badesch D et al. Chest 2010, 137(2):376-387.


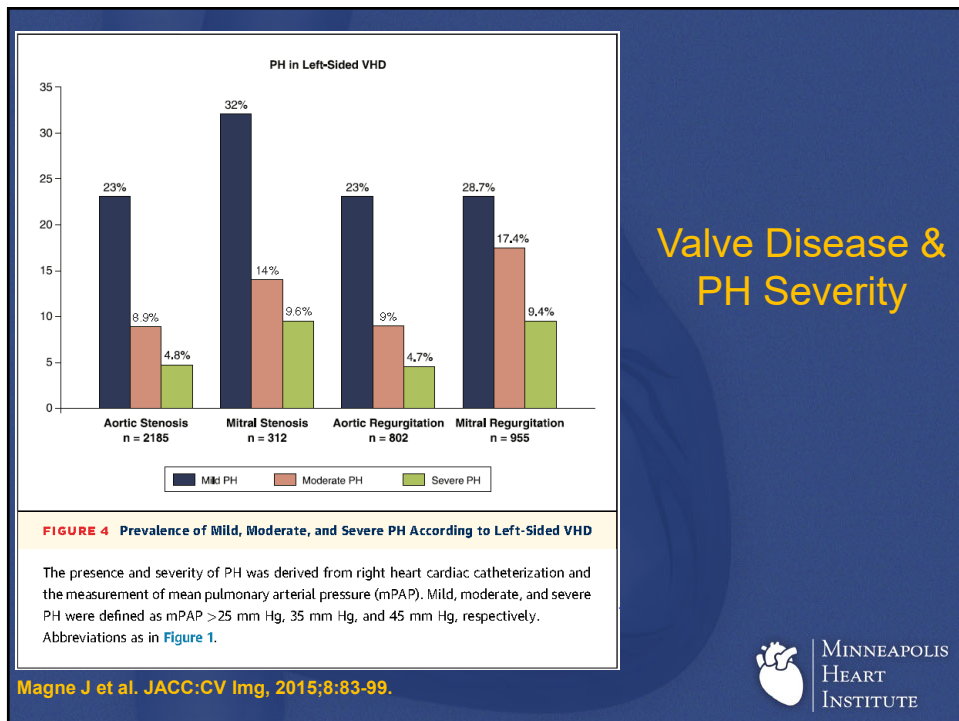




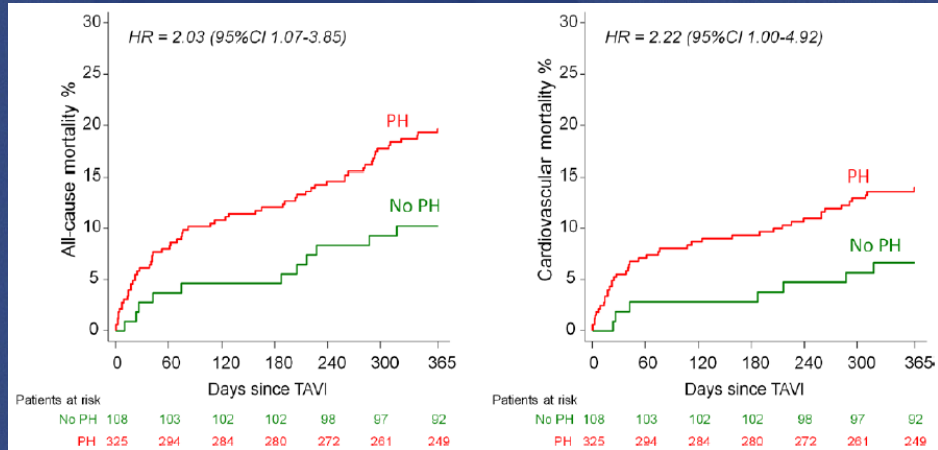
VHD	Condition	Overall prevalence of PH*	Impact of PH on Outcome
Aortic stenosis	Rest	15%-30%	Controversial; ≈2-fold increase of 1 year in mortality after intervention
	Exercise	55%	≈2-fold increase in risk of cardiac event in asymptomatic patients
Mitral stenosis	Rest	>40%	Event-free survival: 77% at 10 years and 41% at 15 yrs
	Exercise	79%	
Aortic regurgitation	Rest	>25%	Controversial
	Exercise		
Primary MR	Rest	20%-30% and 6%-30% in asymptomatic patients; <20% in asymptomatic patients with preserved LVEF	>2-fold increase in risk of post-operative death
	Exercise	≈50%	>3-fold increase in risk of occurrence of symptoms
Secondary MR	Rest	37%-62%	≈1.4-fold increase in risk of death
	Exercise	40%	>3-fold increase of cardiac event; >5-fold increase in risk of death; involved in pathogenesis of acute pulmonary edema

Valve Disease & PH - Epidemiology

Magne J et al. JACC:CV Img, 2015;8:83-99.

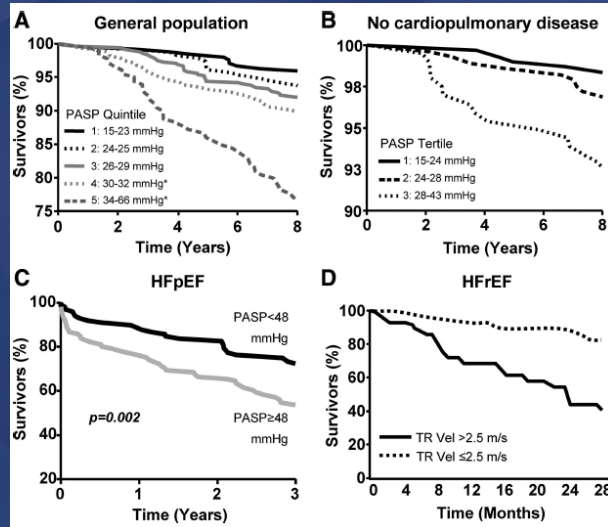
PH is a Significant Comorbidity – Aortic Stenosis



O'Sullivan CJ et al. *Circ Cardiovasc Interv*, 2015;8(7):e002358.



PH as a Comorbidity = ↑ Mortality in HFpEF & HFrEF



Guazzi M. *Circ*, 2012; 126:975-90.



PH as a Comorbidity in COPD

- 90% of severe COPD patients have mPAP > 20 mmHg (PH is dz severity-dependent)
- 1-5% have resting mPAP > 35-40 mmHg
- Vascular lesions are morphologically similarly to those with Idiopathic PA
- PH is stronger association w/ mortality than FEV_1

Nathan SD et al. ERJ, 2019; 53:1801914.

