Pulmonary Arterial Hypertension – ***Cutting edge*** of ***Non-Invasive*** Imaging

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Jewish General Hospital

McGill University

מנהל המחלקה לקרדיולוגיה
בית החולים הכללי היהודי
אוניברסיטת מקגיל

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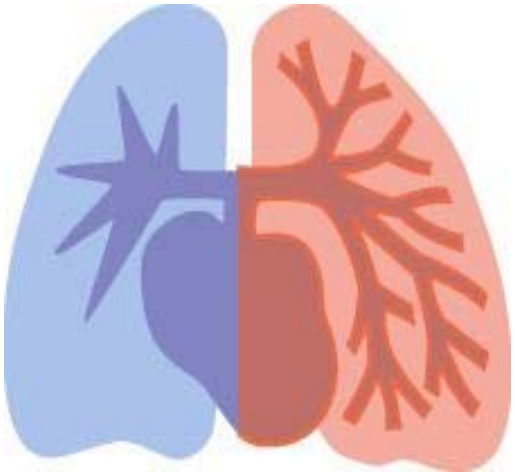
Disclosures

- I own < 1/50,000,000th of GE Stock



Prof. David Langleben

Founder and Director, Center for Pulmonary Vascular Diseases

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$$V = IR$$

$$P = Q \times R$$

Imaging

- Diagnose
- Screen
- Prognosticate
- Guide Therapy
- Give Mechanistic Insights

- Evolution of imaging for the above

DANA POINT CLASSIFICATION 2008

1. Pulmonary arterial hypertension

- **Idiopathic PAH**
- **Heritable**
  - **BMPR2**
  - **ALK1, endoglin**
  - **unknown**
- **Drugs and toxins induced**
- **Associated with:**

– Connective tissue diseases
– HIV infection
– Portal hypertension
– systemic to pulmonary shunts
– Schistosomiasis
– Chronic haemolytic anaemia

1'Pulm. veno- occlusive disease (PVO) and/or pulmonary capillary haemangiomatosis (PCH)

2. Pulmonary hypertension due to left heart disease

- **Systolic dysfunction**
- **Diastolic dysfunction**
- **Valvular disease**

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

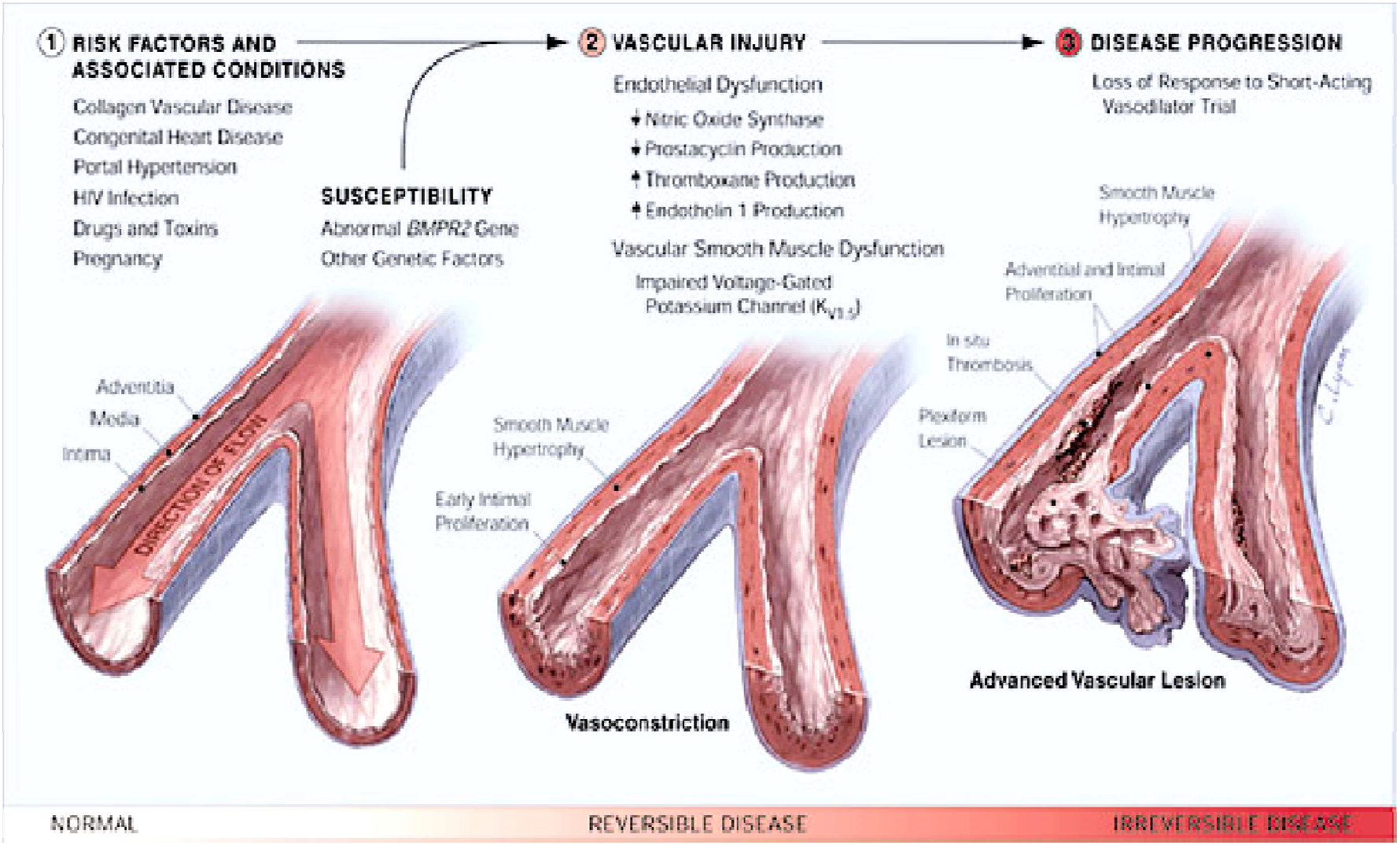
- **Chronic obstructive pulmonary disease**
- **Interstitial lung disease**
- **Sleep-disordered breathing**
- **Chronic exposure to high altitude**
- **Broncho pulmonary dysplasia (BPD)**
- **Developmental abnormalities**

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary Hypertension with unclear and/or mulifactorial mechanisms

- **Haematologic disorders**
  myeloproliferative disorders; splenectomy
- **Systemic disorders**
  Vasculitis sarcoidosis, pulmonary Langerhans cell histiocytosis LAM, neurofibromatosis.
- **Metabolic disorders**
  Glycogen storage disease, Gaucher disease, thyroid disorders
- **Congenital heart disease**
  other than systemic to pulmonary shunt
- **Others**: *obstruction by tumours, fibrosingmediastinitis, chronic renal failure on dialysis*

Simonneau et al, JACC 2009;54:s43-s54



- **Experimental and clinical studies now converge on the intersection and interactions between a genetic predisposition involving the BMPR2 signaling pathway and an impaired metabolic and chronic inflammatory state in the vessel wall.**
- **These deranged processes culminate in an exuberant proliferative response that occludes the pulmonary arterial (PA) lumen and obliterates the most distal intra-acinar vessels.**

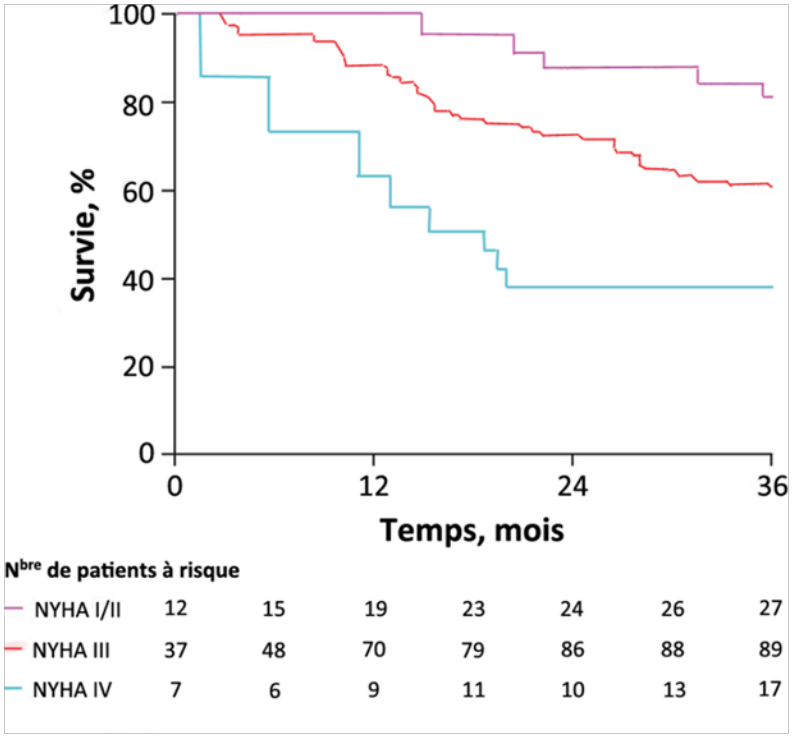
Early Diagnosis – We Need a Better Mousetrap

Rich, Annals Int Med 1987

symptoms to diagnosis: mean 24 months, median 15.2 months

Benza CHEST 2012 (REVEAL)

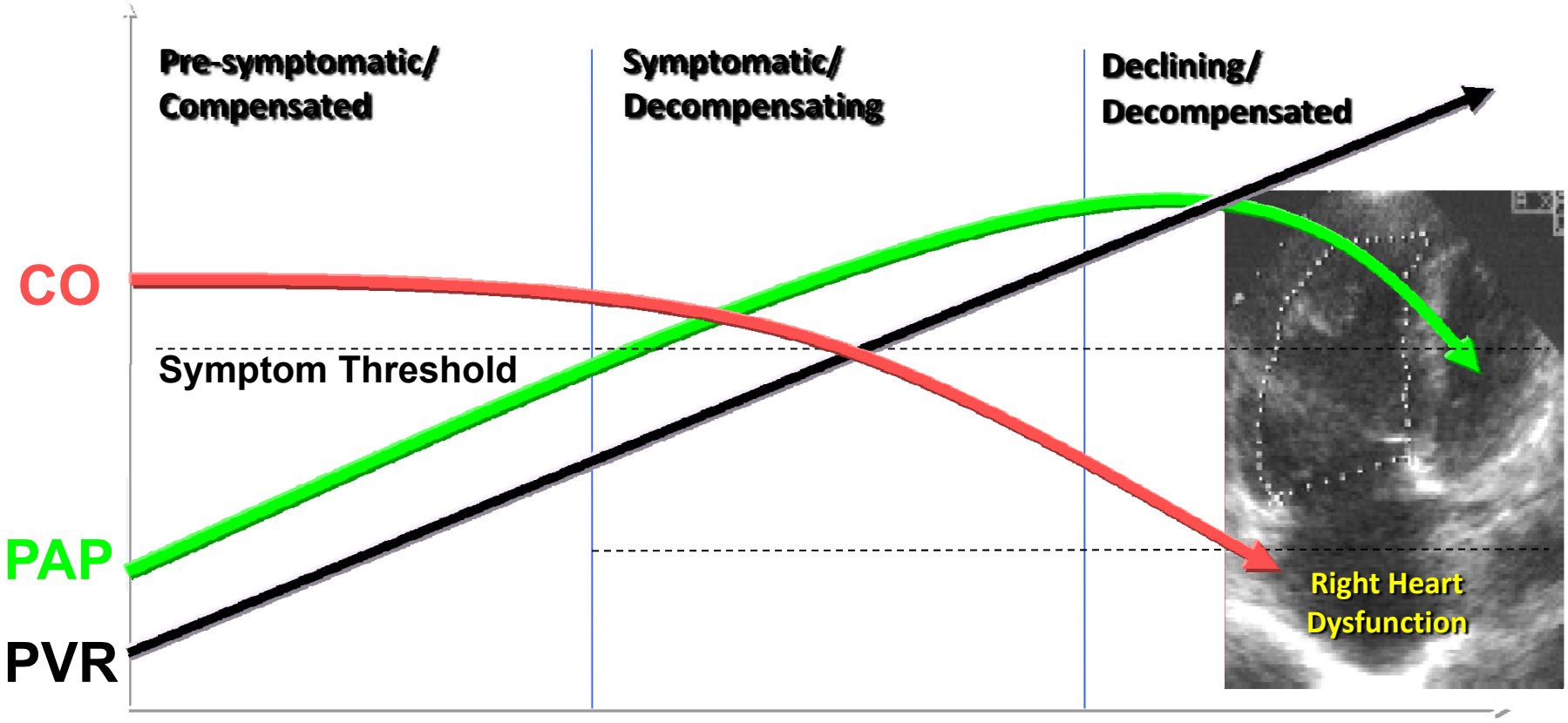
symptoms to diagnosis: mean 31 months, median 12.8 months



Actual Survival in treated patients

Humbert M, *et al. Circulation* 2010;122:156-163.

