Clinical implication of exercise pulmonary hypertension: when should we measure it?

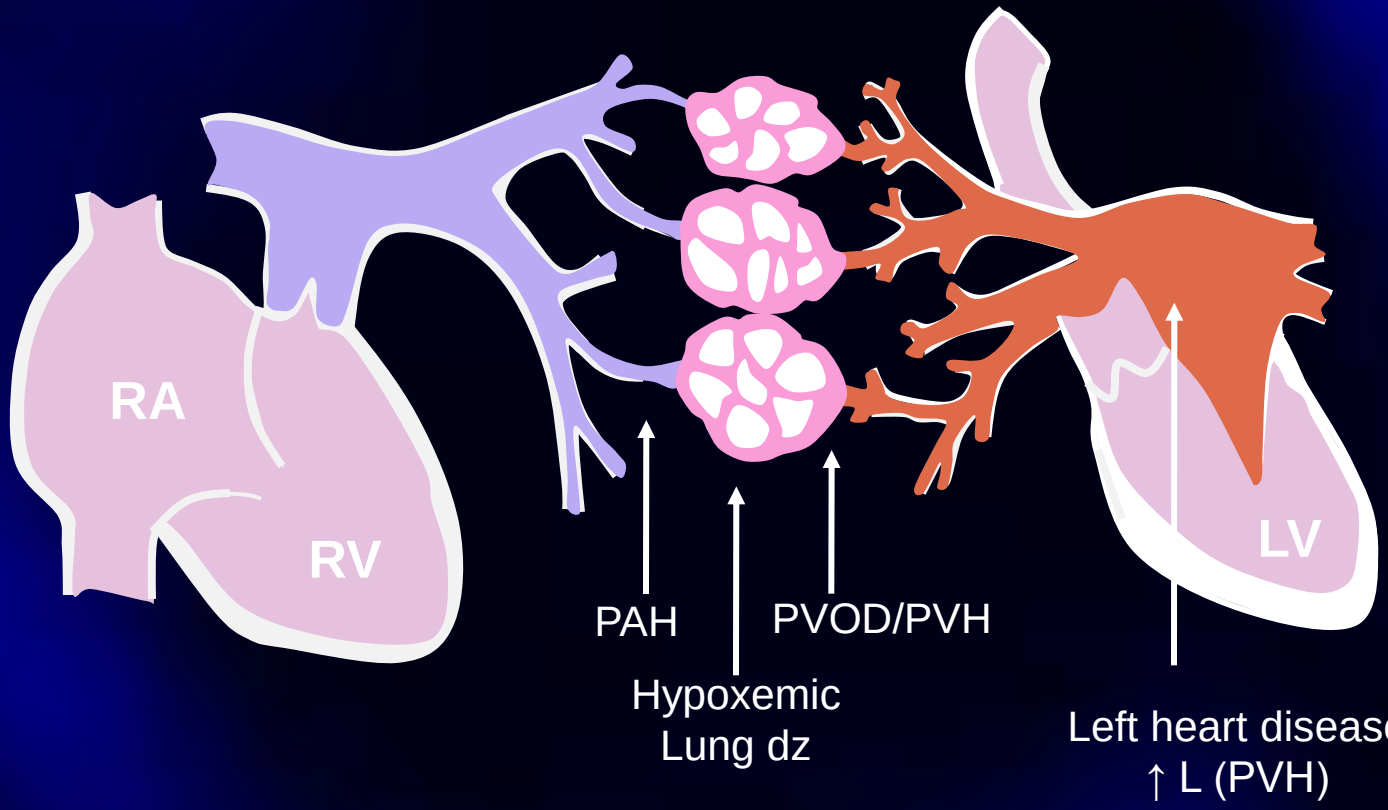
Jang-Young, Kim

Wonju College of Medicine, Yonsei Univ.

Exercise pulmonary hypertension (EPH)

- Introduction of pulmonary hypertension
- Definition of EPH and How we measure it ?
- Clinical implications of EPH
- When should we measure it?

Pulmonary Hypertension: Multiple origin



PVOD: pulmonary venoocclusive disease, PAH: pulmonary artery hypertension, PVH: pulmonary venous hypertension

Physiology of pulmonary hypertension (PH)

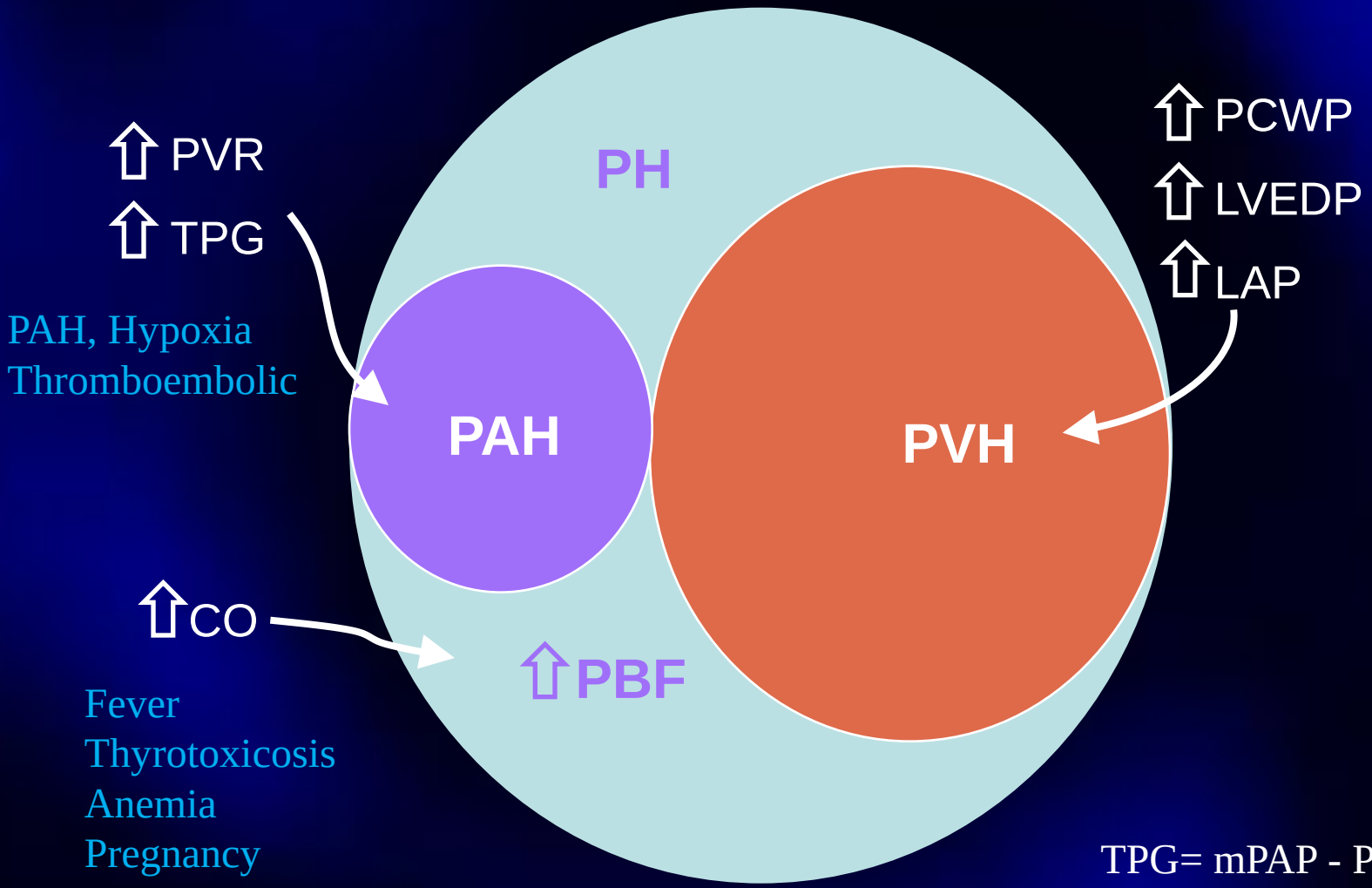
PH = PCWP + PVR x CO

Elevated PH may be due to

- Elevated PVR (resistance dependent)
- Increased CO (flow dependent)
- Increased PCWP

PCWP: pulmonary capillary wedge pressure, PVR: pulmonary vascular resistance, CO : cardiac output

Various haemodynamics in PH



CTEPH: Chronic thromboembolic PH, PAH: pulmonary artery hypertension, PVH: pulmonary venous hypertension
PCWP: pulmonary capillary wedge pressure, PVR: pulmonary vascular resistance, CO : cardiac output

Exercise pulmonary hypertension (EPH)

- Introduction of pulmonary hypertension

- Definition of PH and How we measure it ?