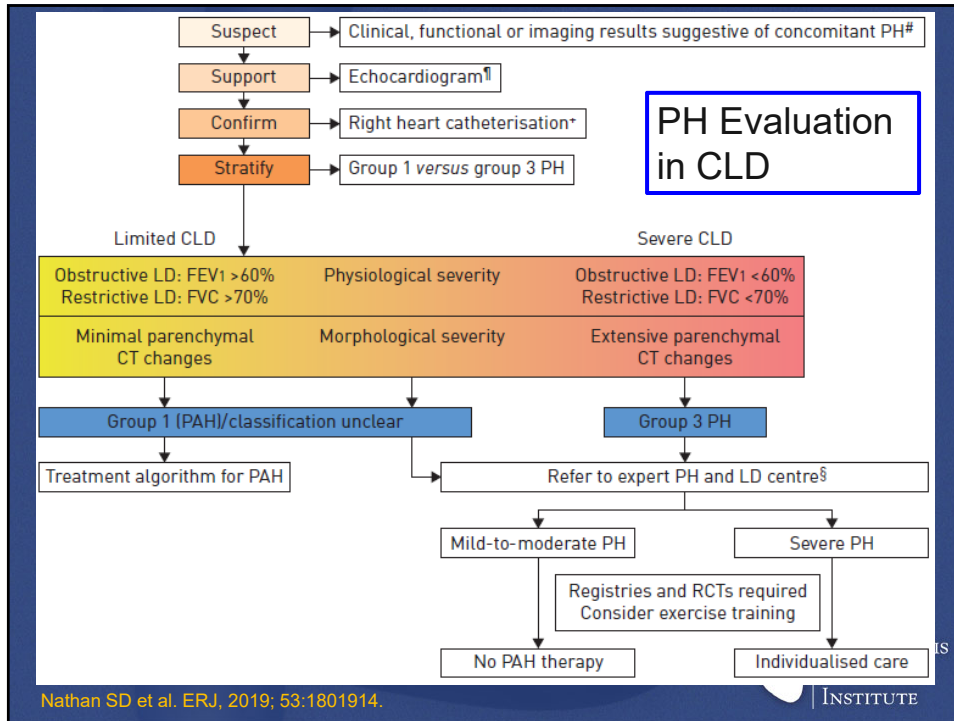


PH as a Comorbidity in ILD

- mPA \geq 25mmHg -- 8-15% of patients w/ IPF, 30-50% prevalence in advanced disease
- Mild PH in most patients
- mPAP increases by 1.8 mmHg/year

Nathan SD et al. ERJ, 2019; 53:1801914.





CTEPH = Group 4 PH

- 1-5% incidence after PE
- 25% pts w/ no PE history
- 96% sensitivity of VQ scan vs. 51% w/ CT

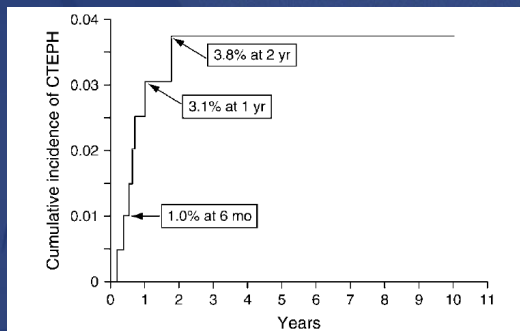


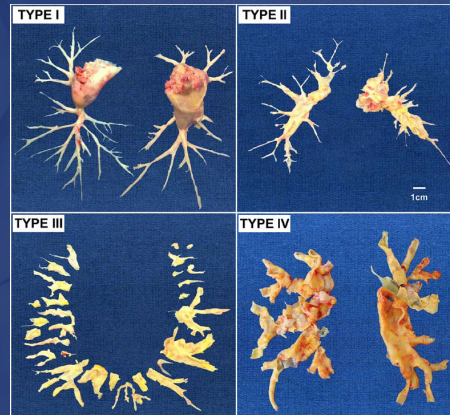
Figure 1. Cumulative incidence of chronic thromboembolic pulmonary hypertension (CTEPH) after a first episode of pulmonary embolism without prior deep vein thrombosis. Reproduced by permission from Reference 30.

Tapson V, Humbert M. Proc Am Thor Soc, 2006;564-67.



CTEPH Treatment

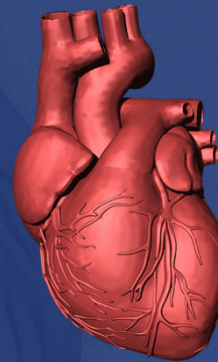
- Proximal disease = surgery (PTEA)
 - 11-35% of pts will have residual PH
- Distal disease = Medication
 - Anticoagulation
 - PH-directed meds
 - **Balloon pulmonary angioplasty**

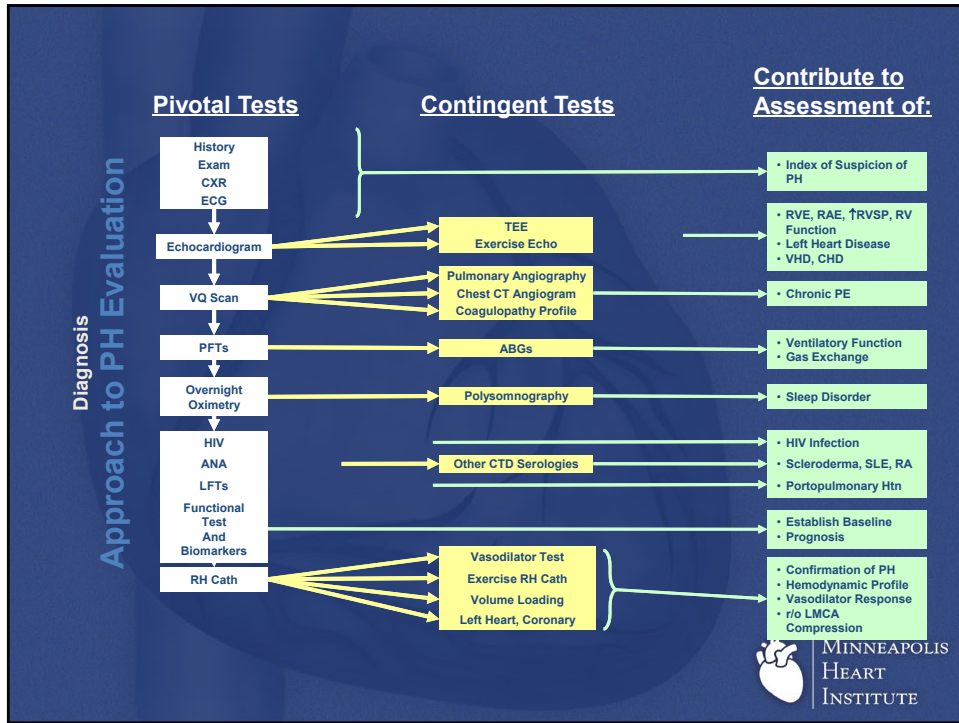


Lang IM, Madini M. Circ, 2014, 130:508-518.