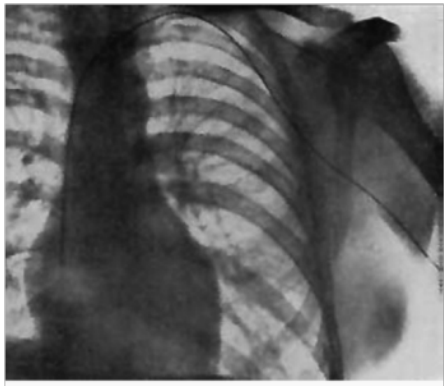
PAH: *A Progressive Disease*

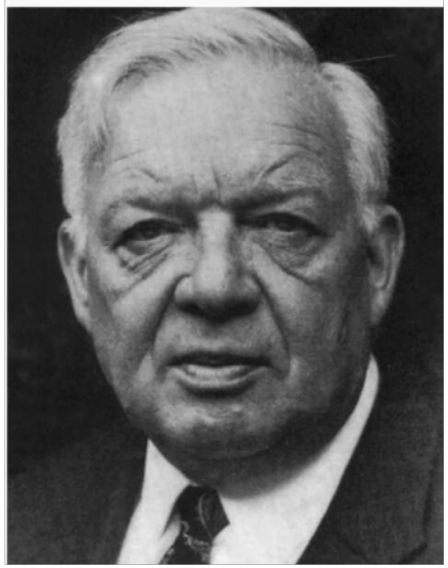


Diagnosis & Screening

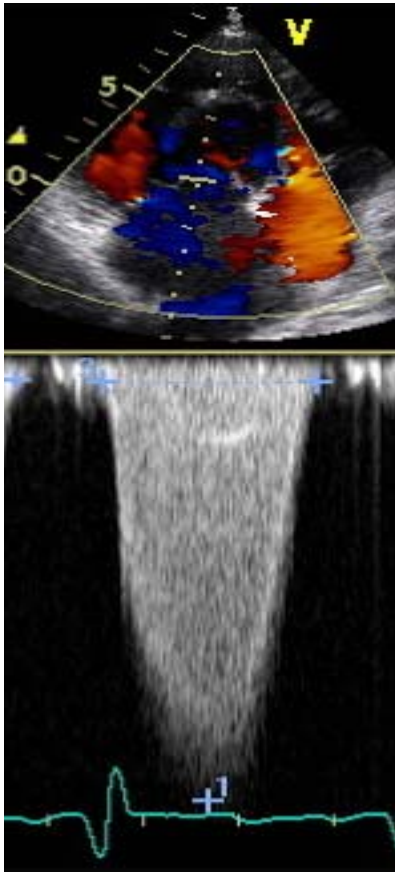
PH, PAH – Hemodynamic Definitions

- Tsintoor- RHC 1929 – Forsmann – The Plumber
- PPH -1951 - Dresdale
- PH – PAPmean > 25
- PAH – with PCWP < 15 & PVR > 3 WU
  - (???with exercise > 30)

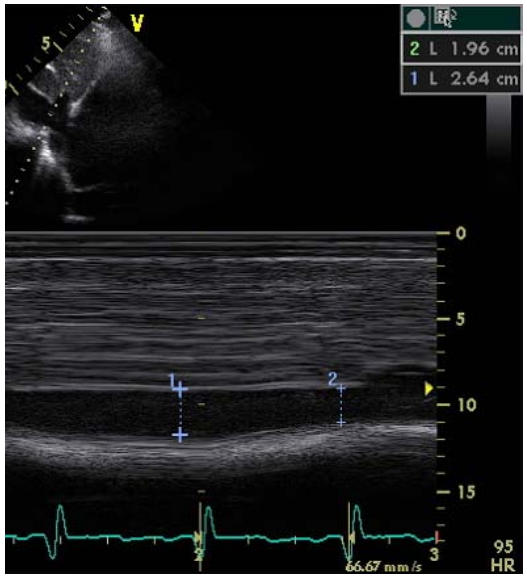




A Leap Forward – Non-Invasive Estimation of RVSP



3	TV TTP	449.2 ms
2	TV TTP	449.2 ms
1	TR Vmax	5.25 m/s
	TR maxPG	110.1 mmHg
	RVSP	110.1 mmHg



Modified Bernoulli Equation

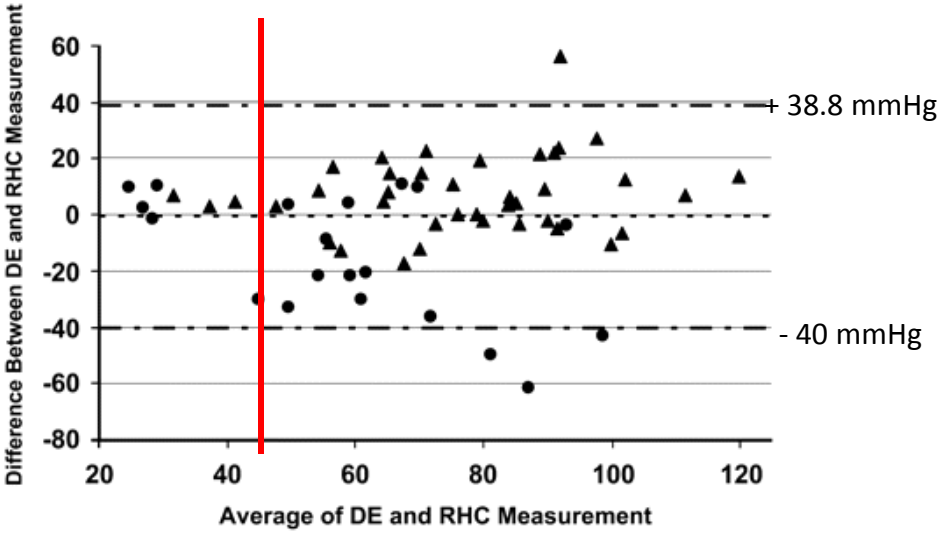
RVSP = 4 X TR_{vmax}^{2} + estimated RA pressure

Yock and Popp Circulation 1984

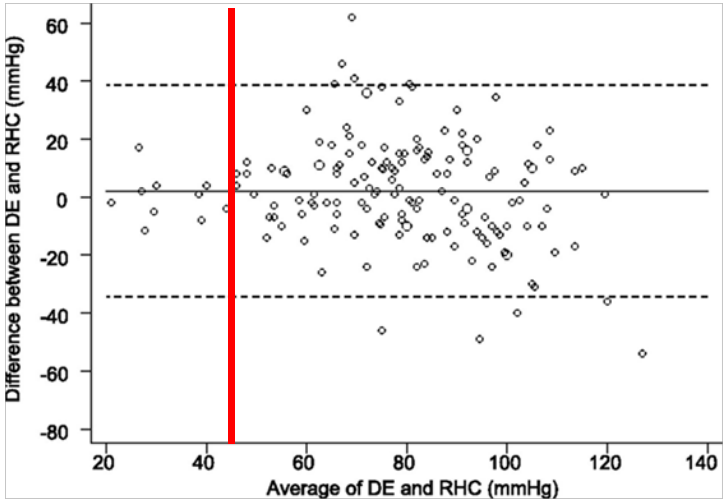
Accuracy of Doppler Echocardiography in the Hemodynamic Assessment of Pulmonary Hypertension

Fisher MR, Forfia P, Chamera E, et al.

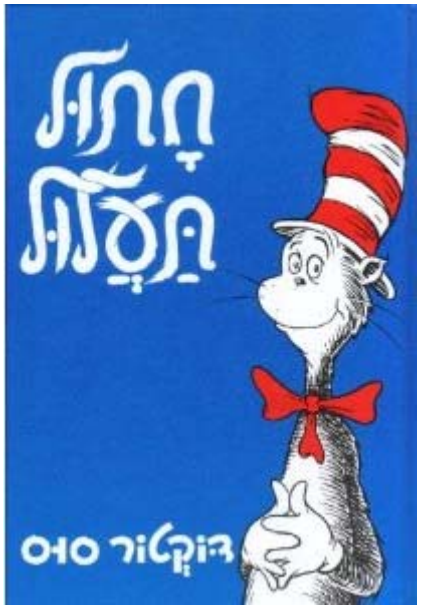
AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 179 2009

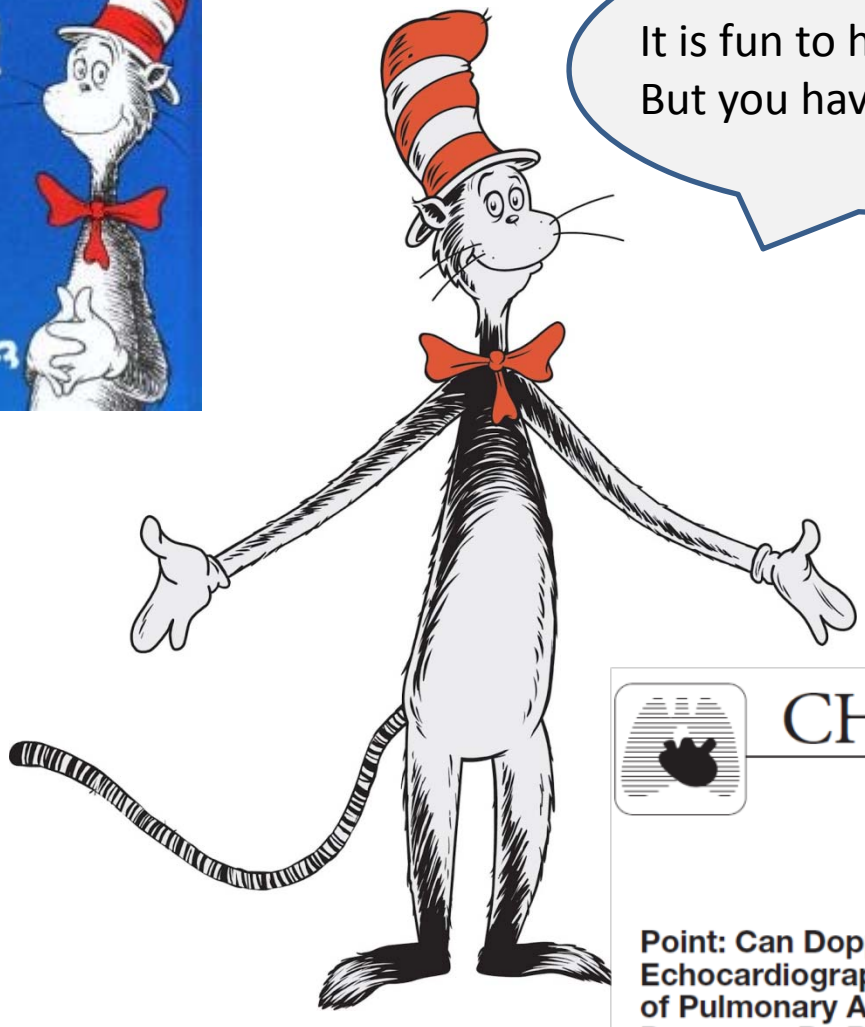


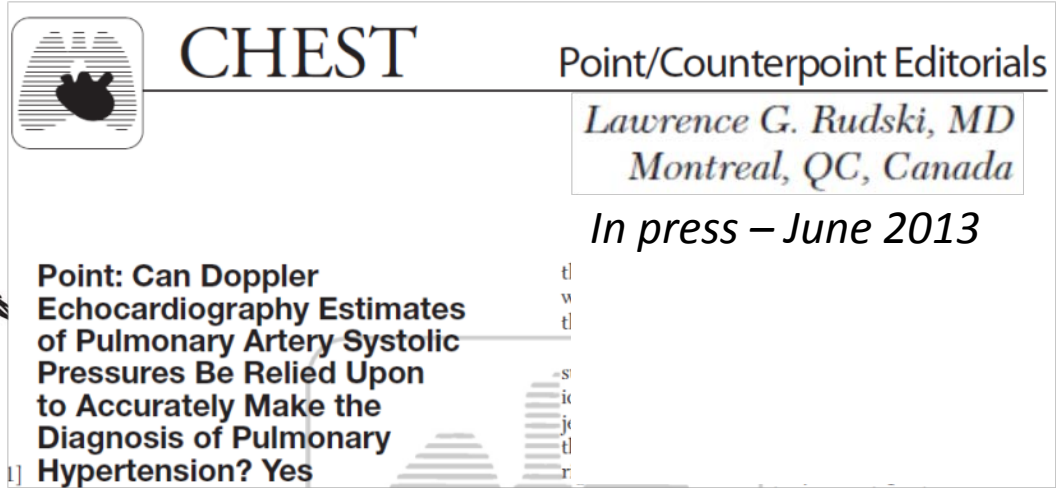
Rich et al. Chest. 2011;139(5):988-993.
doi:10.1378/chest.10-1269