- Clinical implications of EPH

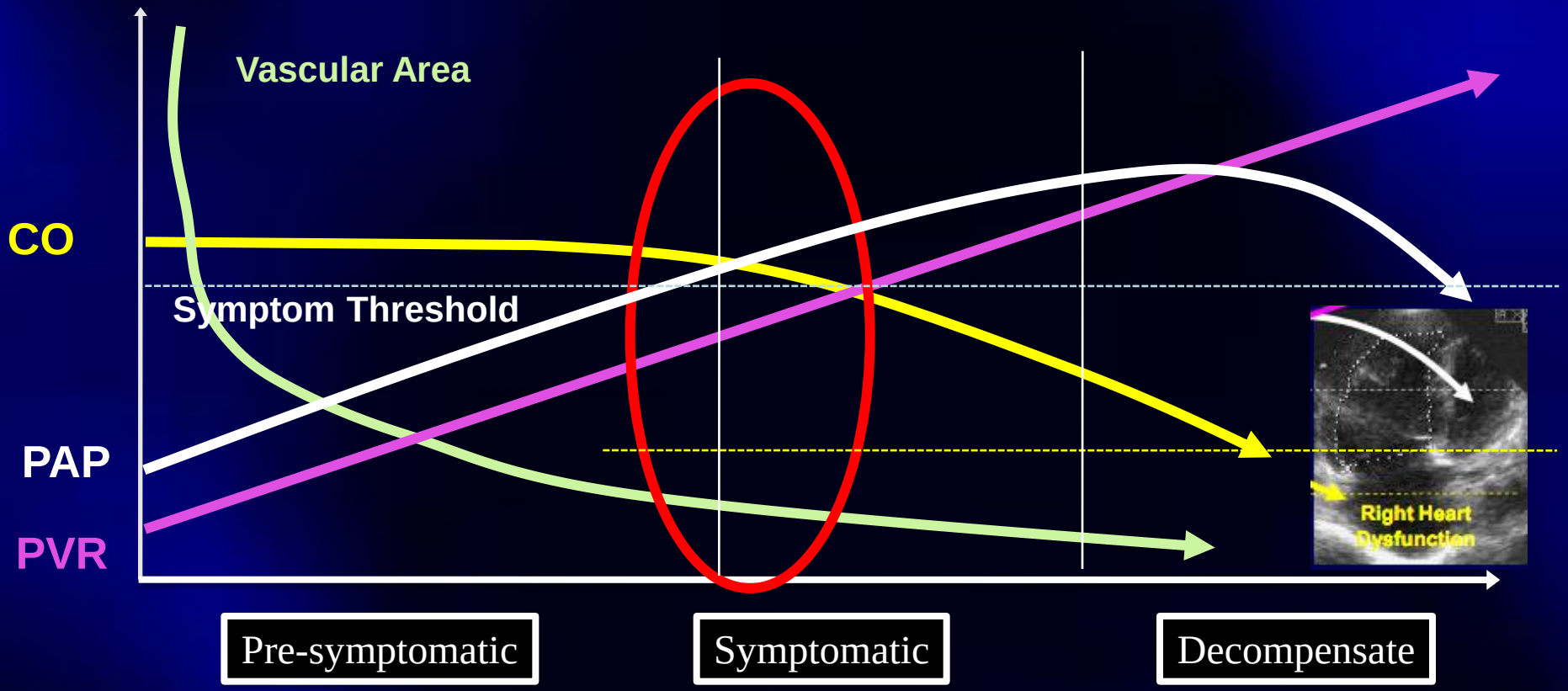
- When should we measure it?

Definition of Pulmonary Hypertension

- Mean PA pressure > 25 mmHg at rest
- **Mean PA pressure > 30 mmHg with exercise at invasive study**
- In the presence of a normal PCWP (≤ 15 mmHg) with above feature : PAH

ACCF/AHA CECD includes PVR > 3 Wood Units

PA Pressure With Exercise Be Useful?

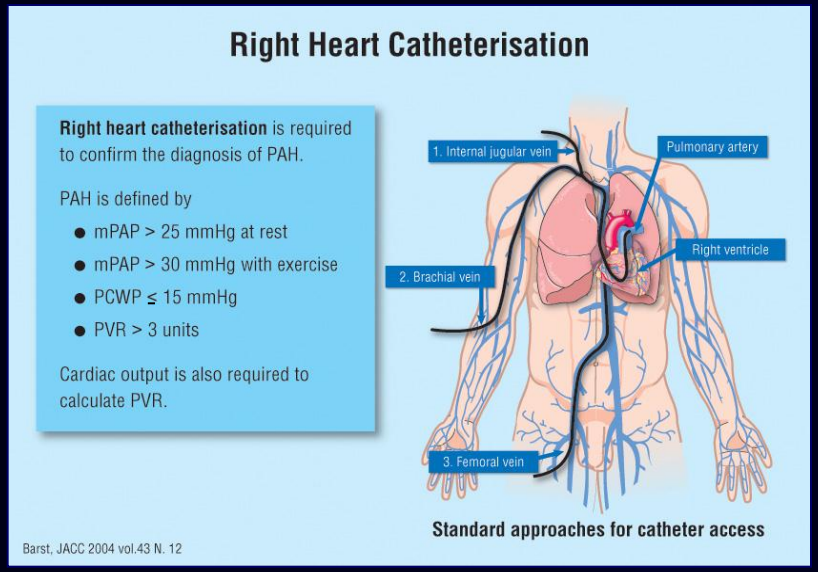


As flow increases, resistance must fall or else pressure will rise

"Stress testing" to increase flow may unmask inability of the pulmonary vasculature to cope with increased flow