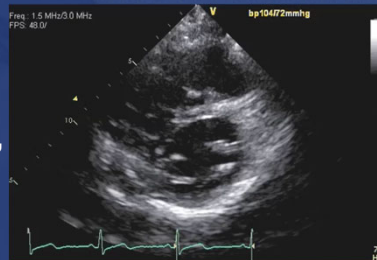
PAH Evaluation and Workup





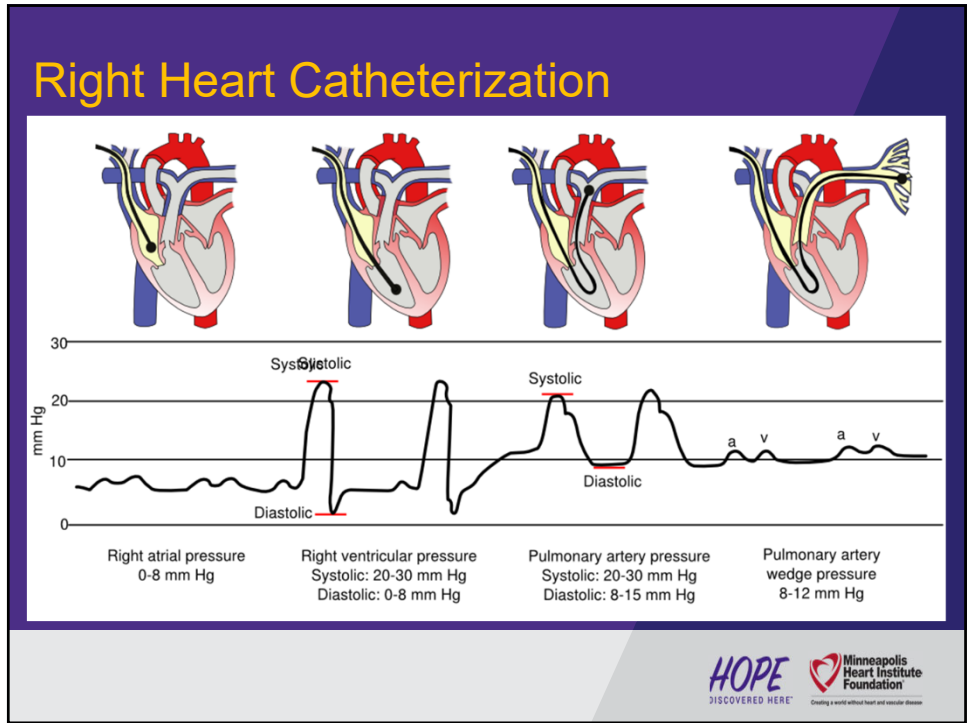
Echo is a Screening Test

- Normal RV pressure < 30 mmHg
- Estimate RVSP with modified Bernoulli equation
 - Can over or underestimate
- RV size and function: TAPSE, S', FAC



Lang RM et al. JASE. 2015; 28(1):1-39.





Right Heart Catheterization

- Gold standard for diagnosis
- **PAH = Mean PA pressure > 20 mm Hg**
 - In PAH → PAWP ≤ 15 mm Hg
 - PVR ≥ 3.0 Wood Units
- Vasodilator response

Positive Vasodilator Test:


1. mPAP ↓ by ≥ 10 mmHg
2. mPAP < 40 mmHg
3. Normal or ↑ in CO

***4.5-10% of patients

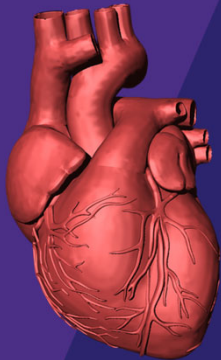


	Epoprostenol	Adenosine	Nitric Oxide
Route of Administration	Intravenous infusion	Intravenous infusion	Inhaled
Dose Titration	2 ng/kg/min every 10 to 15 min	50 mcg/kg/min every 2 min	None
Dose Range	2 to 10 ng/kg/min	50 to 250 mcg/kg/min	10 to 80 ppm
Side Effects	Headache, nausea, lightheadedness	Dyspnea, chest pain, AV block	Increased left heart filling pressure in susceptible patients