Screening

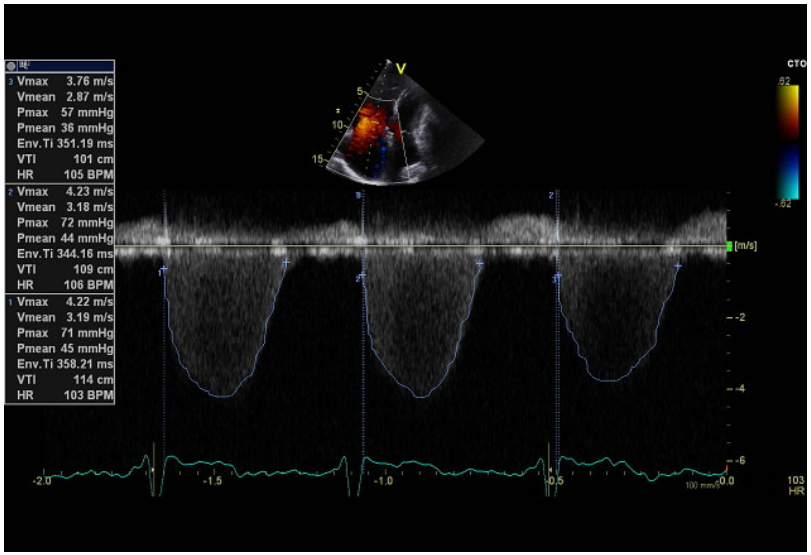


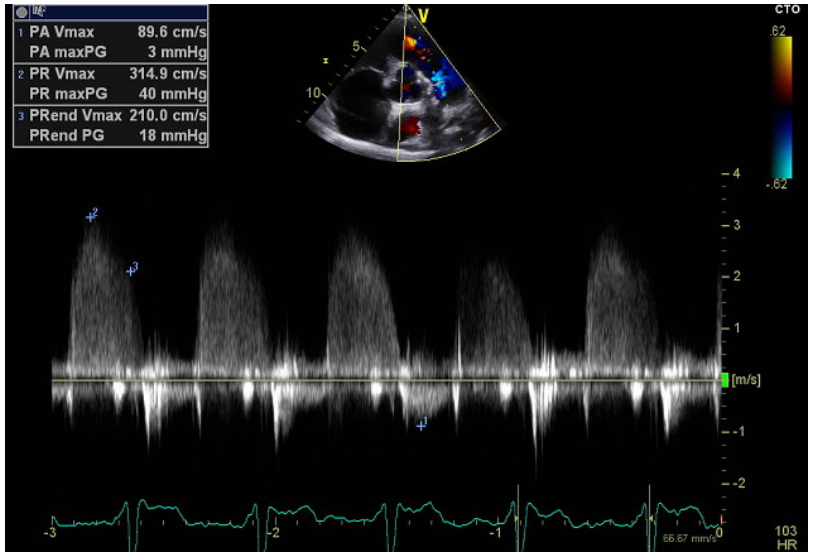


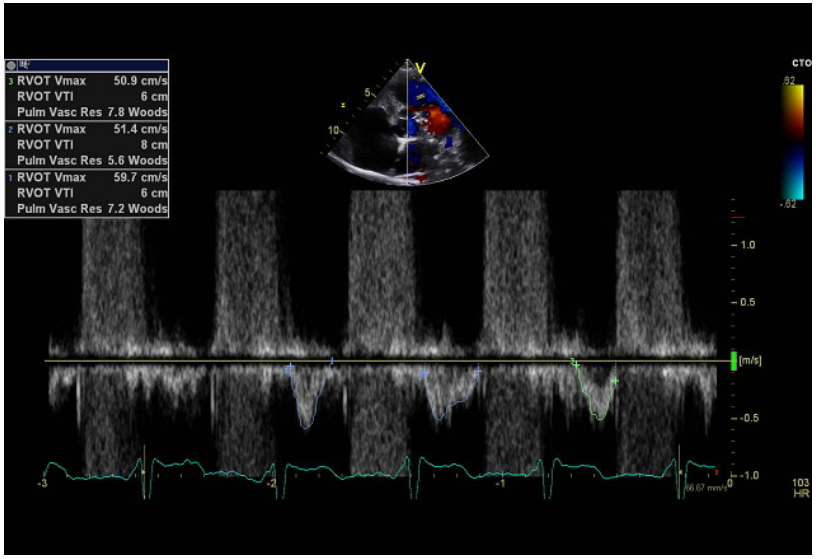


In press – June 2013

mPAP, PAPd







mPAP = 2/3 Diastolic + 1/3 Systolic

4 X peak PR^2 + RAP

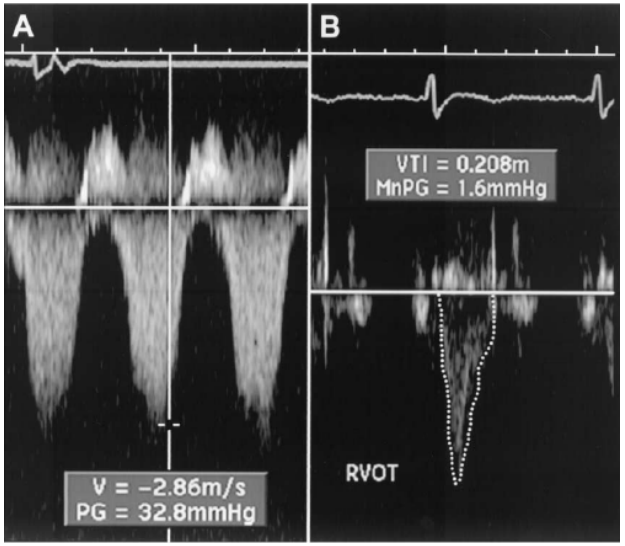
79=.45 X AT

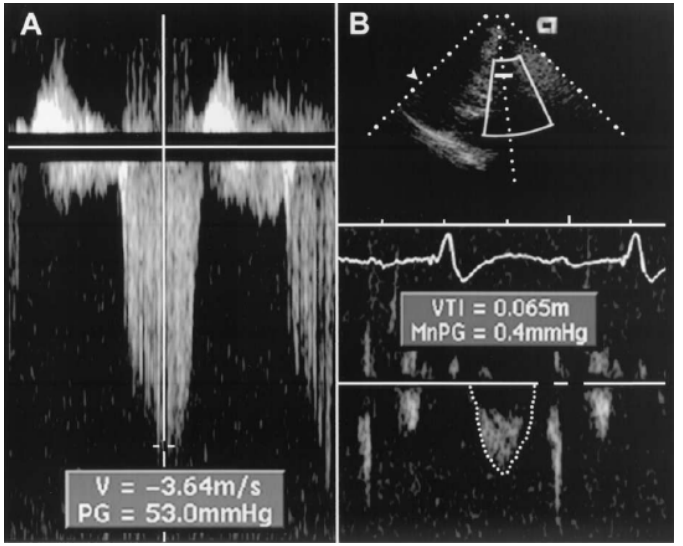
MG VTI + RAP

dPAP = 4 X end PR^2 + RAP

Pulmonary Vascular Resistance

R= V/I or PVR = P/Q

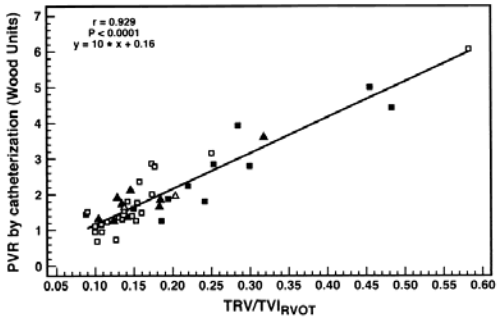




PVR = 10 X 2.86/20.8 + .16 = 1.53 WU
cath = 1.4 WU

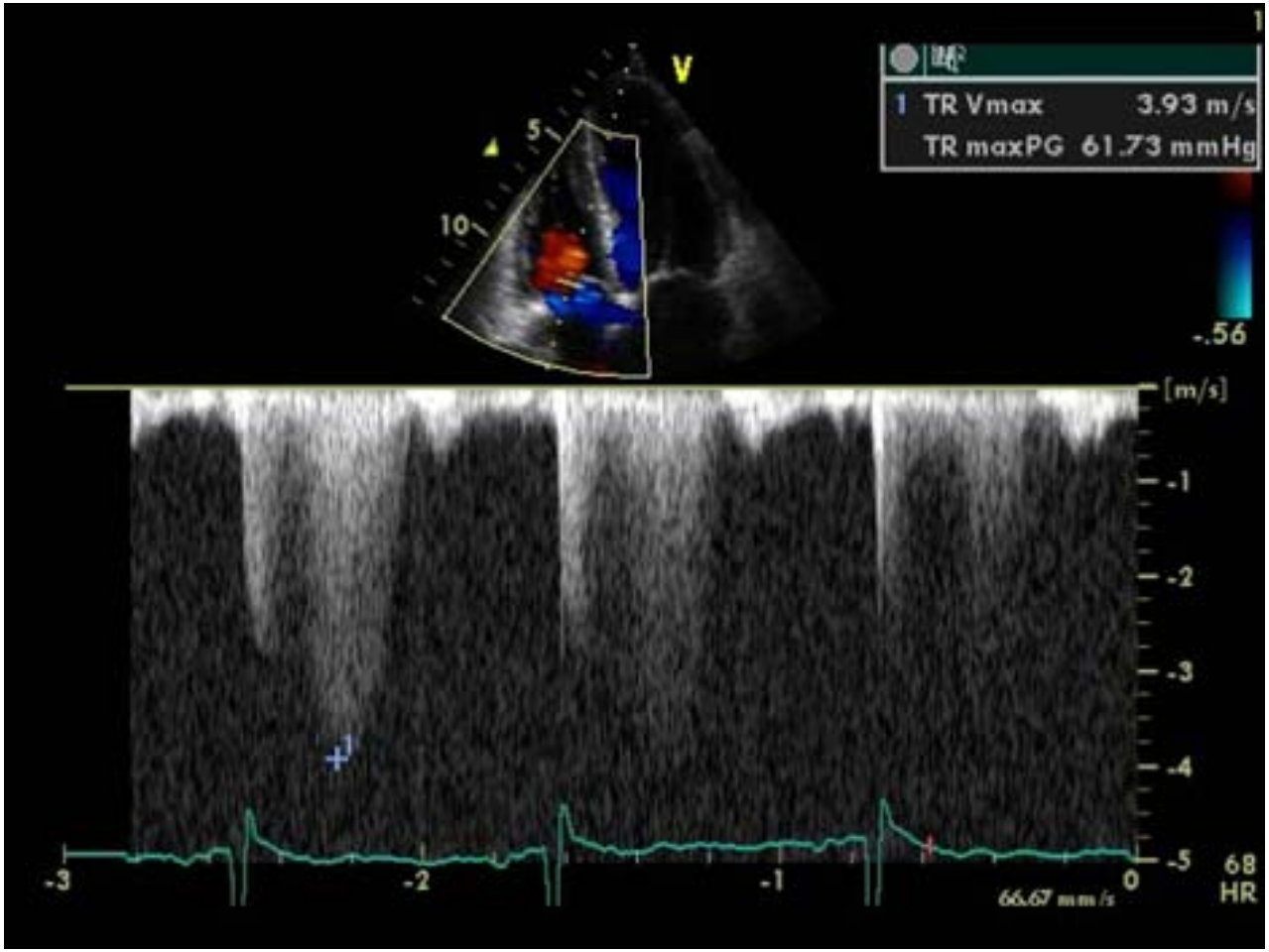
PVR = 10 X 3.64/6.5 + 0.16 = 5.76
cath = 6 WU

$$PVR\,(WU) = 10 \times TRV/TVI_{RVOT}$$

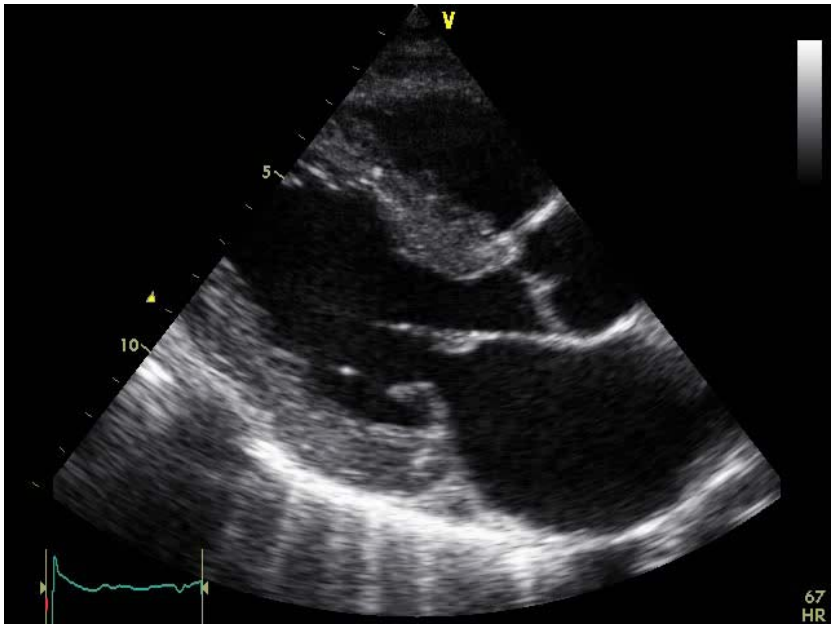


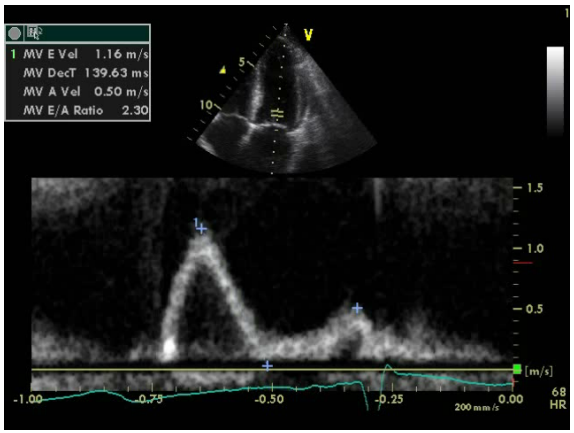
Abbas…Lester JACC 2003

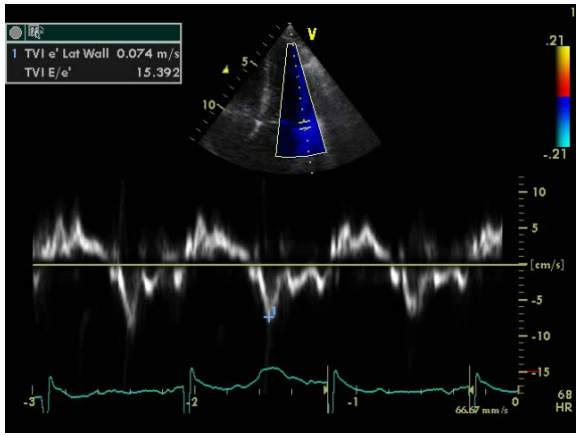
Yes, there's PH…but why?

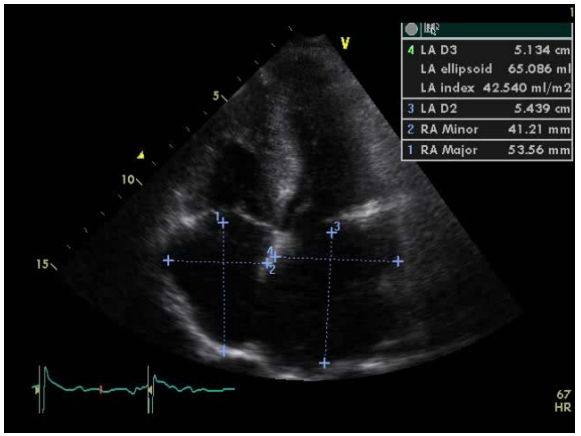


Etiology – Pre- vs. Post-Capillary





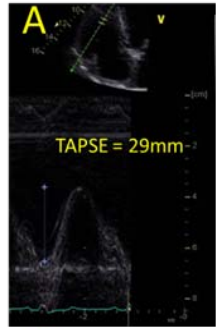


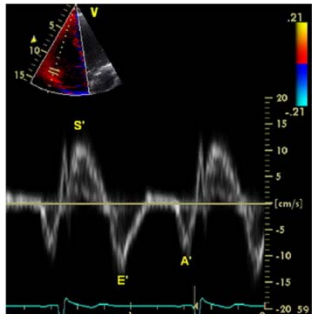


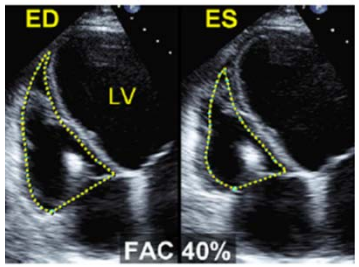
Prognosis

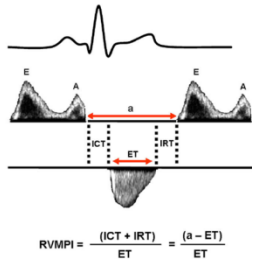
Function

- Prognosis MOST strongly related to Right Ventricular Function
- Definition of RV Failure:
  - Cath – Decreased C.O. or RAP > 10 mmHg
  - Imaging – Multiple Parameters
    - RVEF < 35%
    - TAPSE < 16 mm (18 mm PAH literature)
    - %FAC
    - MPI > 0.45
    - S’ < 10 cm/s
    - Strain < -15%
    - Isovolumic Contraction Velocity ≤ 9 cm/s....