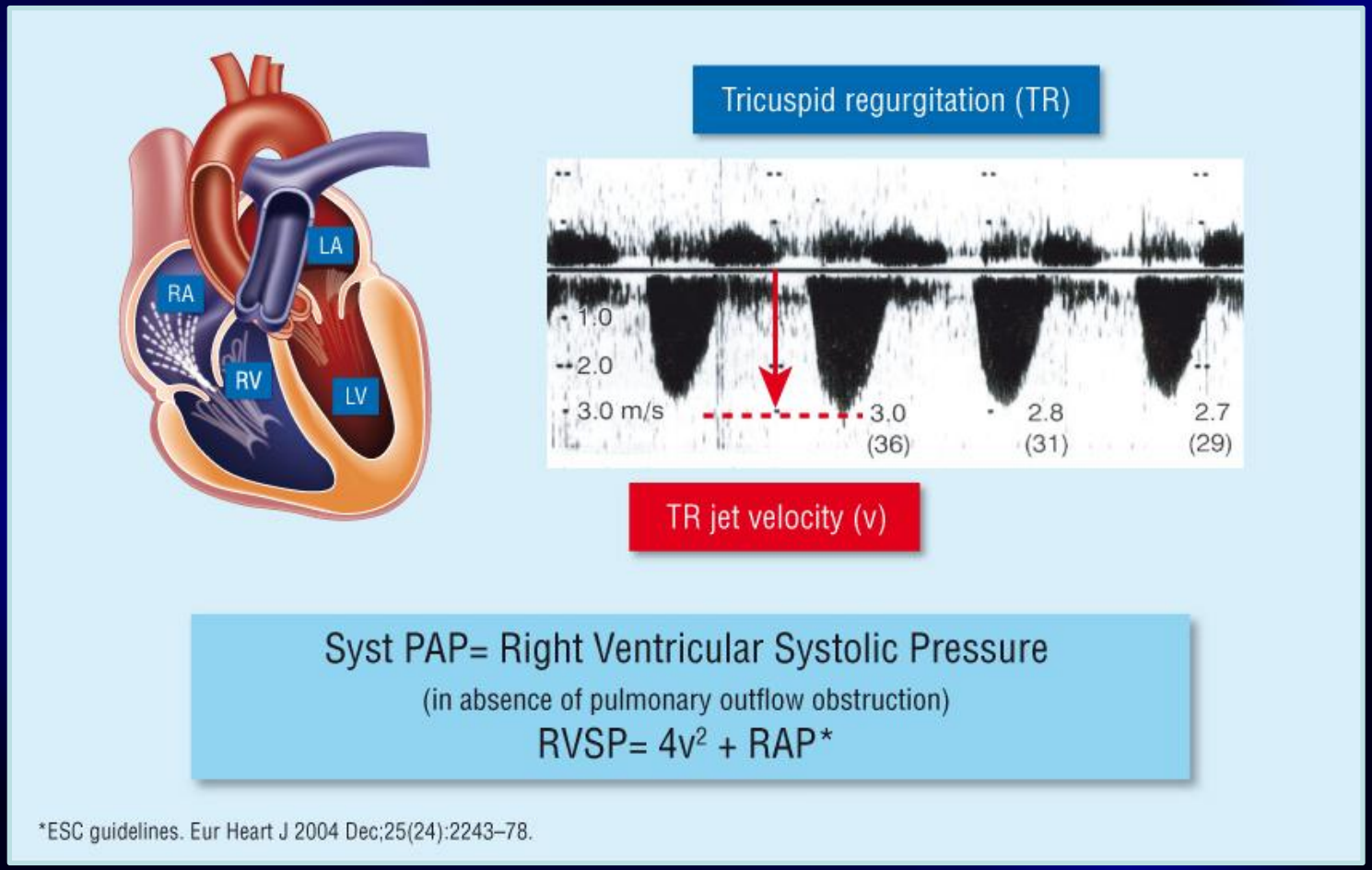
How we measure it ?

- Invasive hemodynamic measurement
  - Rt. side Cath.
    (Gold standard)



- Noninvasive hemodynamic measurement
  - Doppler echo. (screening)

Echocardiography:
its value as a screening tool of pulmonary HTN



How we measure EPH ?

Supine bicycle echo.

- At rest and each stage of exercise

- Mitral inflow PW Doppler

  E, A velocities , DT

- Mitral annulus tissue Doppler

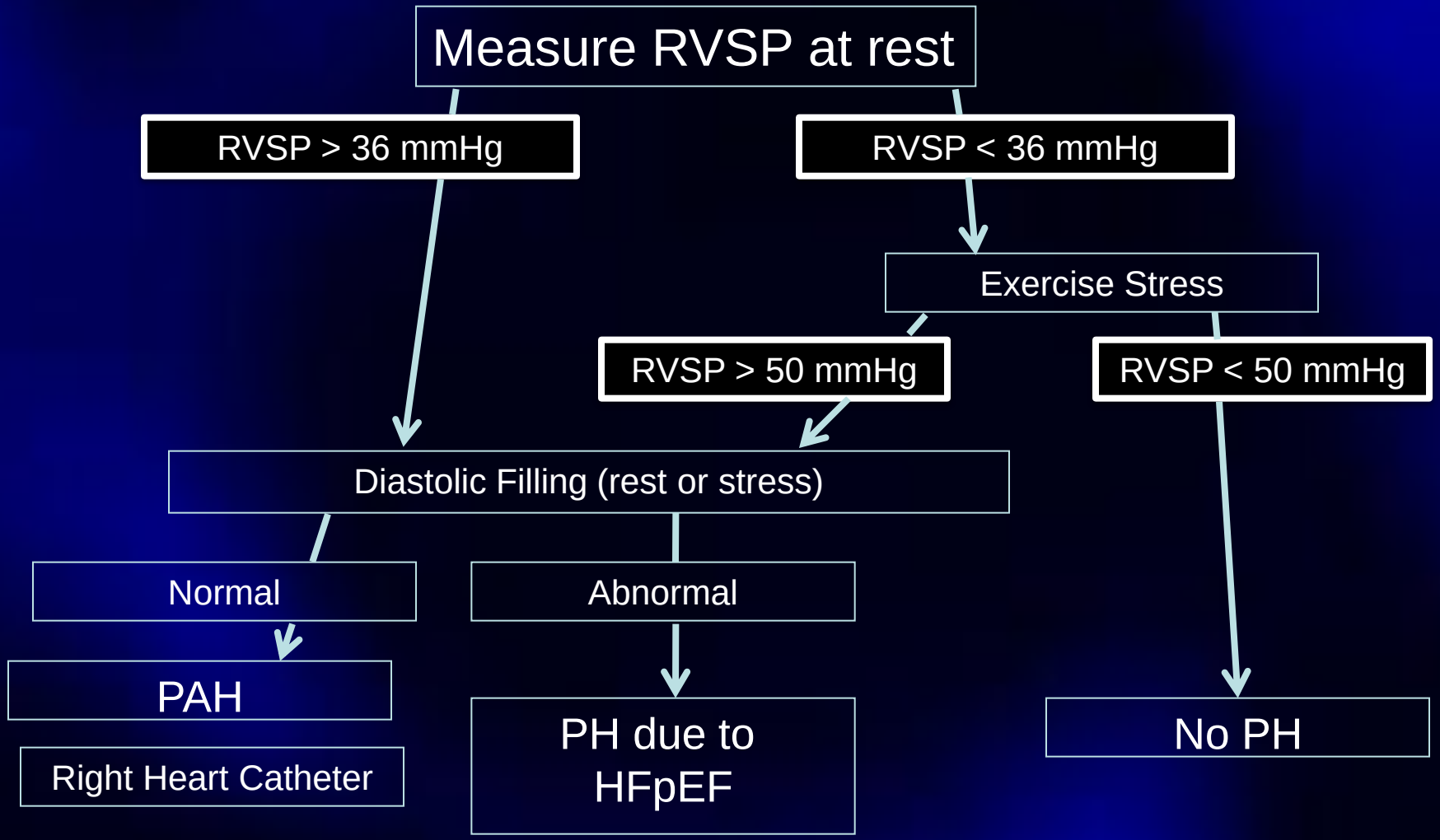
  E', A', S' velocities

- LV Filling Pressure : E/E' ratio

- Pulmonary artery systolic pressure (PASP)

  : 4 x (TR velocity)^2 + 10 mmHg

DDX. of dyspnea by exercise echo.

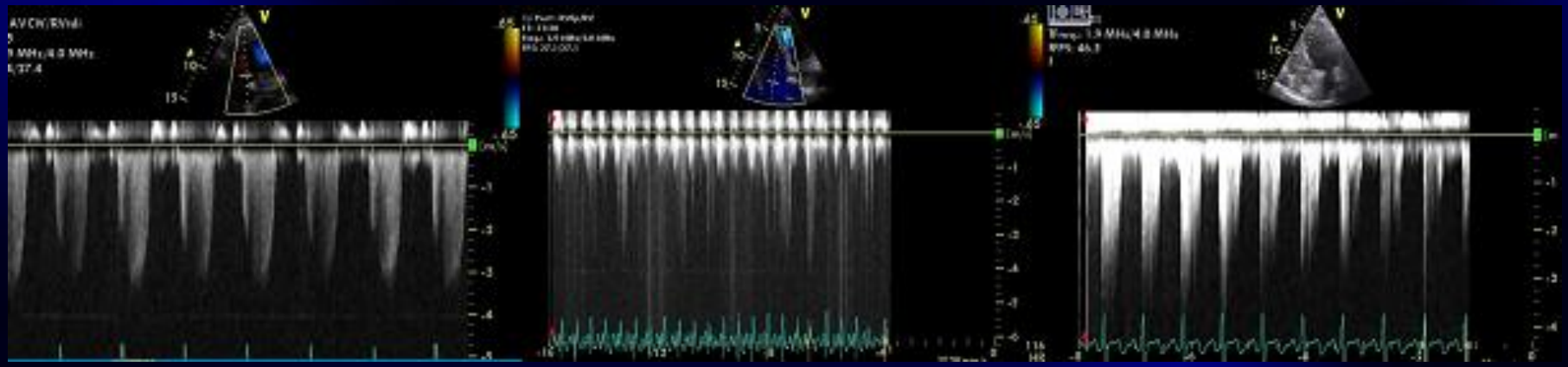


HFpEF: heart failure with preserved ejection fraction, RVSP: right ventricular systolic pressure

How we measure EPH ?