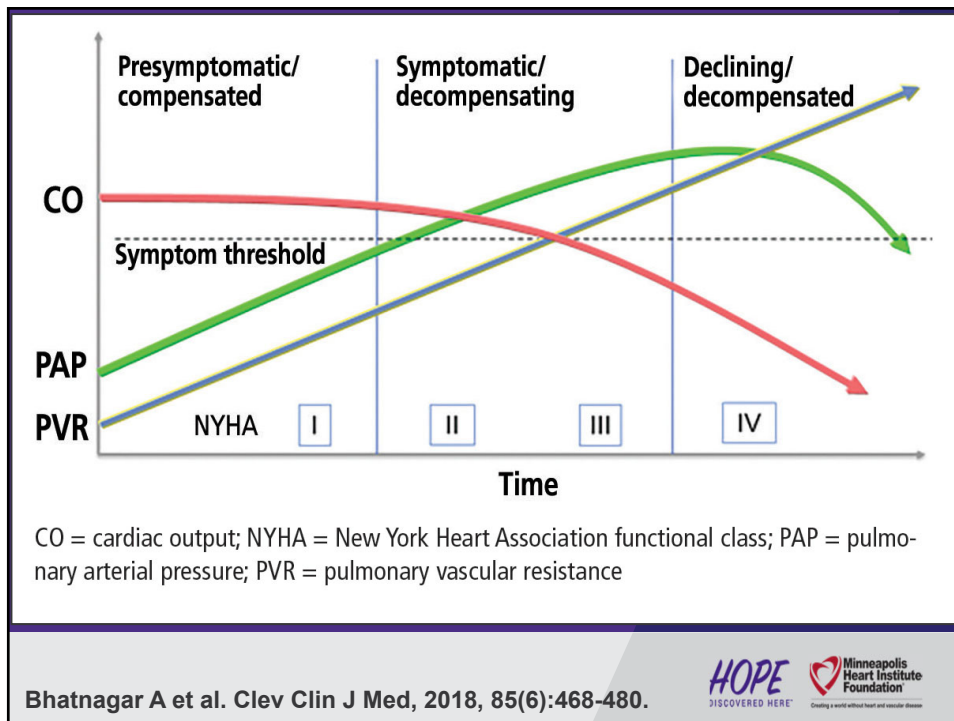
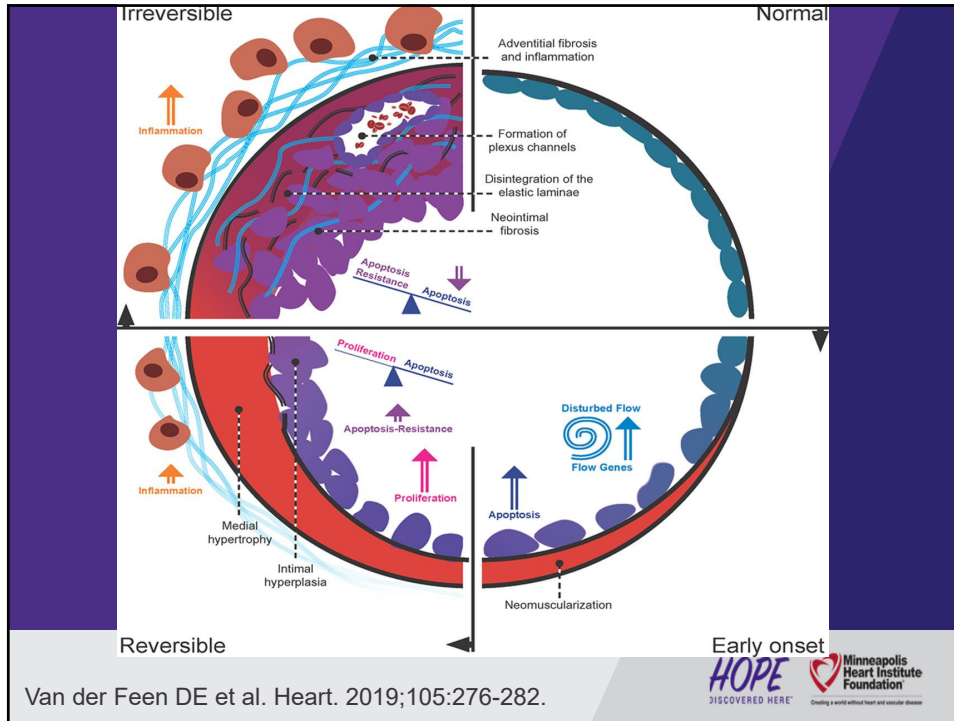
Definitions	Characteristics	Clinical Groups
Pre-capillary PH	<ul style="list-style-type: none"> • mPAP >20 mmHg • PAWP ≤15 mmHg • PVR ≥3 WU 	1, 3, 4, & 5
Isolated post-capillary PH	<ul style="list-style-type: none"> • mPAP >20 mmHg • PAWP >15 mmHg • PVR <3 WU 	2 & 5
Combined pre & post-capillary PH	<ul style="list-style-type: none"> • mPAP >20 mmHg • PAWP >15 mmHg • PVR ≥3 WU 	2 & 5

Frost A et al. ERJ, 2019;53(1).