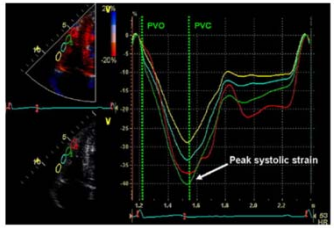




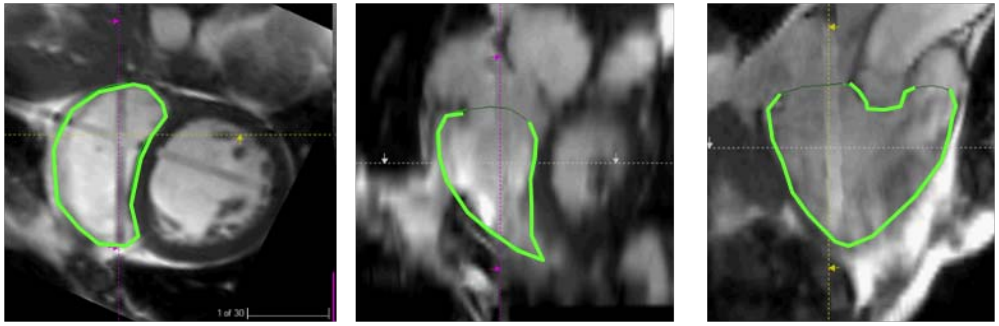


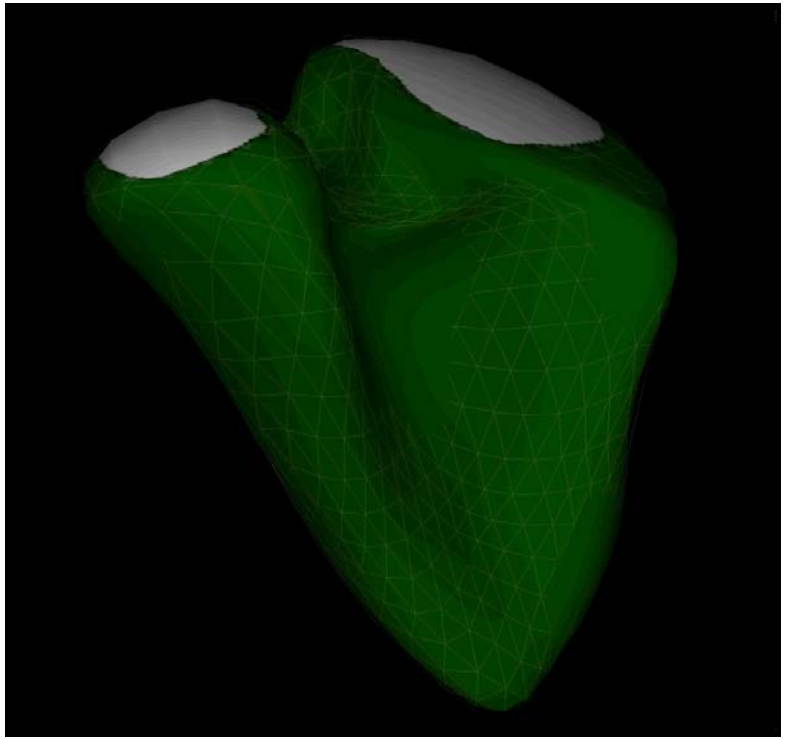


$$RVMPI = \frac{(ICT + IRT)}{ET} = \frac{(a - ET)}{ET}$$



3D Echo RV Volumes and RVEF





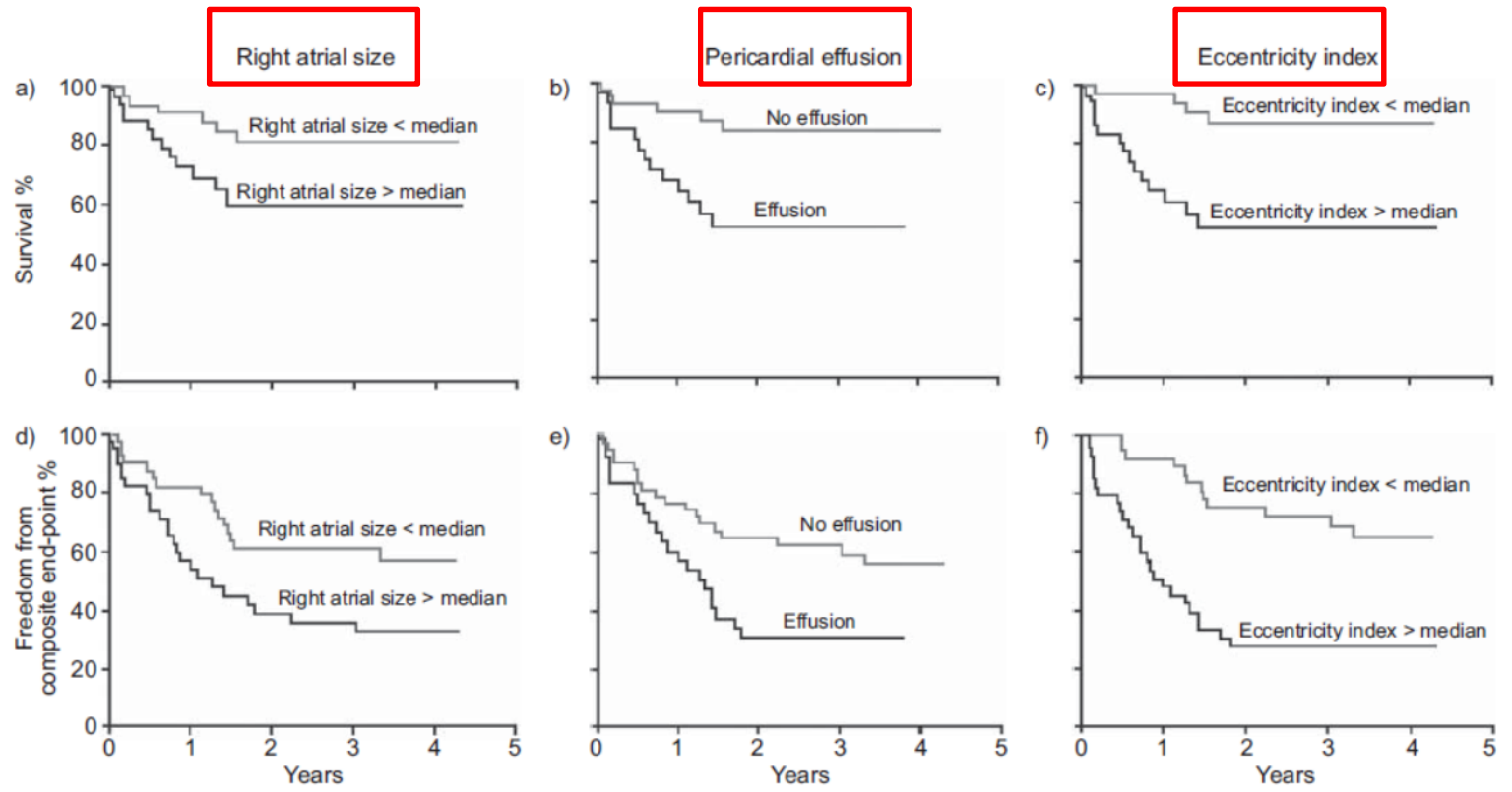


FIGURE 1. Kaplan–Meier survival curves for echocardiographic predictors of outcomes. Reproduced from [25] with permission from the publisher.

Anton Vonk-Noordegraaf
AJC 2012

Canadian Journal of Cardiology xx (2012) xxx

Clinical Research

Incidence and Significance of Pericardial Effusion in Patients With Pulmonary Arterial Hypertension

Avi Shimony, MD, Benjamin D. Fox, MD, David Langleben, MD, and Lawrence G. Rudski, MD

Center for Pulmonary Vascular Disease and Division of Cardiology, Jewish General Hospital, Lady Davis Institute for Medical Research, McGill University, Montreal, Québec, Canada

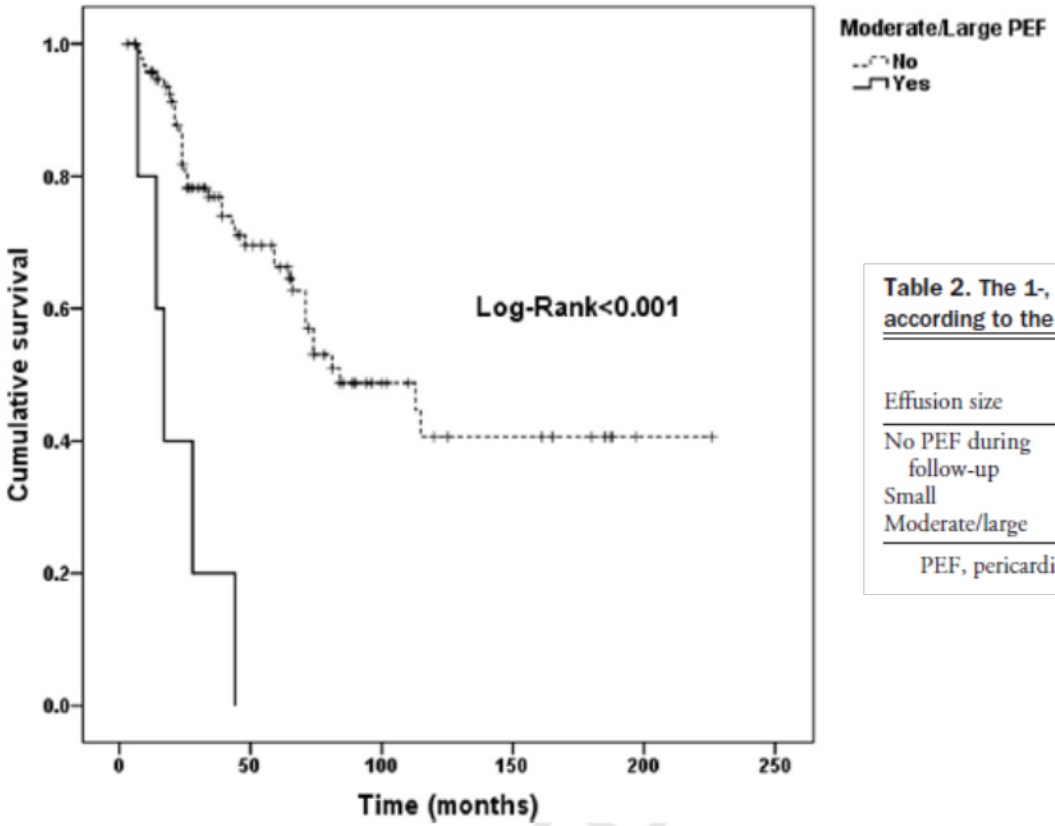


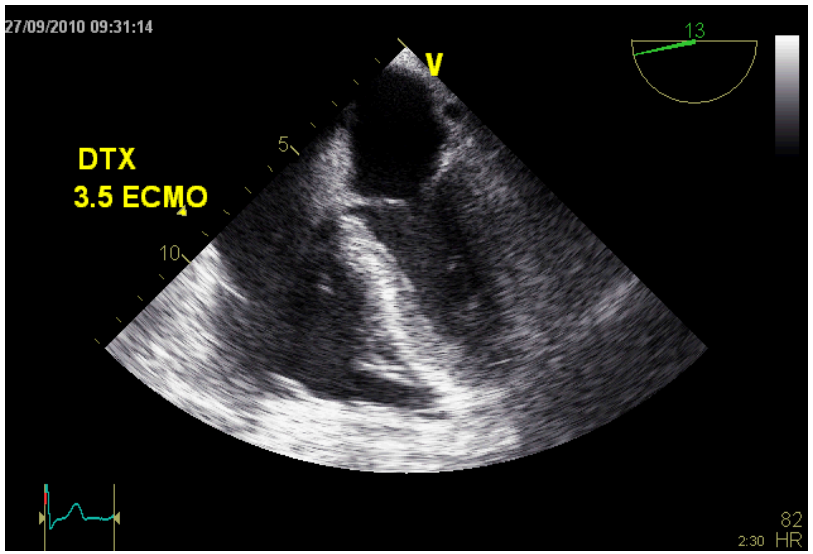
Figure 1. Kaplan-Meier curves survival analysis from time of first screening visit at the clinic. Comparison of pulmonary arterial hypertension patients with at least moderate-sized pericardial effusion at its first appearance with those with small or absent pericardial effusion. PEF, pericardial effusion.

Table 2. The 1-, 3-, and 5-year survival rates of patients stratified according to the size of PEF at its first appearance

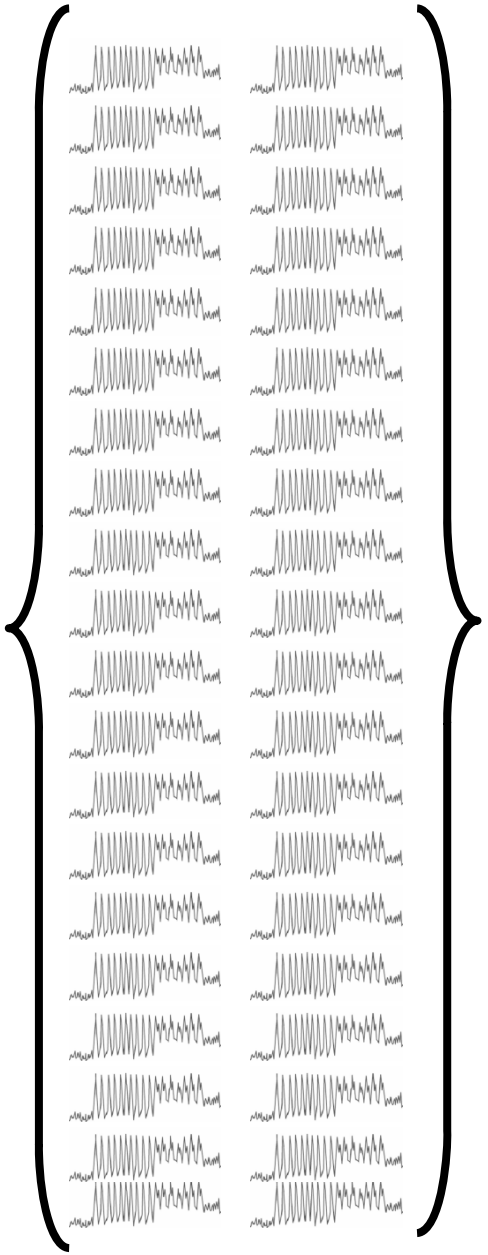
	Survival rates			
Effusion size	Mean ± SD, mo	1 y (%)	3 y (%)	5 y (%)
No PEF during follow-up	123.6 ± 11.8	94.4	79.7	63.8
Small	118.3 ± 17.5	97.5	73.2	69.7
Moderate/large	22.0 ± 6.5	80.0	20.0	0.0

PEF, pericardial effusion; SD, standard deviation.