Exercise Echo.: The Problems Are Technical

- Treadmill exercise – inability to quickly record TR jet
- Supine bicycle exercise better
- Inability to accurately record TR jet
- Accuracy of RVSP in echo: 40% false positive



Exercise pulmonary hypertension

- Definition and How we measure it ?

- Clinical implications of exercise echo.

- When should we measure it?

Unmask early forms of LV dysfunction or PAH

(Heart failure with preserved ejection fraction: HFpEF)

- HFpEF
  - The diagnosis of earlier stage of HFpEF may be challenging, as exertional dyspnea is not specific.
  - Biomarker and hemodynamics in “early stage” of these conditions may be unremarkable at rest.

Determinants of exercise-induced pulmonary hypertension in patients with normal left ventricular ejection fraction

J-W Ha, D Choi, S Park, et al.

Heart 2009 95: 490-494 originally published online July 24, 2008

396 subjects referred exercise echo. with supine bicycle exercise (exclude LVEF < 50%, HCMP and ESRD)

	Group 1 (n = 261)	Group 2 (n = 135)	p Value
Age (SD)	51.3 (13.1)	61.2 (8.9)	<0.0001
Gender (M:F)	124:137	36:99	<0.0001
History of smoking (%)	73 (28)	23 (17)	0.014
Diabetes mellitus (%)	56 (21.7)	33 (24.4)	0.51
Hypertension (%)	156 (59.8)	99 (73.3)	0.005
Heart rate (bpm)	63.7 (9.6)	63.9 (9.6)	0.82
Systolic BP (mm Hg)	125 (18)	132 (18)	0.0003
Diastolic BP (mm Hg)	76 (11)	77 (10)	0.15
Diuretics (%)	19 (7.3)	10 (7.4)	0.86
CCB (%)	63 (24.1)	41 (30.4)	0.22
β-blocker (%)	56 (21.5)	32 (23.7)	0.16
ACEI (%)	12 (4.6)	6 (4.4)	0.91
ARB (%)	35 (13.4)	31 (23.0)	0.02
Exercise duration (s)	614 (227)	508 (165)	<0.0001
Peak VO_2 (ml/kg/min)	21.2 (6.6)	19.6 (5.7)	0.017

Group 1, no exercise-induced pulmonary hypertension; Group 2, exercise-induced pulmonary hypertension.
ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; VO_2, oxygen consumption.

Exercise induced PH defined as present if PASP >50 mm Hg at 50 W of exercise.

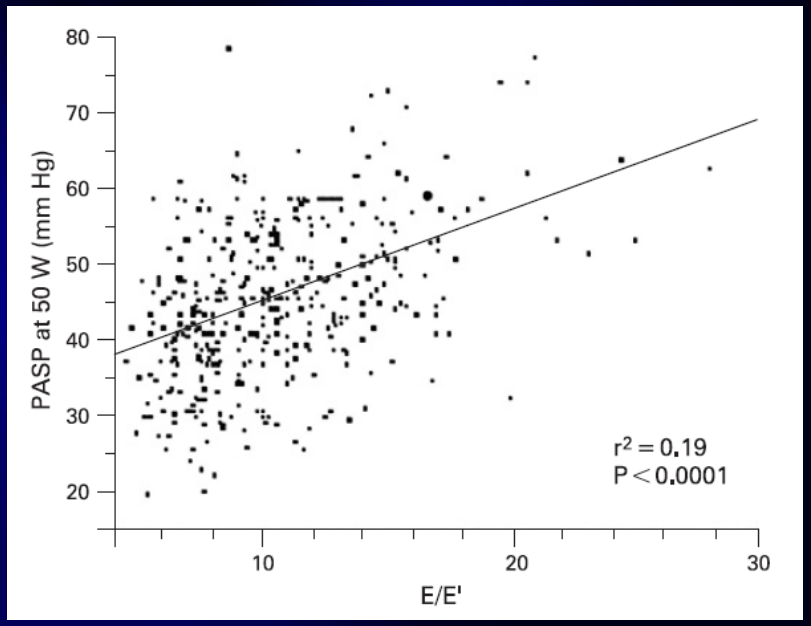
Ha JW et al. Heart 2009;95:490–494

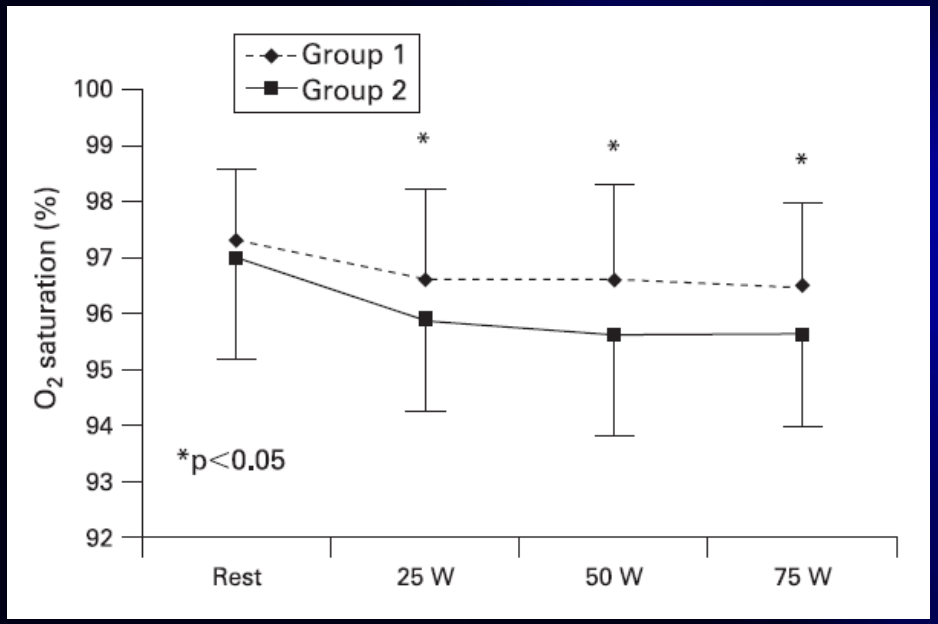
396 subjects referred exercise echo. with supine bicycle exercise (exclude LVEF < 50%, HCMP and ESRD)