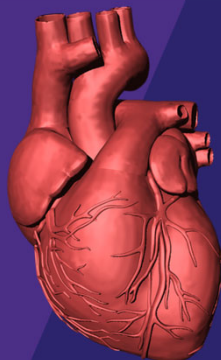


PAH Pathophysiology

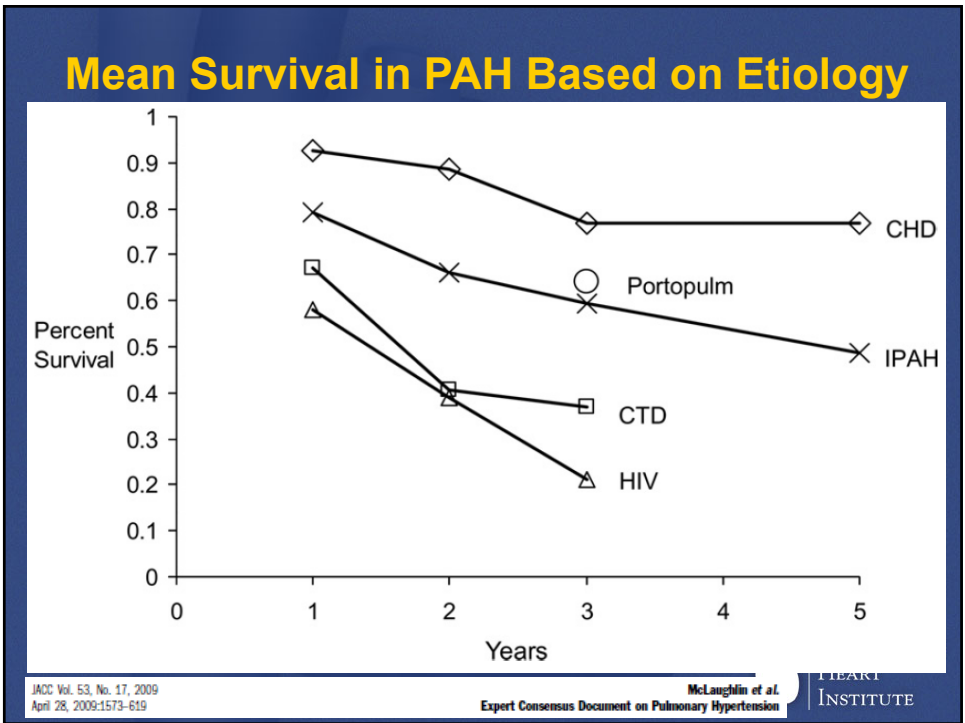


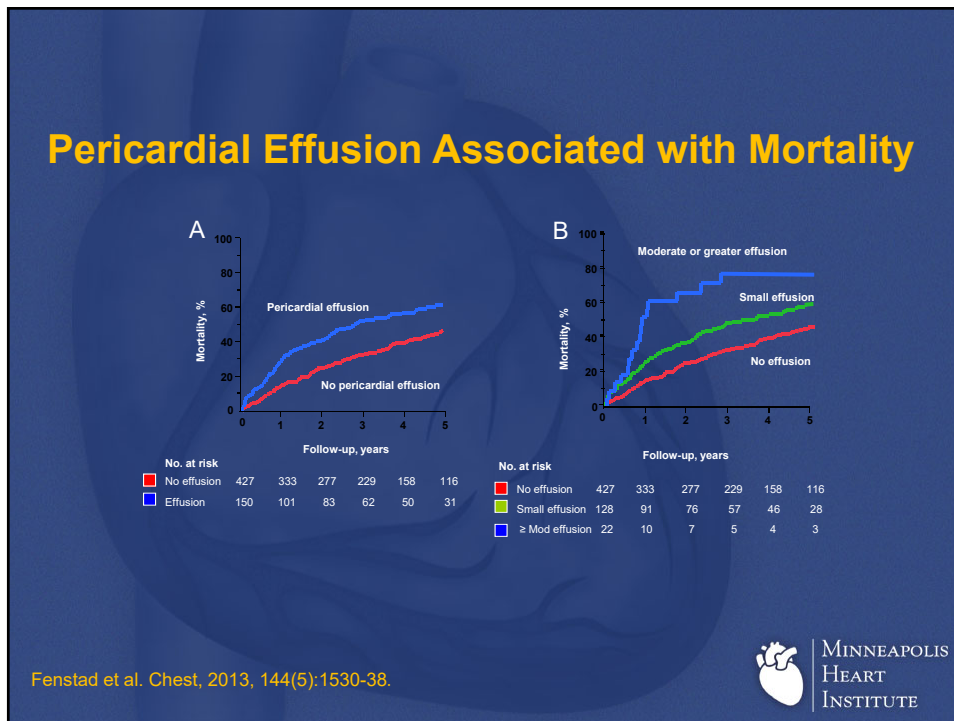
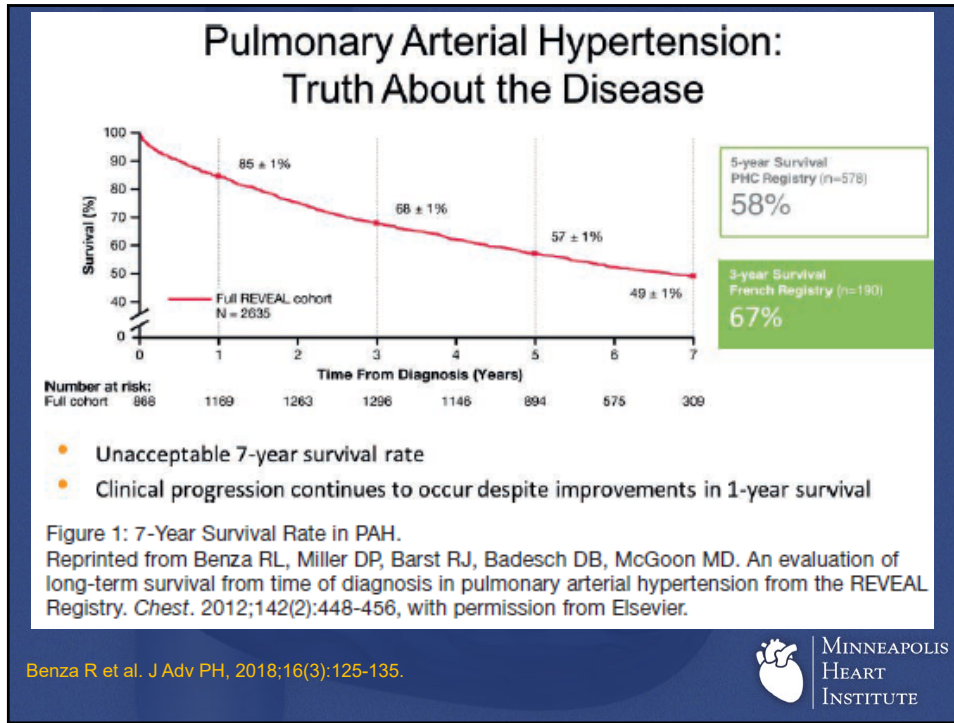
PAH Prognostic Factors & Risk Prediction



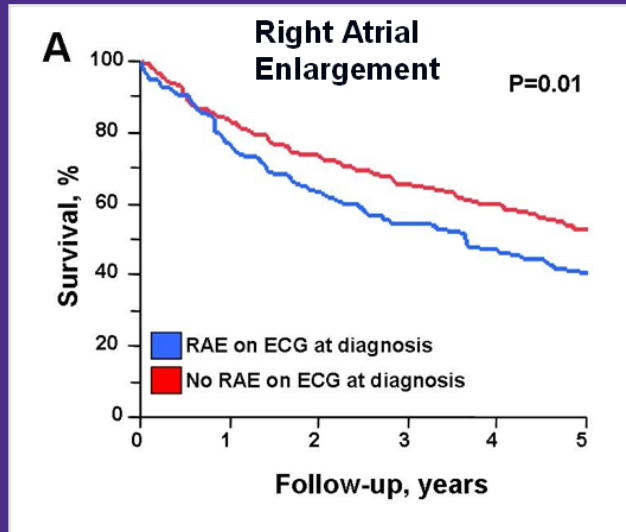
HOPE
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PAH – RAE Associated with Mortality

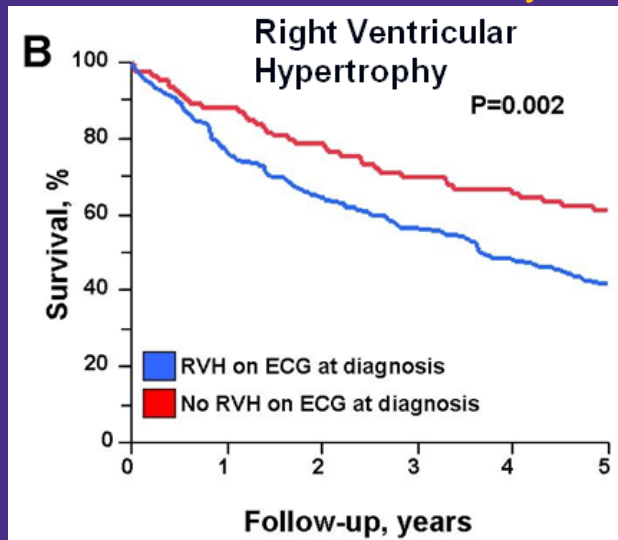


Fenstad et al. Circ, 2011;124:A15999, 21S.

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PAH - RVH on ECG Predicts Mortality




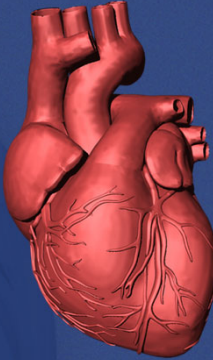
Fenstad et al. Circ, 2011;124:A15999, 21S.