What's an Echo Worth?

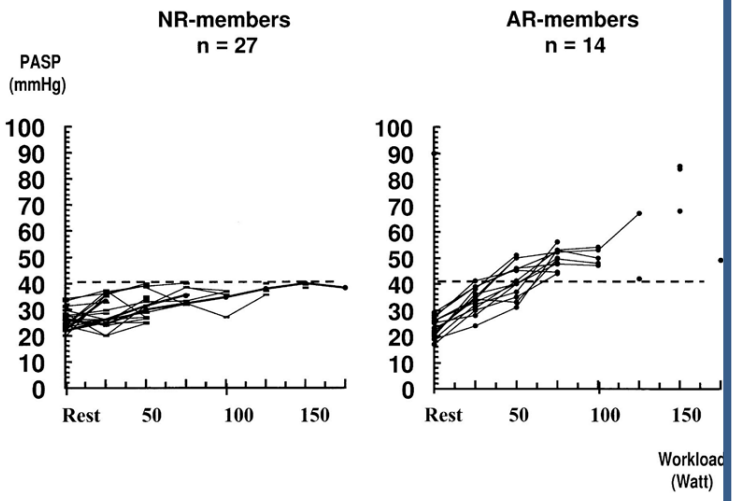


= 50 X



Mechanistic Insights

Mechanistic Insights
Interplay between genetics and stressor



Asymptomatic 2q31-32 haplotype carriers in 2 PPH families (BMPR2)

Grunig et al. Circ 2000

- Exercise 2.76+/- .3 = 3.06 = 42.4
- Hypoxia 2.68 +/- .4=3.08 = 42.9
- 90% Quantile = 3.08m/s

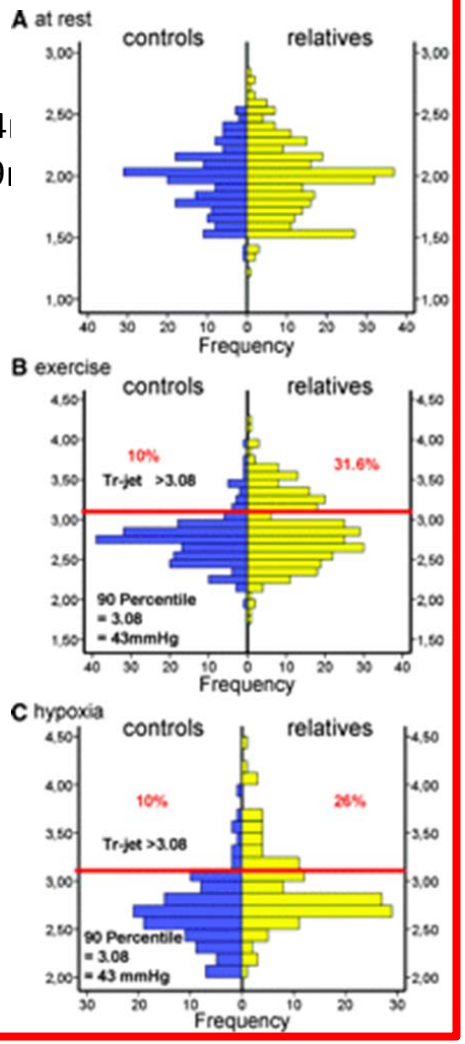
- How often exceed 90%?
- Controls – obviously 10%
- Family Members:

  exercise 31%

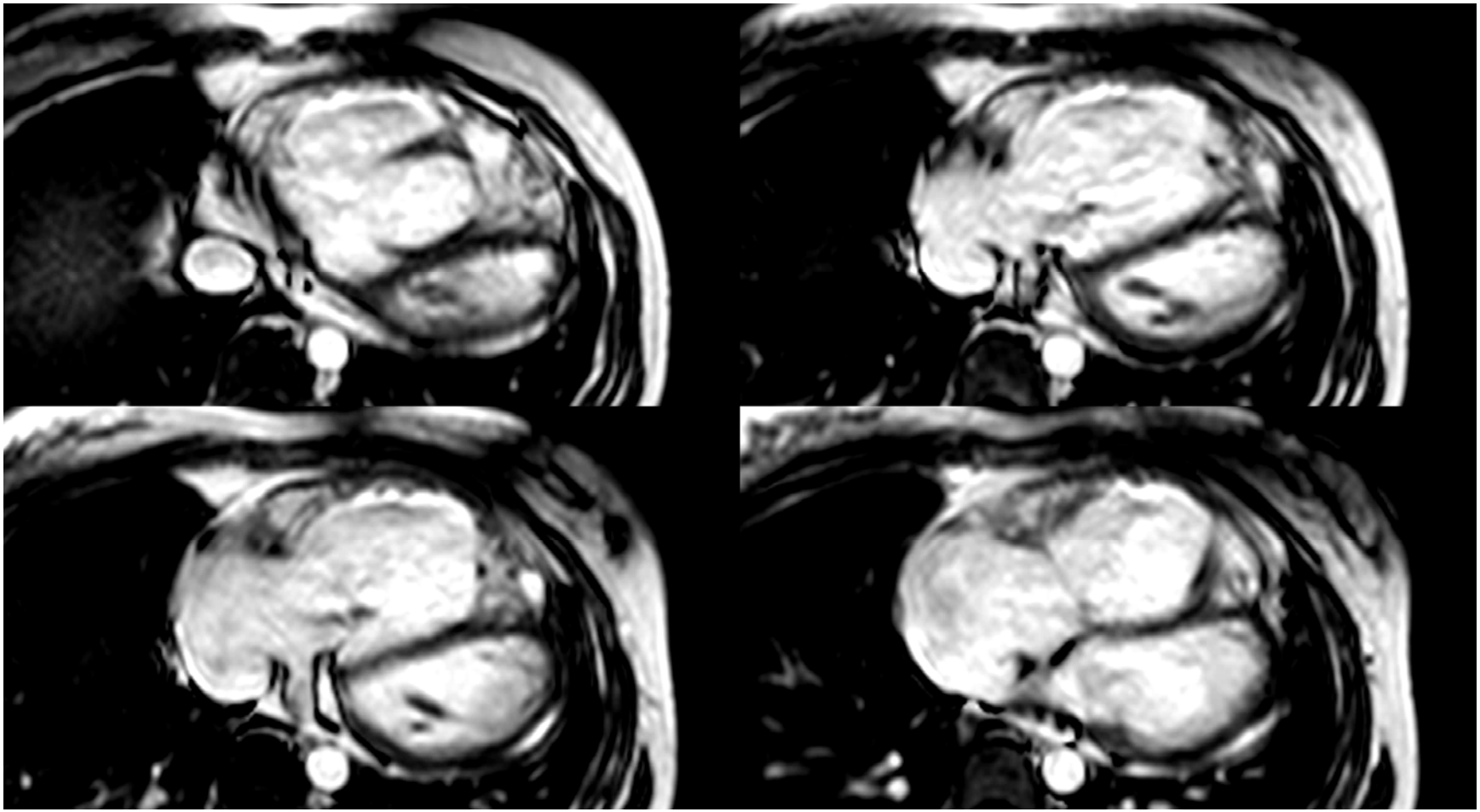
  Hypoxia 26%
- BMPR2 abnormal

50% had abnormal response to ex.

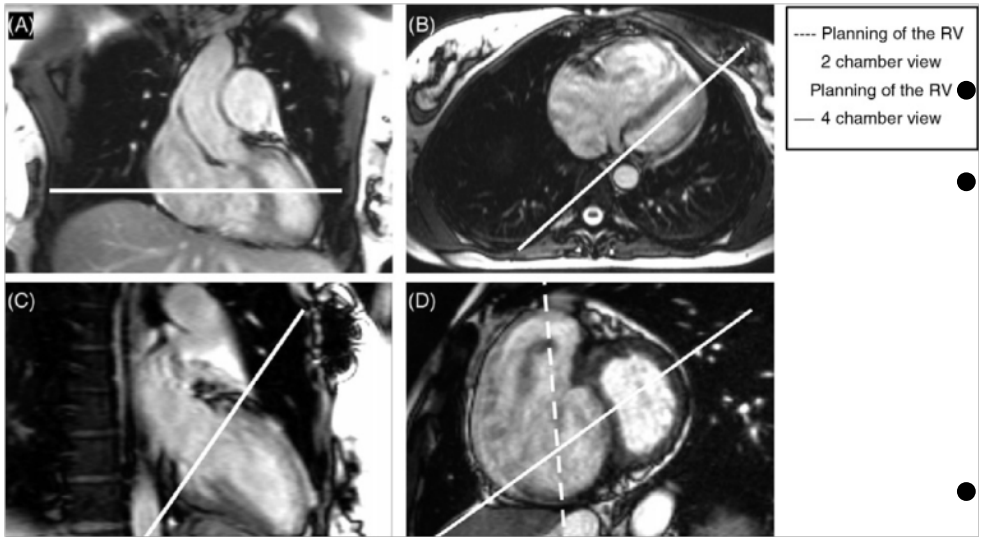
Grunig et al. Circ 2009



MRI – the next frontier

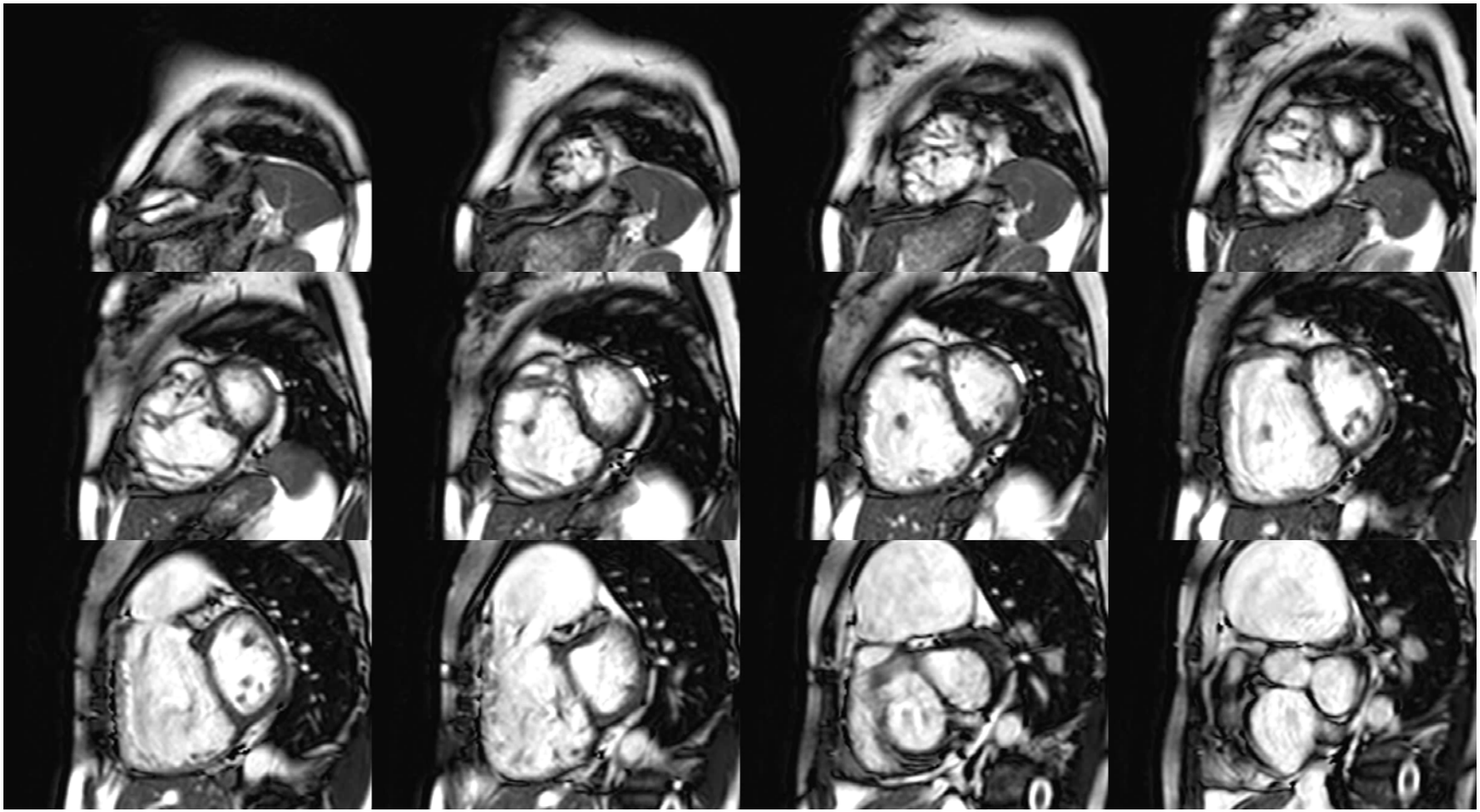


MRI – Size Matters



Vonk-Noordegraaf A, *The American Journal of Cardiology Vol 110 (6S), 2012*

- RV Volumes
  - Short axis stacks – bright blood technique
- RVEF
- RV Mass
  - Myocardial volume X 1.05 g/cc
  - > 59 g/m2 = bad
- RV area : LV area
- Septal configuration
  - Cine MRI



Utility of MRI in PAH - Function

- “Function”
- Stroke Volume & C.O.
  - Velocity encoded imaging > REVDV-RDESV
- Strain
- Longitudinal and Transverse