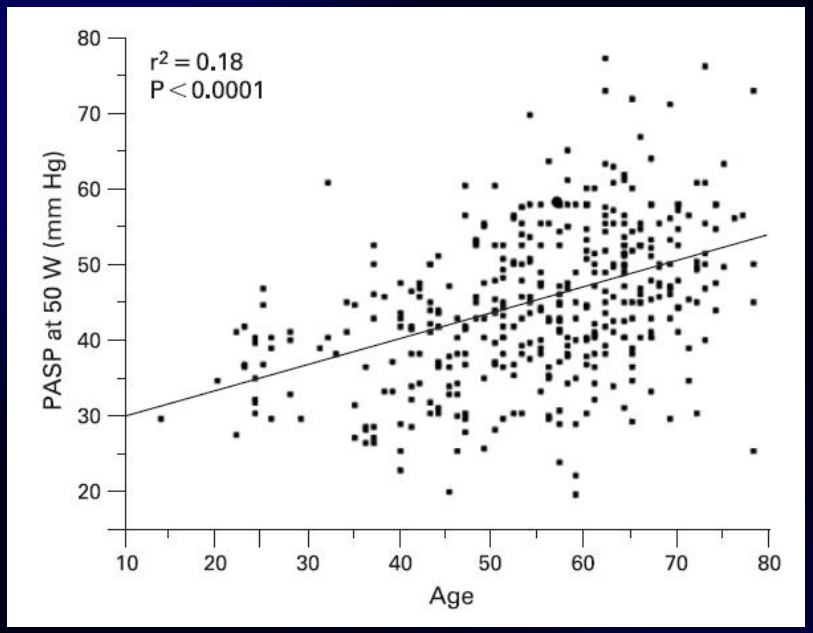
	Group 1 (n = 261)	Group 2 (n = 135)	p Value
LVEDD (mm)	49 (3)	49 (4)	0.61
LVESD (mm)	32 (4)	31 (4)	0.025
Ejection fraction (%)	66.9 (5.5)	68.6 (6.0)	0.0069
IVS (mm)	9.4 (1.5)	9.6 (1.6)	0.15
PW (mm)	9.3 (1.6)	9.5 (1.7)	0.26
LAVI (ml/m^2)	21.7 (6.0)	24.8 (8.8)	0.0032
E (m/s)	0.64 (0.14)	0.65 (0.15)	0.54
A (m/s)	0.60 (0.16)	0.74 (0.16)	<0.0001
E/A	1.1 (0.4)	0.9 (0.3)	<0.0001
DT (ms)	193 (34)	210 (49)	0.0005
TR velocity (m/s)	2.1 (0.2)	2.4 (0.3)	<0.0001
Stroke volume (ml)	67 (13)	69 (13)	0.20
E′ (cm/s)	7.3 (2.6)	5.6 (2.0)	<0.0001
A′ (cm/s)	7.8 (1.6)	7.9 (1.6)	0.79
E/E′	9.5 (3.0)	12.6 (4.2)	<0.0001
S′	6.8 (1.3)	6.4 (1.1)	0.0007

Group 1, no exercise-induced pulmonary hypertension; Group 2, exercise-induced pulmonary hypertension.
LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; IVS, interventricular septal thickness; PW, posterior wall thickness; LAVI, left atrial volume index; E, peak velocity of early diastolic filling; A, peak velocity of diastolic filling during atrial contraction; DT, deceleration time; TR, tricuspid regurgitation; E′ early diastolic mitral annular velocity; A′, late diastolic mitral annular velocity; S′, systolic mitral annular velocity.

Ha JW et al. Heart 2009;95:490–494





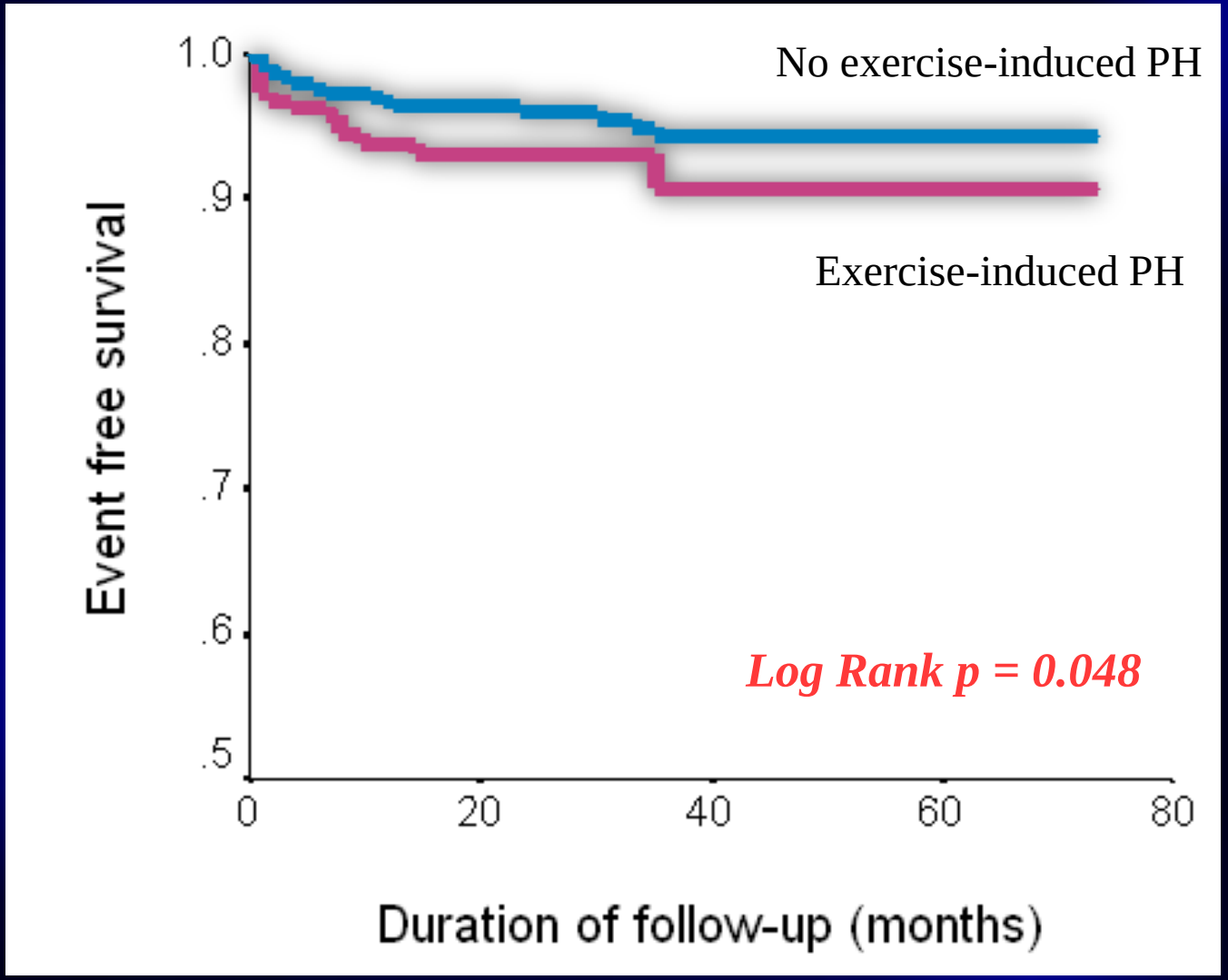


Exercise-induced PH is common even in subjects (34%) with normal LVEF.

EPH is strongly associated with E/E' ratio, TR velocity, age, systolic blood pressure during exercise and gender.