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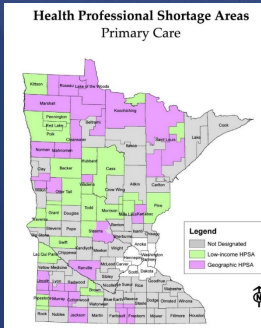
PH Research

Rural vs. Urban Population



Rural vs. Urban PH

- Different demographics & socioeconomic pressures than urban communities
- >25% of MN in rural communities (1.38+ million people)
- Lack of access to specialist physicians:
 - 30 specialists/100,000 pts vs. 263 per 100,000 pts



Rural vs. Urban PH

- PH registries heavily weighted to urban population
- PH classification & prevalence is underreported in rural areas.



Rural vs. Urban PH

- Retrospective consecutive pts w/ RVSP ≥ 50 mmHg or PH symptoms
- PAH = mPA ≥ 25 mmHg & PAWP ≤ 15 with PVR > 3.0 WU (old definition)
- Consecutive patients -- 8/2015-10/1/2018



Patient Characteristics

PH Group	All Patients (n=99)	Group 1 (n=26)	Non-group 1 (n=73)	p-value
Male (%)	50 (50)	9 (35)	41 (56)	0.07
Age (yrs)	73.2 ± 10.6	69 ± 13	75 ± 9	0.01
Mean ± SD (Range)	(37 - 91)	(37 - 89)	(45 - 91)	
BMI	31.8 ± 9.6	30.7 ± 8.0	32.3 ± 10.2	0.47
Mean ± SD (Range)	(18.4 - 59.9)	(15.6 - 44.8)	(18.4 - 59.9)	
Age at RHC	71.0 ± 11.3	66.2 ± 14.3	72.7 ± 9.6	0.01
Mean ± SD (Range)	(37-90)	(37 - 89)	(45 - 90)	
OSA (%)	39 (39)	9 (35)	30 (41)	0.64
DM (%)	35 (35)	8 (31)	27 (37)	0.64
HTN (%)	70 (70)	17 (65)	53 (73)	0.62
CAD (%)	43 (43)	7 (27)	36 (49)	0.07
AFIB (%)	51 (51)	8 (31)	43 (59)	0.02
SVT (%)	5 (5)	0 (0)	5 (7)	0.32
Liver Disease (%)	3 (3)	2 (8)	1 (1)	0.17
Connective Tissue Diseases (%)	2 (2)	1 (4)	1 (1)	0.46
6 minute walk distance (m)	274 ± 120	246 ± 138	289 ± 108	0.05
Mean ± SD (Range)	(82 - 527)	(82 - 527)	(123 - 523)	

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Echo Characteristics

	All Patients (n=99)	Group 1 (n=26)	Non-Group 1 (n=73)	p-value
RAP (mmHg); Mean ± SD	10.1 ± 5.4	9.2 ± 4.6	10.5 ± 5.7	0.29
RVSP (mmHg); Mean ± SD	61.8 ± 20.1	71.3 ± 23.2	58.4 ± 17.8	0.01
RA Enlargement (%)	48 (48)	14 (54)	34 (47)	0.65
Mod/Severe RV Enlargement (%)	32 (32)	10 (38)	22 (30)	0.63
Mod/Severe RV Dysfunction (%)	22 (22)	9 (35)	13 (18)	0.17
TAPSE (mm)	16.7 ± 8.6	16.7 ± 8.0	16.7 ± 8.8	0.98
Pericardial Effusion (%)	21 (21)	8 (31)	13 (18)	0.17
LVEF Mean ± SD	56.5 ± 12.1	62.1 ± 10.7	54.6 ± 12.1	0.01
Mod/Severe LA Enlargement (%)	48 (48)	7 (27)	41 (56)	0.01
E/e' (median; IQR)	12.7 (9.5, 17.9)	11.1 (7.8, 14.1)	13.6 (10.1, 18.6)	0.07

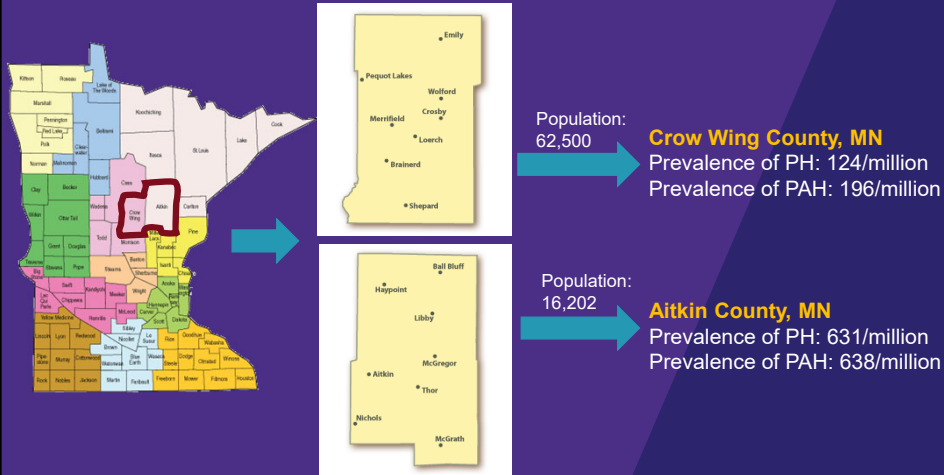
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Right Heart Cath Characteristics

	All Patients (n=99)	Group 1 (n=26)	Non-Group 1 (n=73)	p-value
RAP (mmHg) Mean ± SD	11.6 ± 6.0	8.4 ± 4.0	12.6 ± 6.2	0.002
RVSP (mmHg) Mean ± SD	57.2 ± 18.0	68.3 ± 22.1	53.4 ± 14.7	0.002
Mean PAP (mmHg) Mean ± SD	37.7 ± 12.1	44.6 ± 16.6	35.3 ± 9.1	0.003
PAWP (mmHg) Mean ± SD	18.1 ± 7.4	11.7 ± 6.6	20.3 ± 6.3	<0.001
Cardiac Index (L/min/m2)	2.5 ± 0.7	2.6 ± 0.8	2.5 ± 0.7	0.71



Prevalence of PH in Rural MN



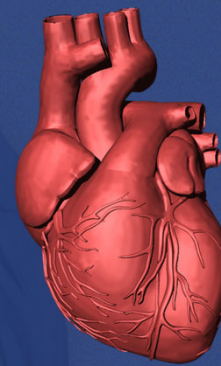
Conclusions

- PAH prevalence in rural Minnesota appears 2.5-13 times higher than the estimated 15-50 cases/million compared to national data.
- Why? Lower socioeconomic area, access to care, environmental exposures? Or Nationwide trend of underrecognition?