- PA Dimensions
- PA blood flow

- Experimental
  - PA distensibility
  - PBF – Pulmonary blood flow
  - Gd MRA

Prognostic Markers - MRI

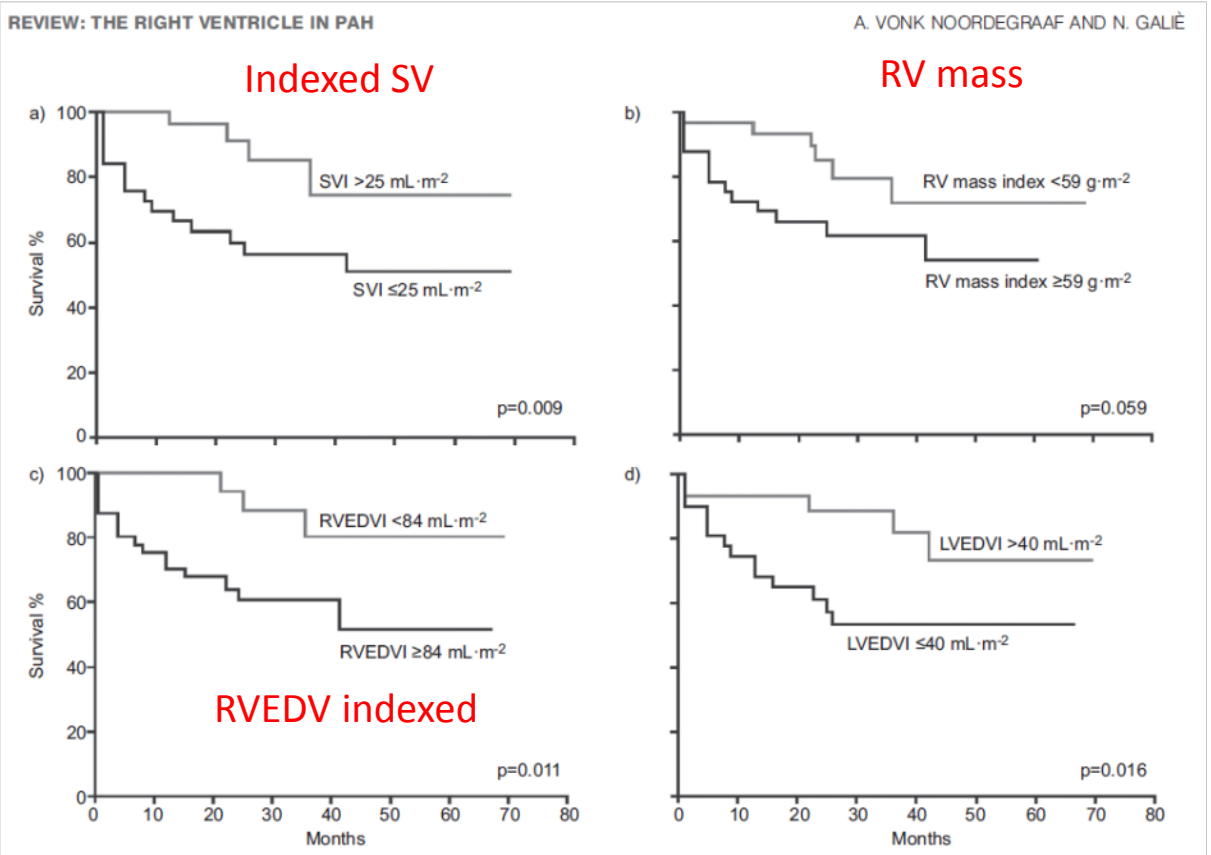


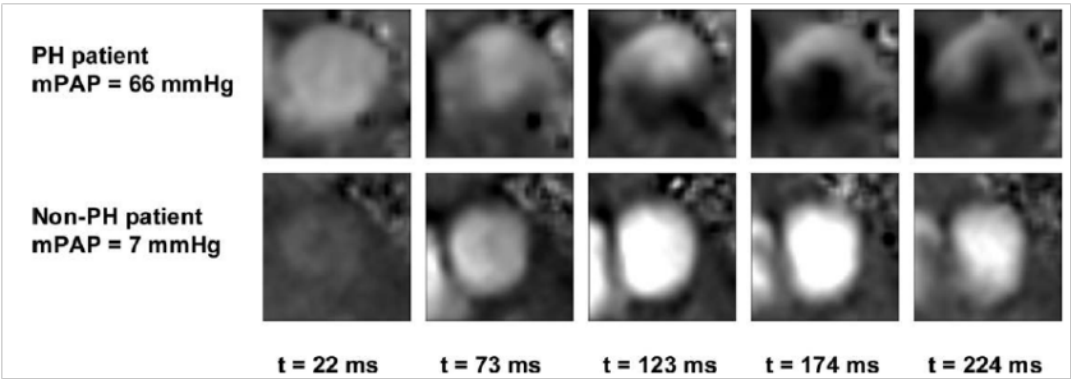
FIGURE 2. Kaplan–Meier survival curves for baseline cardiac magnetic resonance imaging variables according to the median value in patients with pulmonary hypertension. SVI: stroke volume index; RV: right ventricular; RVEDVI: RV end-diastolic volume index; LVEDVI: left ventricular end-diastolic volume index. Reproduced from [48] with permission from the publisher.

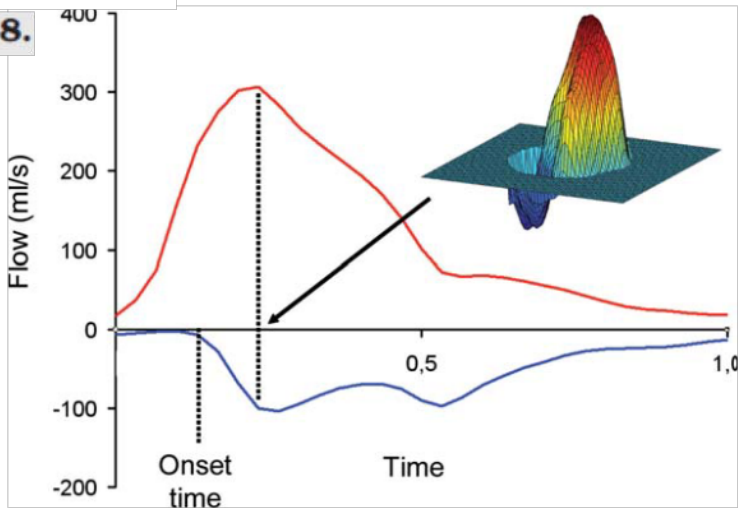
Anton Vonk-Noordegraaf
AJC 2012

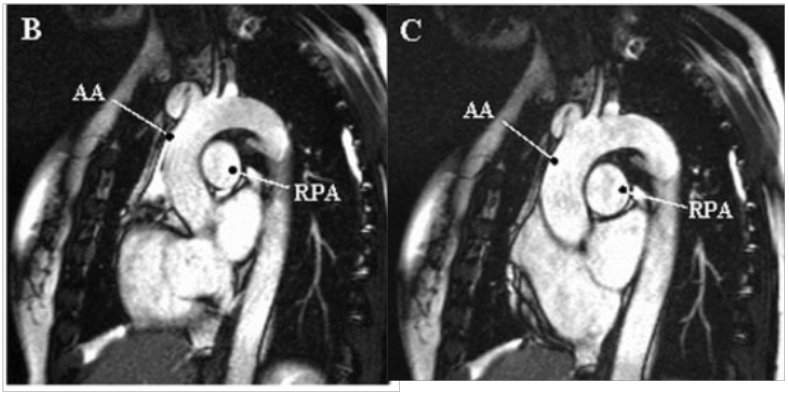
Early Onset of Retrograde Flow in the Main Pulmonary Artery is a Characteristic of Pulmonary Arterial Hypertension

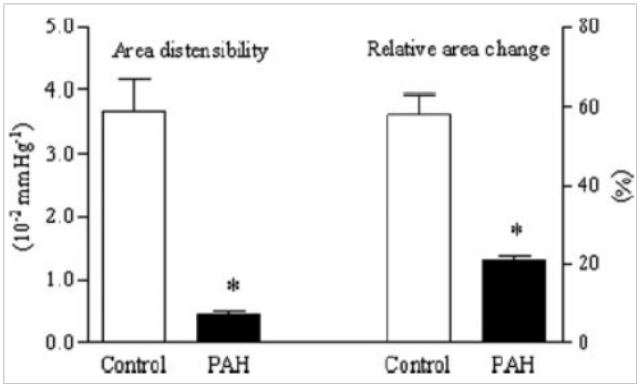
Frank Helderman, MS,[1,2] Gert-Jan Mauritz, MS,[2] Kirsten E. Andringa, BS,[1] Anton Vonk-Noordegraaf, MD, PhD,[2] and J. Tim Marcus, PhD[1*]

J. Magn. Reson. Imaging 2011;33:1362–1368.









C. Tji-Joong Gan et al. CHEST 2007; 132:1906–1912

Ditto by echo – and easier

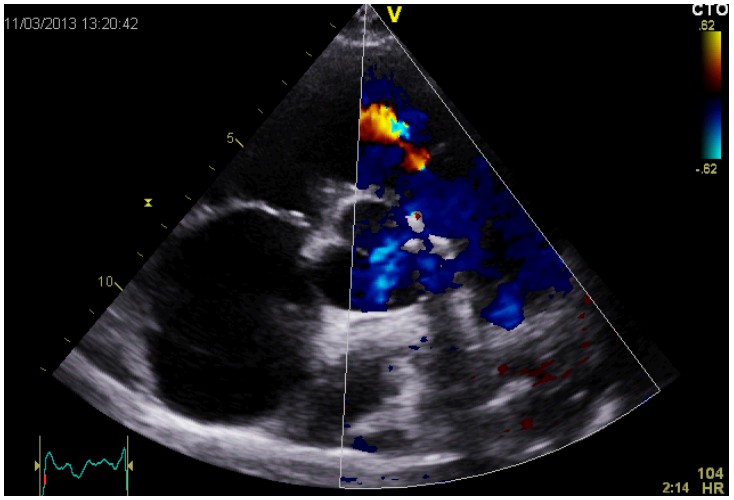


Fig. 1A

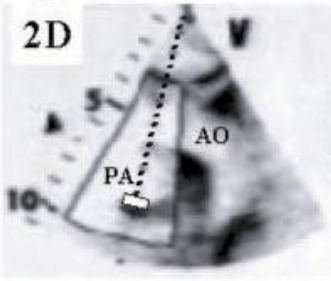
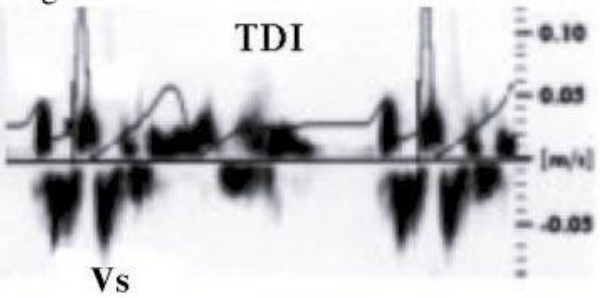
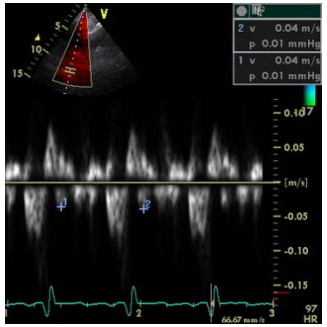


Fig. 1B

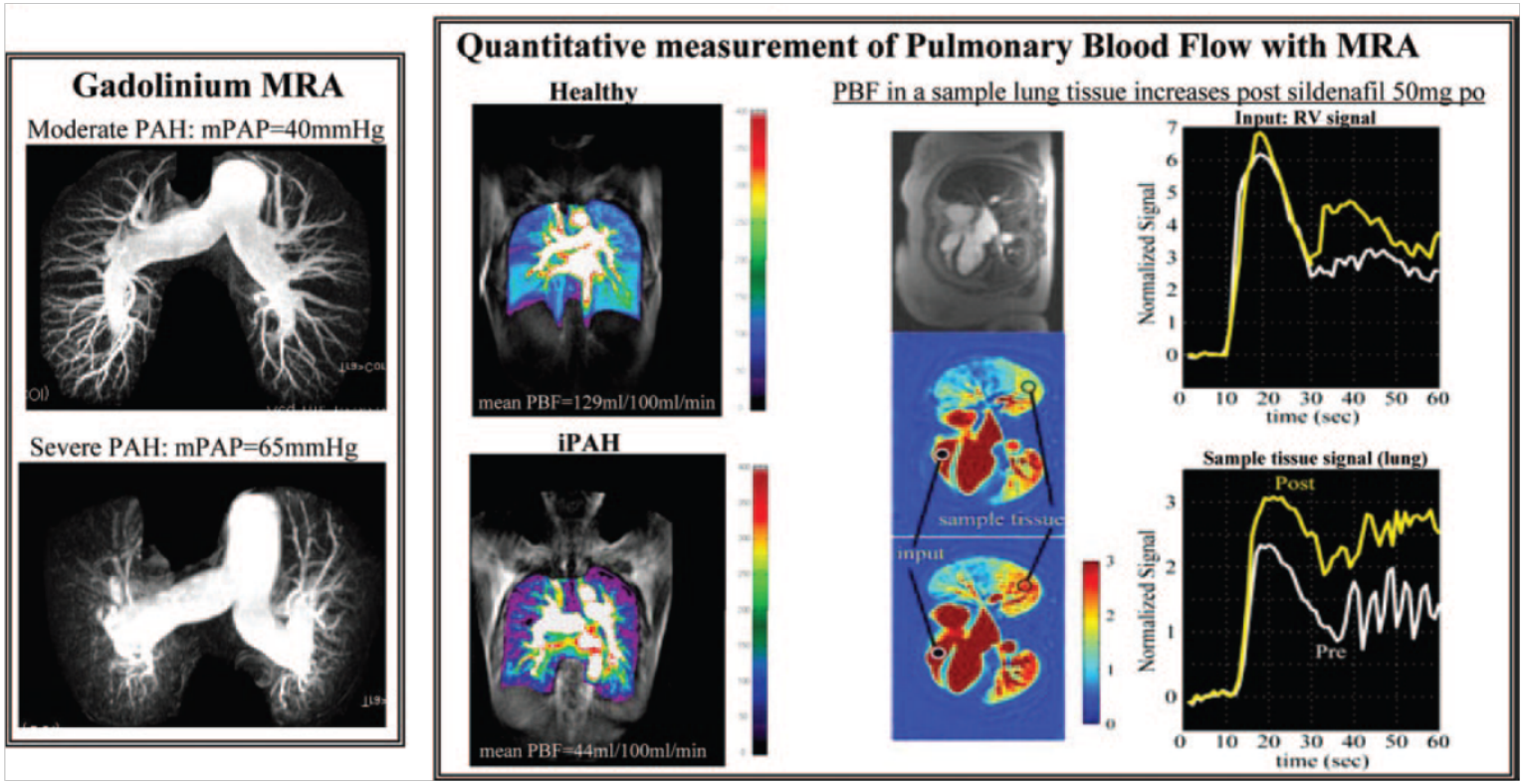




Vs max velocity was 7.1 ± 1.5 cm/s in normals vs. 4.5 ± 0.7 cm/s in PAH ($p<0.001$).