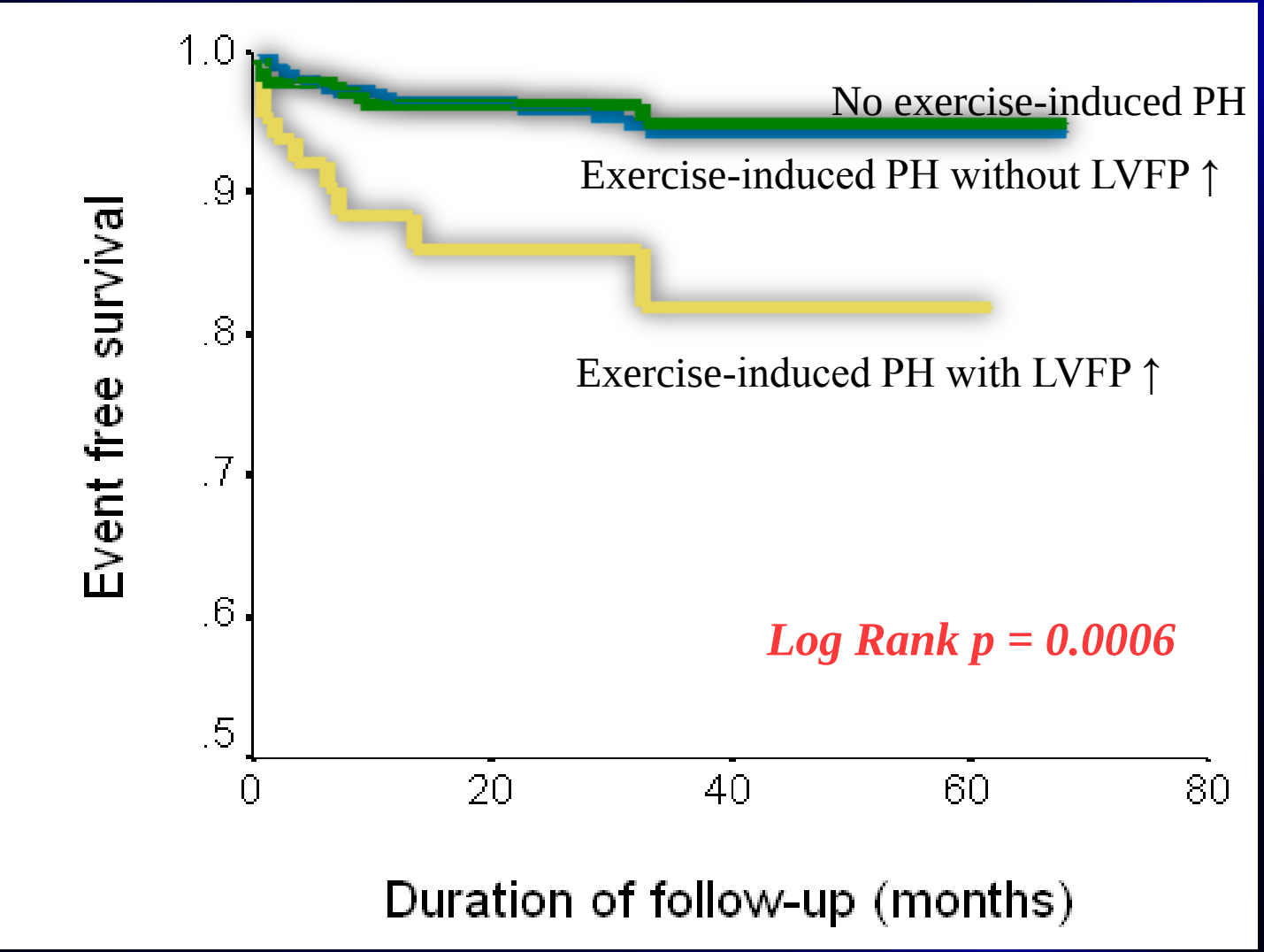
Ha JW et al. Heart 2009;95:490–494

How about prognosis ?



Shim CY et al. AHA 2009 Presentation

How about prognosis ? ?



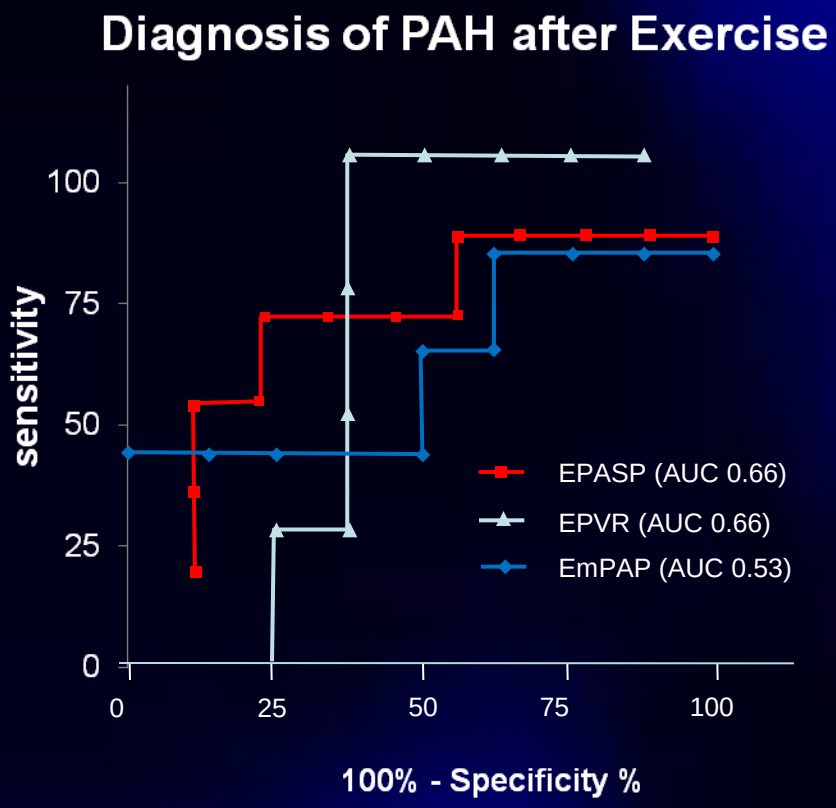
Increased LVFP during exercise : E/E' ≥ 15 at 50 W of exercise

Shim CY et al. AHA 2009 Presentation

Unmask early forms of PAH

(Pulmonary artery hypertension: exercise echo. in scleroderma)

- Echo cut-off 40 mmHg
  - 100% sensitivity
  - 16% specificity
- Echo cut-off 55 mmHg
  - 66% sensitivity
  - 77% specificity



Burns et al. 2009

EIPAH is an intermediate phenotype between normal and resting PAH.

	Normal (n=16)	Exercised PAH (n=78)	Overt PAH (n=15)
Age, y...	45.9±14.9	25.8±15.1*	58.5±15.7*
Female gender, %	68.8	65.8	46.7
Body mass index	25.5±4.2	30.2±5.3*	28.1±6.2
Work max, W	155.5±43.1	90.3±41.7*	70.0±41.5*
VO_2max, mL/min	2022±468	1284±58*	1127±507*
VO_2max, % predicted	91.7±13.7	66.5±16.3*	55.8±20.3*†
P/A, aio-max, mm Hg	14.7±7.6	32.0±18.0*	52.7±17.3*†
Cao_2, mg/mL	19.0±1.2	18.0±2.5	16.8±3.3
$Paco_2$-max, mmHg	32.9±4.4	35.1±6.1	37.1±7.6
Vco_2max, mL/min	2380±722	1561±705*	1310±626*
mPAP rest, mm Hg	13.9±2.9	18.6±3.2*	30.9±8.9*†
mPAPmax, mm Hg	27.4±3.7	36.6±5.7*	48.4±11.1*†
PCWPmax, mm Hg	14.8±4.5	15.0±2.4	15.2±3.1
O_2max, L/min	15.5±3.2	11.4±3.0*	10.4±3.6*
O_2max, % predicted	99.4±11.1	83.1±18.9	71.8±22.4*†
PVR rest, dyne + s + cm=$^{-5}$	154±61	223±82*	352±141*†
PVR rest, dyne + s + cm=-^{5}	62±20	161±60*	294±158*†
PAPmax, mmHg	0.4±3.5	9.6±3.0	11.0±6.1
RVEF max	0.58±0.06	0.53±0. 08*	0.43±0.11*†
v/Vco_2 at anaerobic threshold	36.0±8.9	37.8±8.0	43.1±6.9*

P(A-a)o_2 indicates alveolar-arterial difference in partial pressure of O_2;Vco_2, carbon doxide production
*P<0.05 vs normal; †P<0.05 vs exercised-induced PAH

Am Rev Respir Dis 1984

Px. of Exercise PH in overt heart disease

(Heart failure with reduced LVEF)

- Resting pulmo. hypertension in systolic failure
  - RV dysfunction
  - Reduced exercise tolerance
  - Poor prognosis

JACC, 1999, 34;1802, /2001;37:183/ 1992; 19:48

How are the prognostic value of the PA pressure response patterns during exercise ?