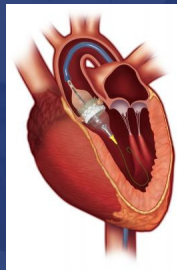
PH Research

PH Post-TAVR



Post TAVR PH

- PH with aortic stenosis impacts 1- and 2-year survival following TAVR
- Many PH patients post-TAVR normalize RVSP, yet a subset have residual PH

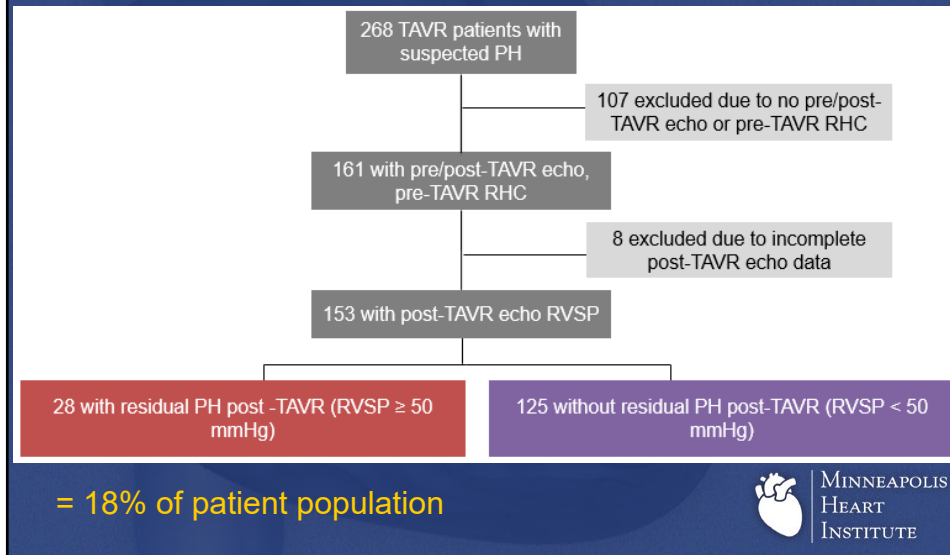


Post TAVR PH Methods

- Retrospective review – TAVR from 1/1/2009-4/29/2019
- Pre/post TAVR echo & pre-TAVR right heart cath
- PH = RHC mean PAP > 20 mmHg
- Residual PH = RVSP \geq 50 mmHg on post-TAVR echo



Results - Post TAVR PH

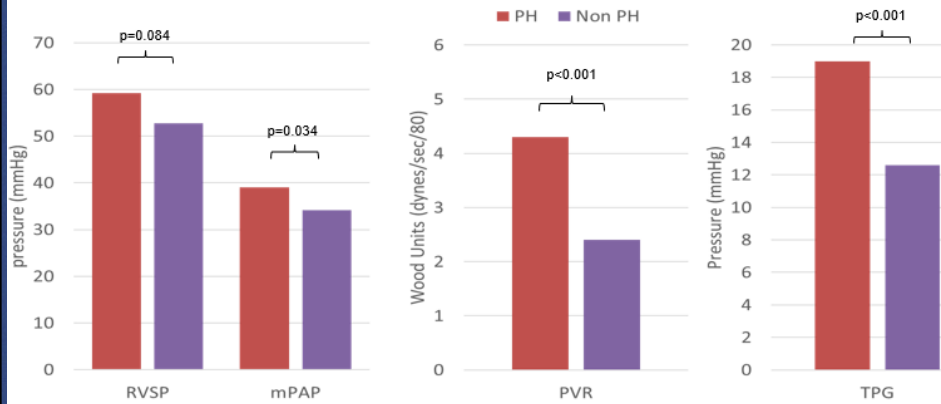


Results – Patient Characteristics

	All pts (n=153)	PH pts (n=28)	Non PH pts (n=125)	p-value
Male (%)	78 (51)	13 (46)	65 (52)	0.746
Age at TAVR (yrs) Mean ± SD (range)	81.5 ± 8.7 (48-99)	82.3 ± 7.0 (64-92)	81.3 ± 9.0 (48-99)	0.589
BMI Mean ± SD (range)	29.6 ± 8.1 (17.4-63.0)	28.7 ± 6.4 (17.4-44.8)	29.8 ± 8.5 (18.1-63.0)	0.524
Chronic dialysis (%)	11 (7)	2 (7)	9 (7)	1
OSA (%)	18 (12)	0 (0)	18 (14)	0.045*
COPD (%)	48 (31)	12 (43)	36 (29)	0.221
DM (%)	67 (44)	12 (43)	55 (44)	1
HTN (%)	143 (93)	24 (86)	119 (95)	0.086
CAD (%)	93 (61)	19 (68)	74 (59)	0.526
AFIB (%)	89 (58)	21 (75)	68 (54)	0.074
Connective Tissue Diseases (%)	8 (5)	2 (7)	6 (5)	0.639
BNP Median (25th, 75th percentile)	696 (301, 1176)	879 (360, 1576)	685 (295, 1006)	0.178
Creatinine Median (25th, 75th percentile)	1.24 (0.99, 1.57)	1.31 (1.07, 1.57)	1.22 (0.98, 1.57)	0.485
Hemoglobin Mean ± SD	11.1 ± 1.9	11.2 ± 1.9	11.1 ± 2	0.882
Platelets Mean ± SD	188.6 ± 71.1	205.2 ± 87.4	184.9 ± 66.7	0.174
NYHA FC 3&4 (%)	141 (92)	27 (96)	114 (91)	0.696
Frailty (%)	30 (20)	6 (21)	24 (19)	0.996
STS Risk Score Mean ± SD	7.7 ± 4.6	8 ± 4.5	7.6 ± 4.7	0.675
Prior Valve Surgery (%)	48 (31)	6 (21)	42 (34)	0.303

Right Heart Cath Hemodynamics

Figure 2. RHC Hemodynamics of PH and non-PH groups



Pre-TAVR RHC Hemodynamics

- 10 pts – PAH
- 130 pts – Group 2/3
- 4 pts – incomplete data
- 9 pts – mPA < 20 mmHg