Politis et al. ASE 2004

The Flow Knows



- Microvessel loss early in the disease or proliferative obliterative remodeling in more proximal vessels later on
- Result is loss of blood flow and tissue perfusion
- Need method to quantify and measure response to therapy aimed to increase tissue perfusion

MRI

Revolution or Evolution?

It Depends...זה תלוי

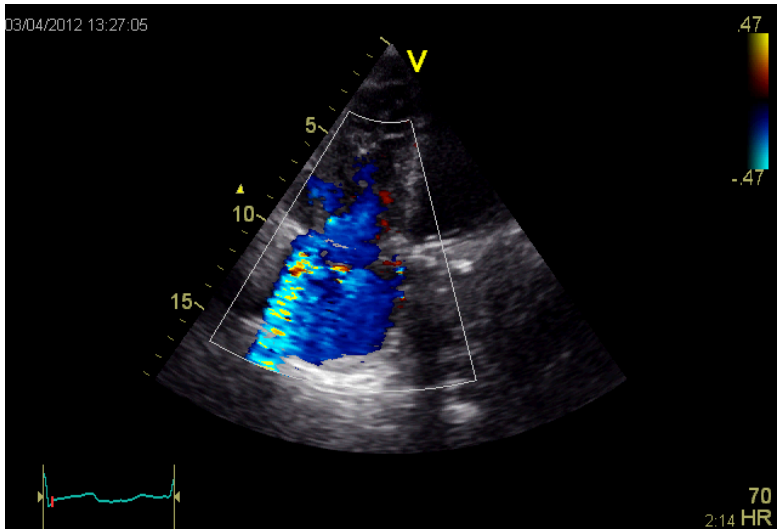
Comparison of Cardiac Magnetic Resonance Imaging (CMRI), Echocardiography, and Right Heart Catheterization (RHC) for the Characterization of Different Parameters

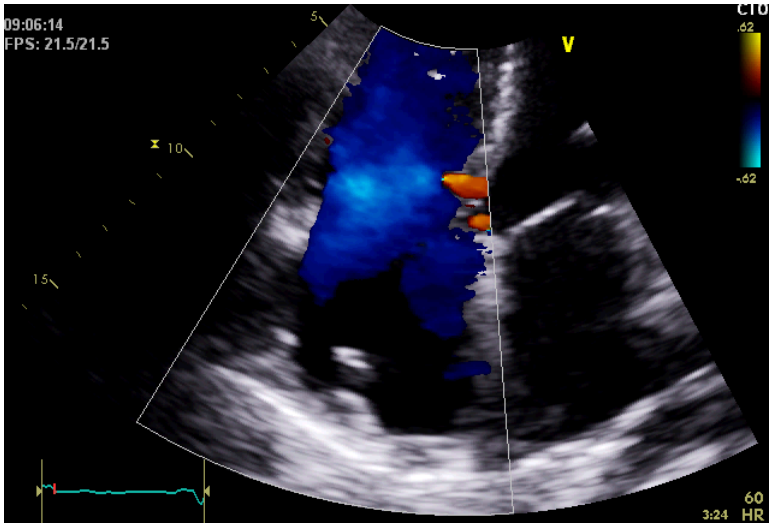
Parameter	CMRI	Echocardiography	RHC
RV assessment			
Volumes	+++	++	+
RVEF	+++	++	+
Strain	+++	++	−
Pressure	−/+	++	+++
SV	+++	+	+++
Mass	++	−/+	−
RV remodeling/septal curvature	+++	+	−
Tricuspid regurgitation	++	+++	+
Isovolumetric time	+++	?	−
RA assessment			
Structure	++	+	−
Pressure	−	−	+++
LV assessment			
Volumes	+++	++	+
LVEF	+++	++	+
Pulmonary artery			
Dimensions	+++	+	+
Distensibility	+++	+	−/+
Hemodynamics	−/+	+	+++
Quantitative lung flow	+++	−	−

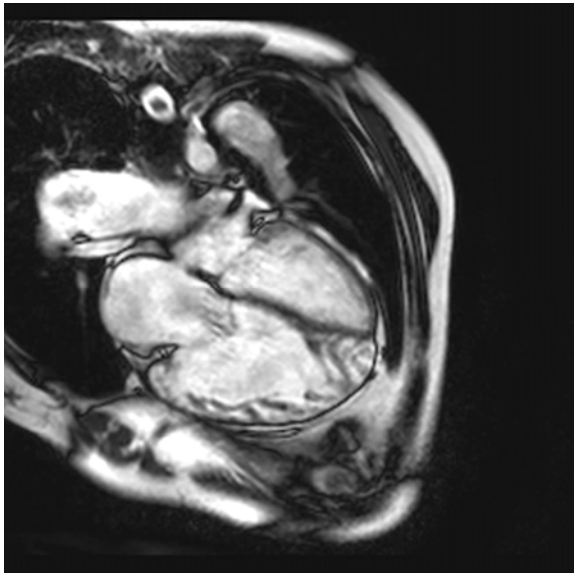
LV = left ventricle/left ventricular; LVEF = left ventricular ejection fraction; RA = right atrium/right atrial; RV = right ventricle/right ventricular; RVEF = RV ejection fraction; SV = stroke volume; – = not useful; + = may be useful; ++ = useful; +++ = extremely useful.

Anton Vonk-Noordegraaf
AJC 2012

TR


03/04/2012 13:27:05
.47
-.47
V
5
10
15
70
2:14 HR


09:06:14
FPS: 21.5/21.5
V
10
15
60
3:24 HR

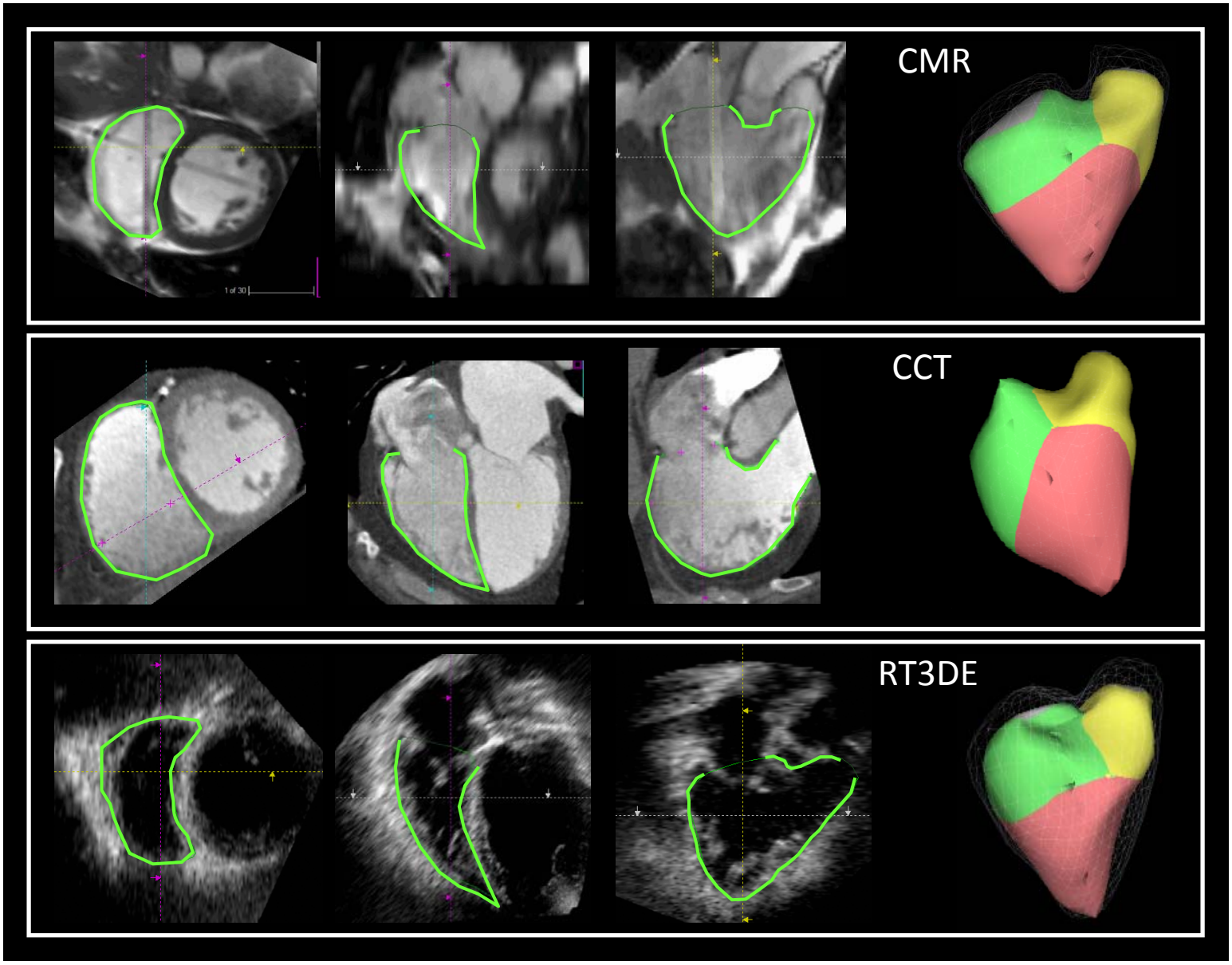


MRI

ECHO

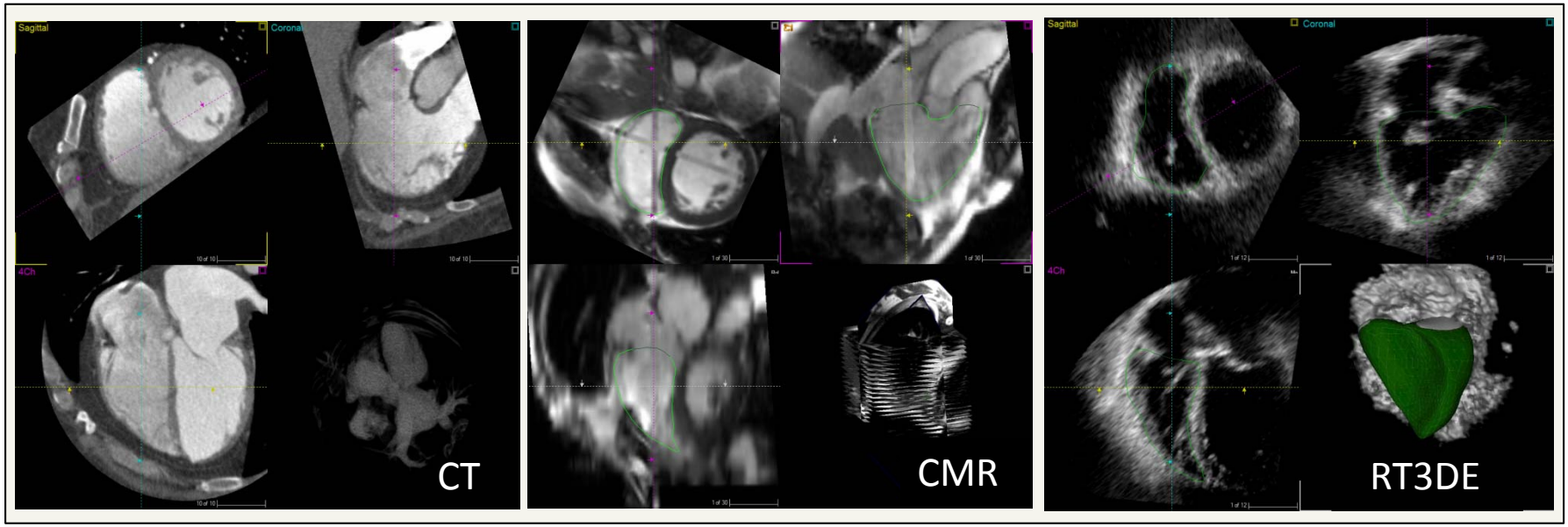
CT – not much in ***PAH***

- Can use to diagnose acute and CTEPH – CT Angiogram
- Diagnosis of pulmonary parenchymal disease
- RV volumes and RVEF



Sugeng et al., JACC imaging

Multi-Modality Comparison (CT-3DE-CMR)



	CCT RVA		RT3DE RVA	
	r	Bias ± LOA	r	Bias ± LOA
ESV	0.84	17 ± 68	0.92	-8 ± 42
EDV	0.85	11 ± 78	0.89	-23 ± 68
EF	0.84	- 5 ± 12	0.81	-3 ± 13

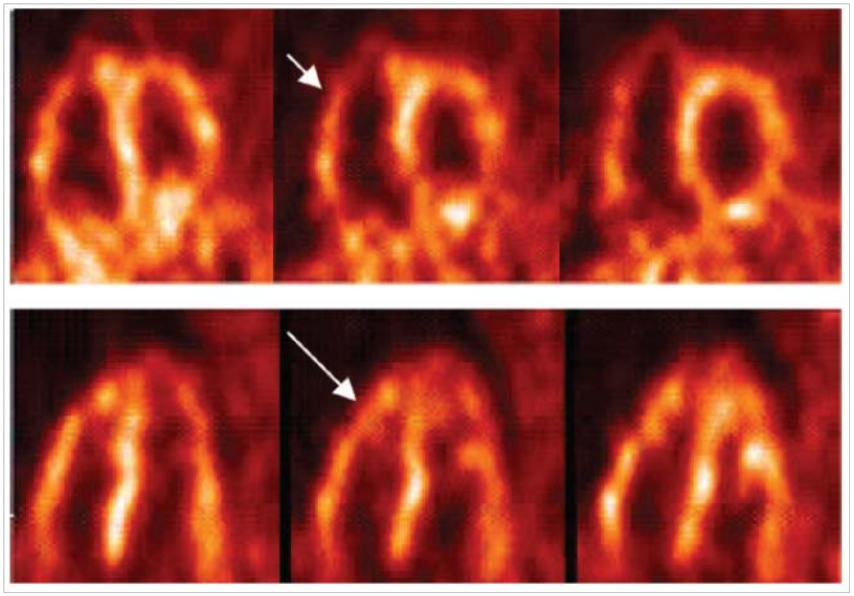
Sugeng et al., JACC imaging

Does PAH behave Like Cancer ?