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PII S0735-1097(98)00672-X

Use of Cardiopulmonary Exercise Testing With Hemodynamic Monitoring in the Prognostic Assessment of Ambulatory Patients With Chronic Heart Failure

Table 2. Hemodynamic Variables of Survivors and Nonsurvivors

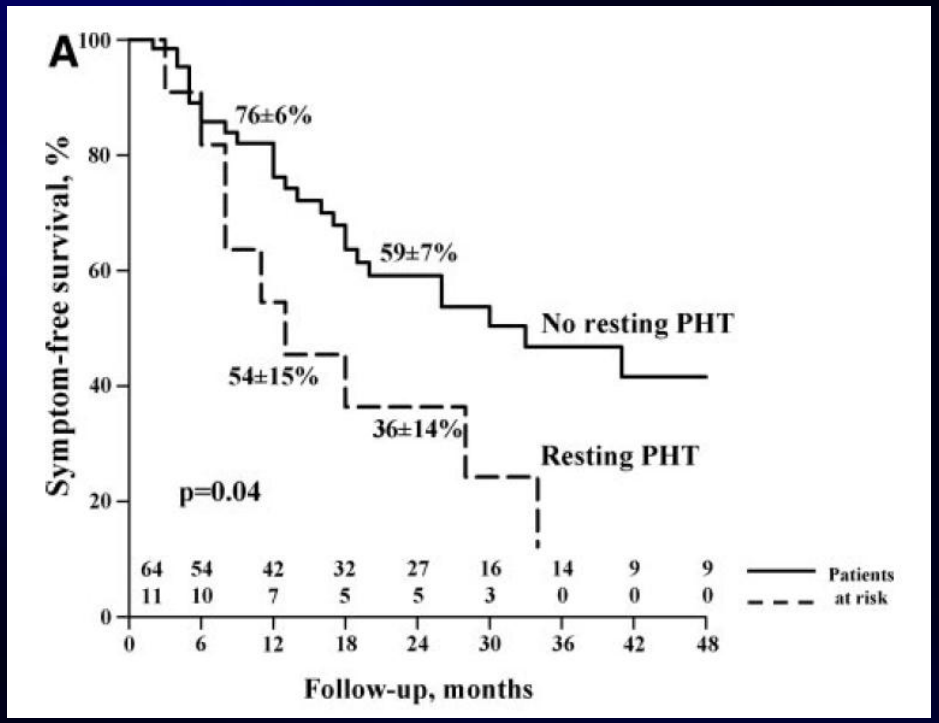
	Rest (Supine)		Rest (Sitting)		Peak Exercise	
	Survivors	Nonsurvivors	Survivors	Nonsurvivors	Survivors	Nonsurvivors
Heart rate (beats/min)	76 ± 14	82 ± 11*	80 ± 15	87 ± 15†	134 ± 25	131 ± 25
Systolic blood pressure (mm Hg)	118 ± 20	108 ± 20†	121 ± 21	111 ± 18†	150 ± 31	129 ± 25‡
Diastolic blood pressure (mm Hg)	75 ± 10	73 ± 11	76 ± 10	74 ± 11	86 ± 15	80 ± 14*
Cardiac index (liters·m·m^{-2})	2.48 ± 0.54	2.28 ± 0.48*	2.37 ± 0.57	2.16 ± 0.50*	4.63 ± 1.77	3.52 ± 0.99‡
Stroke volume index (ml·m^{-2})	34 ± 9	28 ± 7†	31 ± 9	26 ± 7†	35 ± 12	27 ± 7‡
Stroke work index (g·m·m^{-2})	31 ± 13	22 ± 9‡	31 ± 12	23 ± 10‡	35 ± 19	20 ± 10‡
Systemic vascular resistance (dyn·s·cm^{-5})	1,450 ± 399	1,455 ± 359	1,655 ± 475	1,703 ± 413	1,006 ± 385	1,119 ± 354
Peripheral O_2 extraction (%)	35 ± 9	38 ± 9	33 ± 8	36 ± 9*	71 ± 9	70 ± 9
Right atrial pressure (mm Hg)	10 ± 5	12 ± 5*	6 ± 5	7 ± 5	12 ± 7	14 ± 8
Mean pulmonary arterial pressure (mm Hg)	32 ± 13	39 ± 10‡	25 ± 11	30 ± 10*	48 ± 13	54 ± 12†
Mean pulmonary wedge pressure (mm Hg)	22 ± 9	29 ± 9‡	18 ± 9	23 ± 9†	37 ± 11	43 ± 11†
Pulmonary vascular resistance (dyn·s·cm^{-5})	188 ± 116	221 ± 97	145 ± 100	155 ± 106	125 ± 107	169 ± 143*

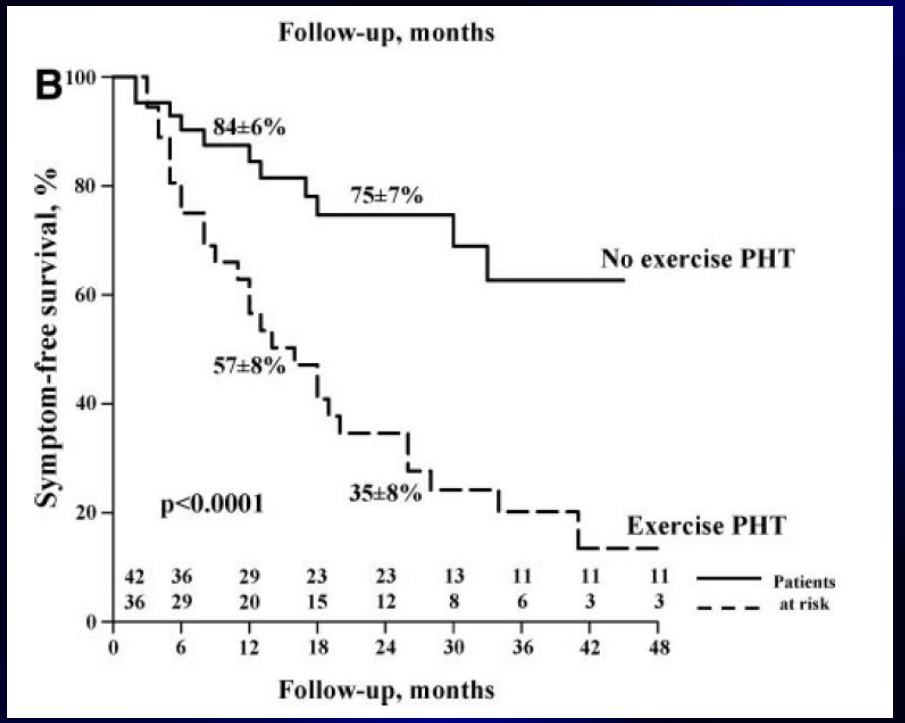
*$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$ between survivors and nonsurvivors.

Px. of Exercise PH in overt heart disease

(Mitral valve disease : MR)

Exercise PHT was defined as a systolic pulmonary arterial pressure 60 mm Hg.
Exercise PHT was present in 46%