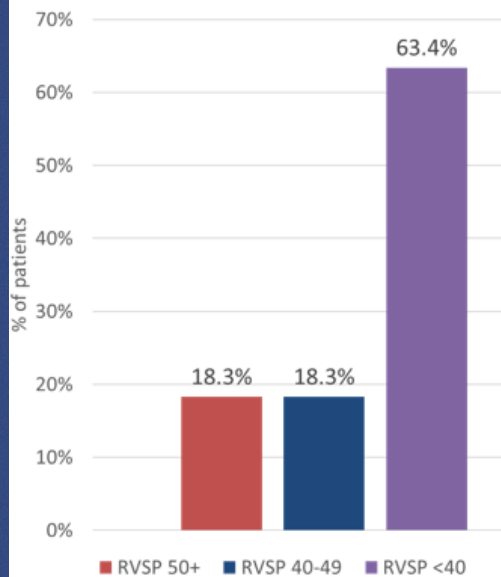
Post-TAVR RHC Hemodynamics

Patient	RAP	mPAP	PAWP	TD CO	PVR
1	10	32	19	2.4	5.13
2	11	42	19	2.7	7.25
3	13	43	21	4.23	5.20
4	8	36	21	4.63	2.96
5	13	48	18	6.11	4.91
6	8	30	21	3.87	2.04
7	11	42	19		9.36
8	5	19	ND	3.6	
9	11	30	24		

- 9 pts had RHC post-TAVR;
1 pt on PH meds



Figure 1b. Prevalence of PH in patients status post-TAVR via Echo



- Pts with residual PH
– 16% lower AVMG
– Avg change in pre/post RVSP = 1.16 mmHg



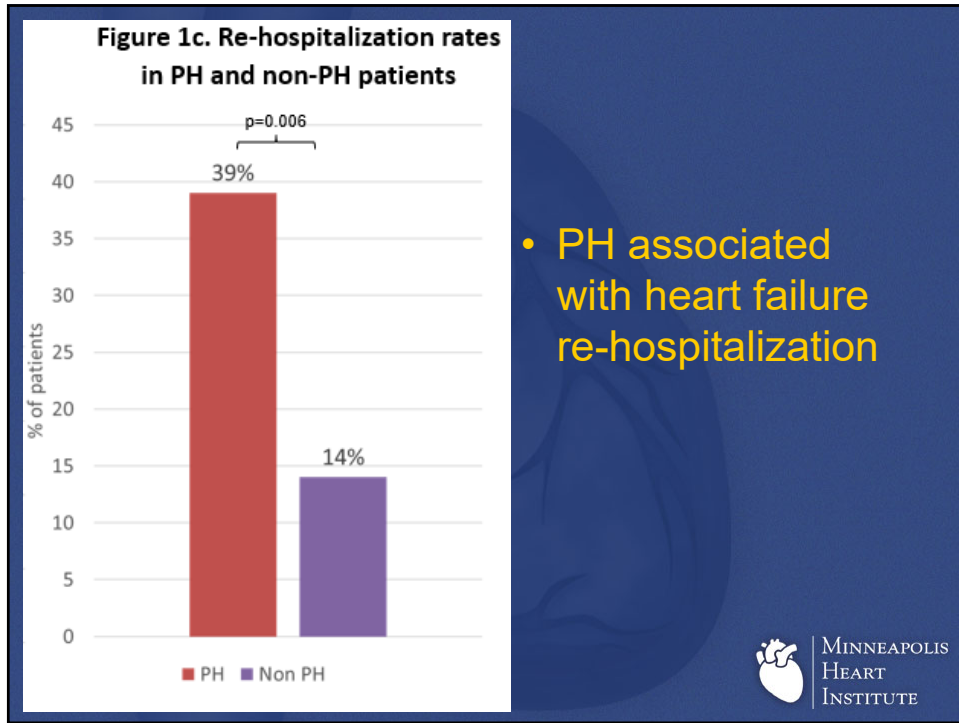


Table 3. Odds ratios for PH by Echo characteristics, adjusted for age and gender

Variable	OR (95% CI)
Moderate/Severe RV enlargement	4.23* (1.59,11.3)
Moderate/Severe RV dysfunction	2.72* (1.06,7.01)
RA enlargement	1.76 (0.95, 3.24)
Moderate/Severe LA enlargement	1.56 (0.82, 2.97)
Pericardial effusion	1.42 (0.49, 4.12)

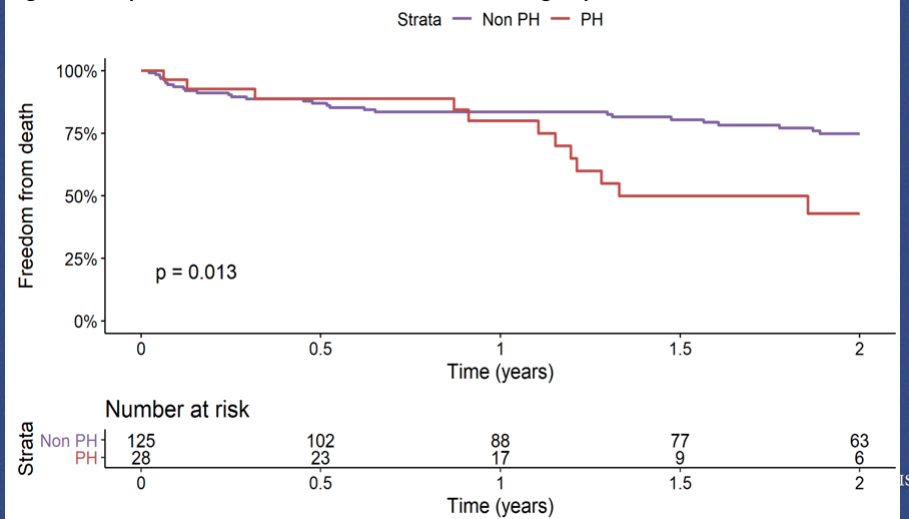
Table 2. Likelihood Ratios of Echo and RHC Hemodynamics for PH and non-PH groups

Factor	Likelihood Ratio +	Likelihood Ratio -
RVSP > 55 mmHg	1.94	0.75
RVSP > 60 mmHg	2.81	0.79
Moderate/severe RV enlargement	2.67	0.89
Moderate/severe RA Enlargement	1.59	0.65
Pericardial Effusion	2.62	0.90
Moderate/severe LA Enlargement	1.25	0.64
E/e' > 15	0.93	1.14
E/e' > 20	0.75	1.15
PVR > 4.0 wood units	2.77	0.57
TPG > 12	1.59	0.47
TPG > 15	2.03	0.63
TPG > 17	3.36	0.59
mPA > 30 mmHg	1.30	0.59
mPA > 40 mmHg	1.62	0.72
mPA > 50 mmHg	2.44	0.89



Results – Survival

Figure 1a. Kaplan Meier Survival Curve of PH and non-PH groups



Take Home Messages

- 5 groups for PH (Group 1 = PAH)
 - RHC is gold standard
- PAH = mPA >20 mmHg, PAWP ≤ 15 & PVR ≥ 3.0 Wood Units
- PH is underreported in rural population
- Post-TAVR PH in 20% of MHI population



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