PET Imaging May Provide a Novel Biomarker and Understanding of Right Ventricular Dysfunction in Patients With Idiopathic Pulmonary Arterial Hypertension

Sabahat Bokhari, MD; Amresh Raina, MD; Erika Berman Rosenweig, MD; P. Christian Schulze, MD; Justin Bokhari; Andrew J. Einstein, MD; Robyn J. Barst, MD; Lynne L. Johnson, MD

(*Circ Cardiovasc Imaging*. 2011;4:641-647.)



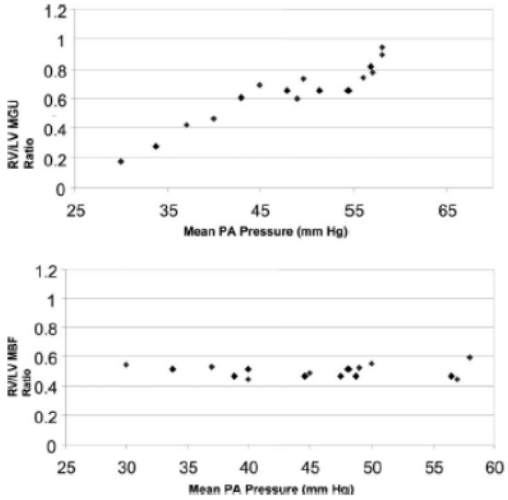
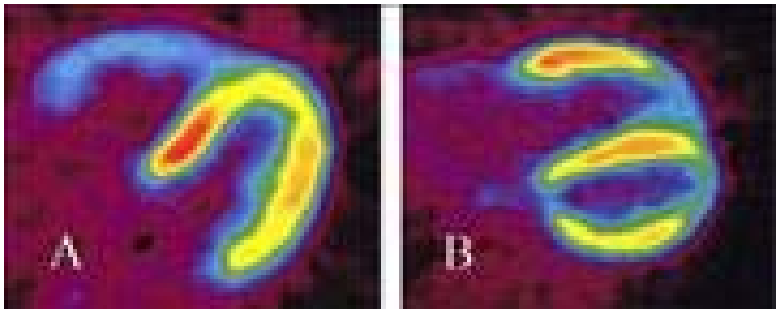


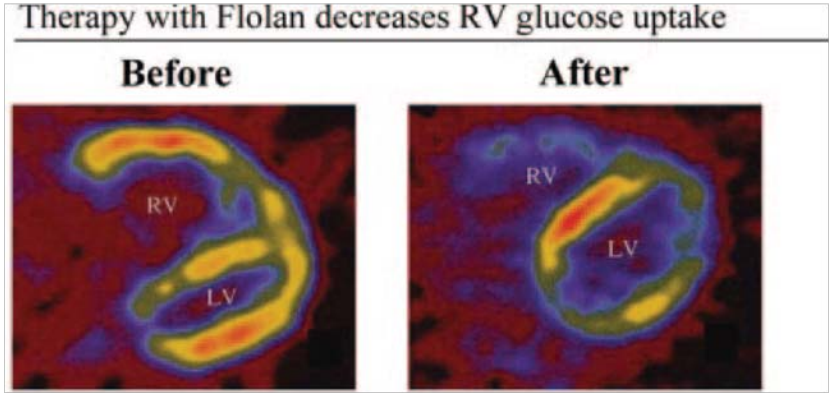
Figure 3. Relationship of RV/LV MGU and MBF to mean PA pressure. LV indicates left ventricle; MBF, myocardial blood flow; MGU, myocardial glucose utilization; PA, pulmonary artery; RV, right ventricle.

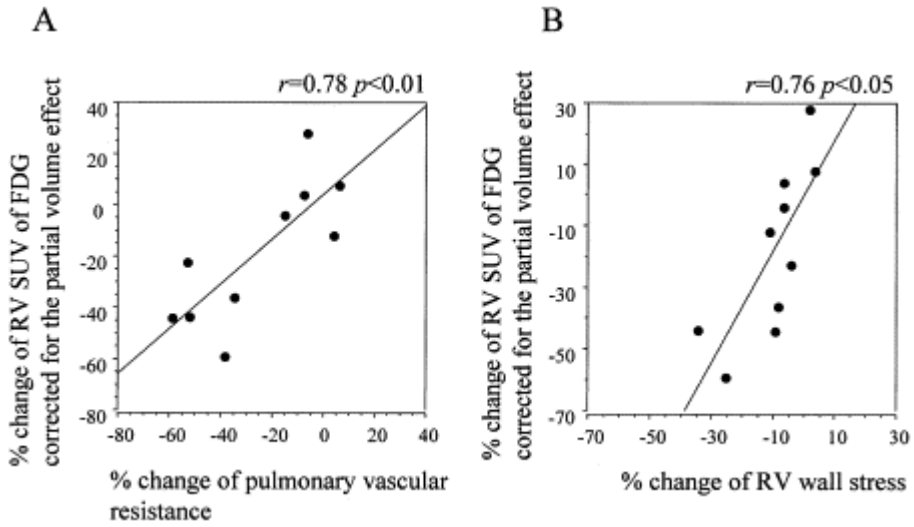
- **Increased glucose uptake is usually associated with a glycolytic phenotype.**
- **A switch from the mitochondria-based glucose oxidation to the cytoplasm-based glycolysis, even in the absence of hypoxia, is recognized in many disease states characterized by increased proliferation and suppressed apoptosis. (Warburg effect)**
- **This is well described in cancer and has been suggested more recently in PAH vascular remodeling.**

PAH is a Cancer – that can be treated

Normal RV PAH RV







Oikawa et al. J Am Coll Cardiol. 2005;45:1849 –1855.

Early Detection

- Of critical importance – especially in high risk populations
- Detect PRIOR to symptom development and prior to RV dysfunction
- EARLY trial- Bosentan – WHO class 2
  - Endpoints – mostly PVR, 6MWT, but also clinical worsening
  - Tells us that early detection may provide benefit
  - **But how to detect early ???**

Pulmobind

- Traditional **Lung Scan** - 99mTC Macroaggregate to detect larger physical obstruction
- is larger than small pulmonary vessels, limiting its sensitivity to detect small vascular defects

- **DFH-12 (PulmoBind) is a peptide derived from human adrenomedullin (hAMI-52)**
- **PulmoBind is labeled with 99mTc**
- **90% specific binding to pulmonary vasculature**
- **PH results in *early vessel pruning***
- **Phase 1 trial – Montreal Heart Institute – safety and dose finding**
- **Ultimate goal – non-invasive early diagnosis of PH**

PH sniffing dog

- **UN CHIEN CONTRE LE CANCER**
- Grâce à son flair exceptionnel, le berger malinois Aspirant arrive à détecter la maladie.

Thanks for Inviting Me…

LVH

Diastolic Dysfunction

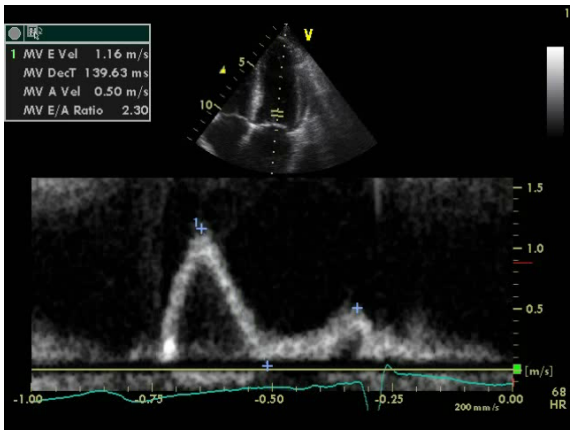
(E:E’)

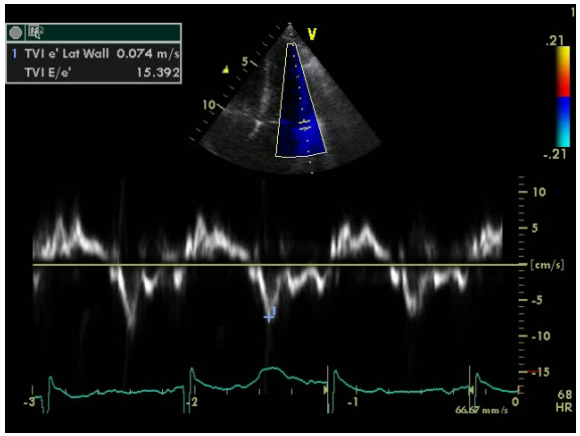
Systolic Dysfunction

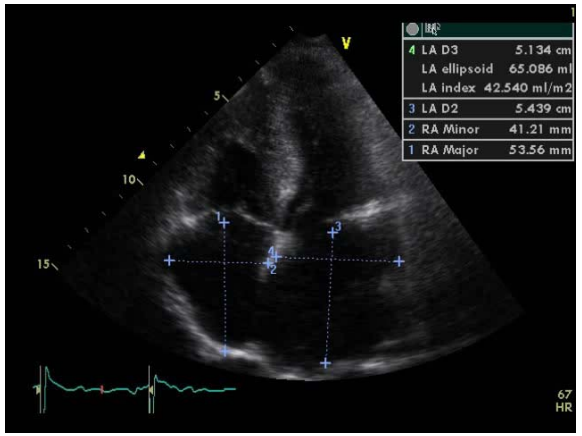
Dilated LA

(LA volume)

Valvular Heart Disease







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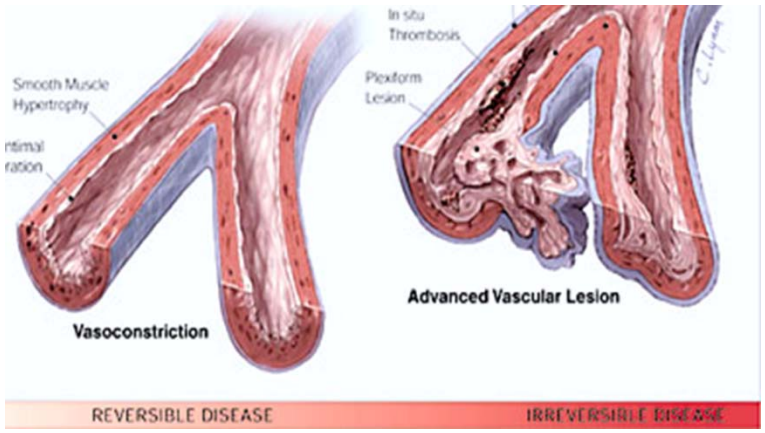
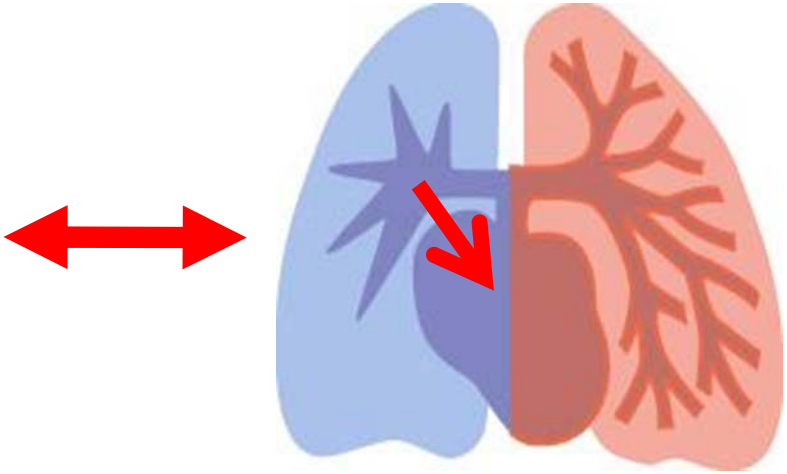
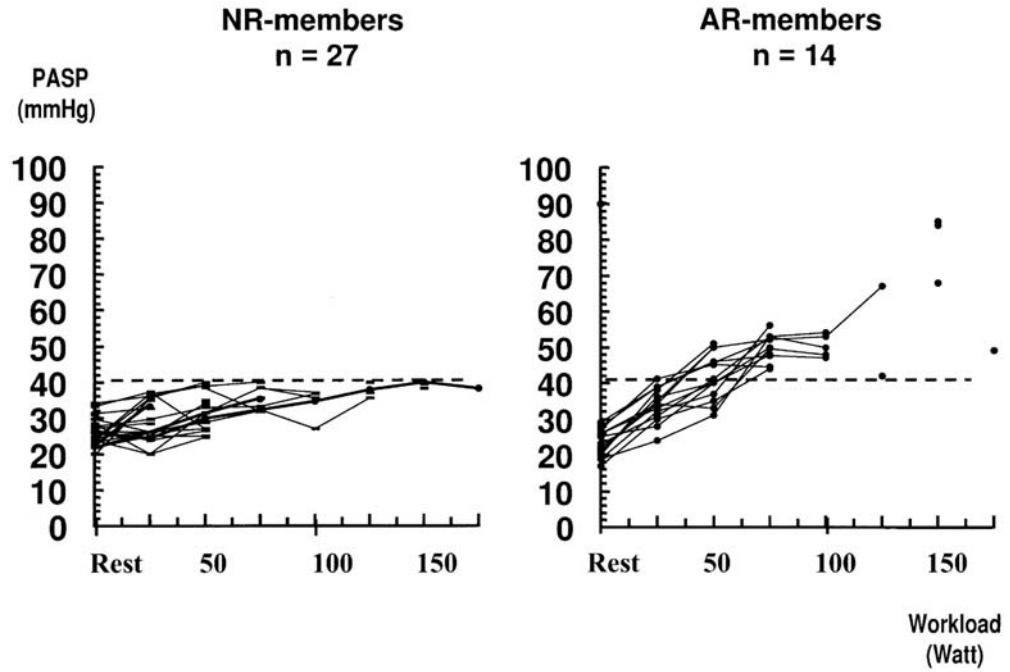

In situ
Thrombosis
Plexiform
Lesion
Smooth Muscle
Hypertrophy
ntimal
ration
Advanced Vascular Lesion
Vasoconstriction
REVERSIBLE DISEASE



Role of Stress Echo in PAH



Asymptomatic 2q31-32 haplotype carriers in 2 PPH families (BMPR2)

Grunig et al. Circ 2000

Grunig et al. Circ 2000