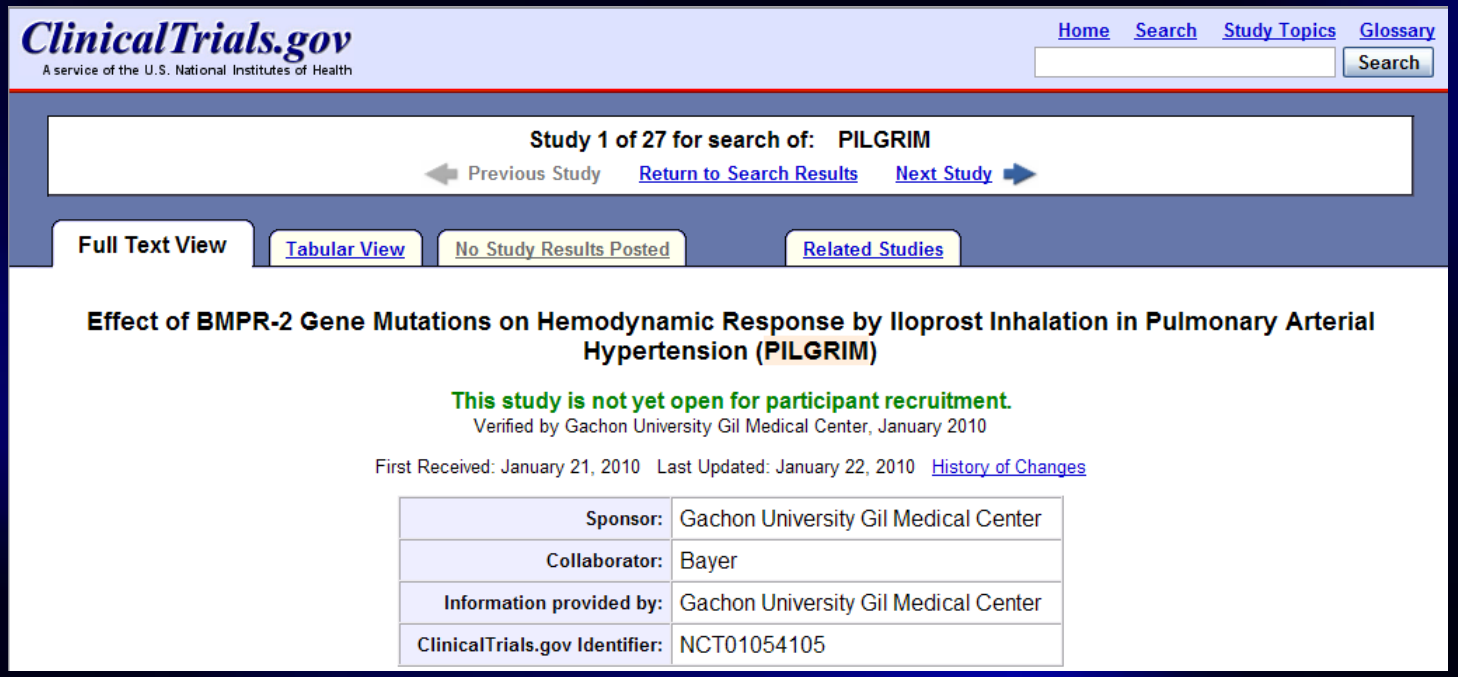
Circulation.2010;122:33-41

Pharmacotherapy of PH alter exercise PAP

- Small study (11 pts): iloprost
  - resting PAP: Δ 6 ± 8% decreased
  - exercise PAP (25 or 50W): Δ 18 ± 11% decreased

Circulation 2000;101:2388

In Korea



ClinicalTrials.gov
A service of the U.S. National Institutes of Health

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Study 1 of 27 for search of: PILGRIM
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Effect of BMPR-2 Gene Mutations on Hemodynamic Response by Iloprost Inhalation in Pulmonary Arterial Hypertension (PILGRIM)

This study is not yet open for participant recruitment.
Verified by Gachon University Gil Medical Center, January 2010

First Received: January 21, 2010 Last Updated: January 22, 2010 History of Changes

Sponsor:	Gachon University Gil Medical Center
Collaborator:	Bayer
Information provided by:	Gachon University Gil Medical Center
ClinicalTrials.gov Identifier:	NCT01054105

Introduction of PILGRIM Step-II

Newly diagnosed patients with PAH
1. RHC : mean PAP > 25 & PCWP < 15 mmHg)
2. Echo: peak PAP > 40mmHg & mean PAP > 30mmHg
With WHO/NYHA class III/IV

Patients having but refractory to conventional treatment (WHO/NYHA class III/IV) after previously confirmed as having PAH (Can be used concomitantly with PDE-5 inhibitors)

WHO functional classification
Assessment of exercise capacity (6M walk test)
Cardiopulmonary exercise echocardiography
NT-proBNP

Iloprost inhalation 2.5 - 5mcg 6 times per day

After 3 months (Active FU)

WHO functional classification
Assessment of exercise capacity (6M walk test)
Cardiopulmonary exercise echocardiography
NT-proBNP

After 2 years (Extended FU)

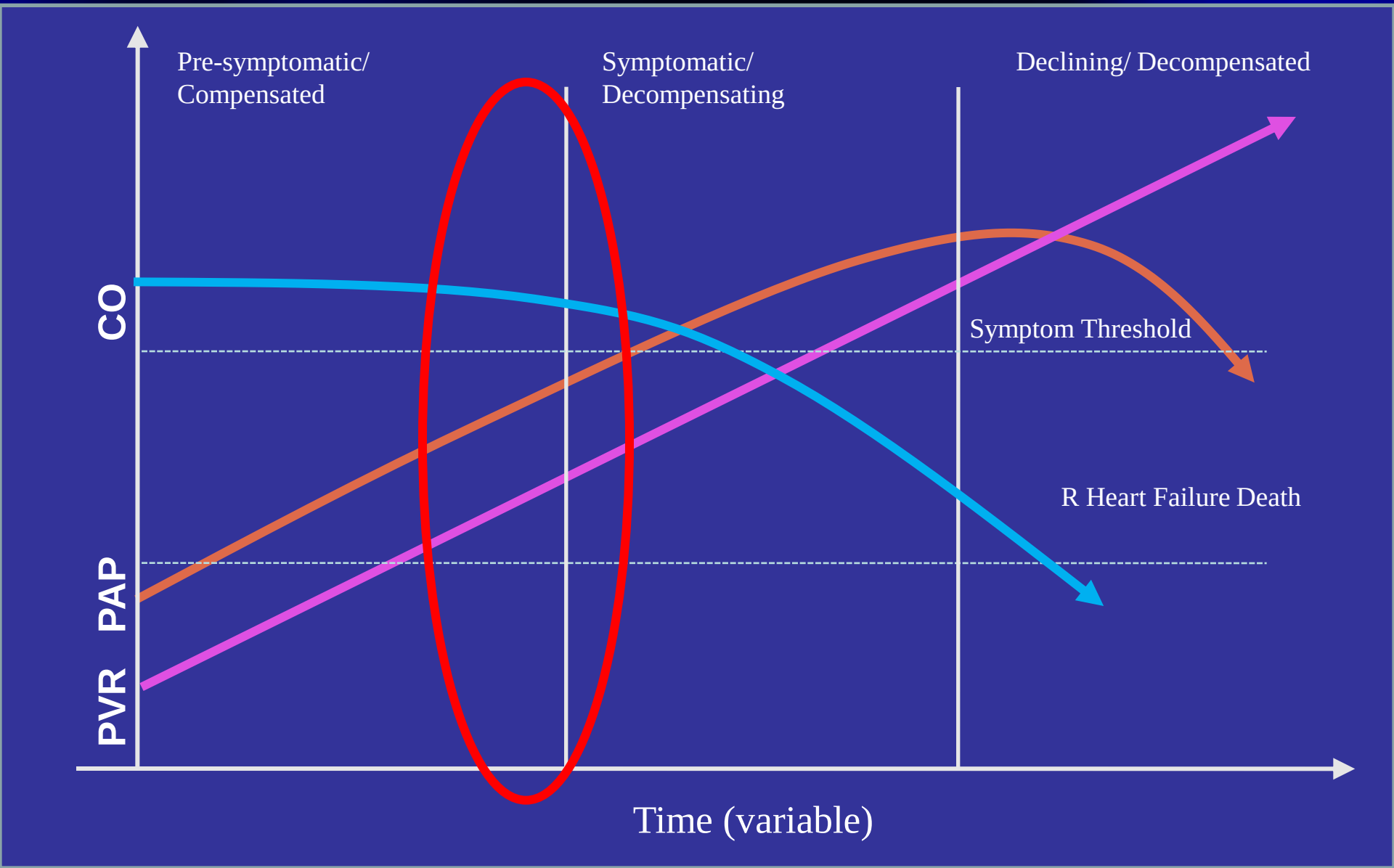
Major Cardiovascular Events

(CV mortality, All cause mortality, hospitalization

Exercise pulmonary hypertension

- Definition and How we measure it ?
- Clinical implications
- When should we measure it?

Patient Presentation: Nonspecific Sxs



When should we measure it?

- Unexplained exertional dyspnea (primary indication)
- Dynamic assessment and Px. Indicator of asymptomatic valve disease
- Possible exertional fatigue, limited exercise capacity, screening of high risk of PH and Px. assessment of PH

Future research

(Exercise Echo. in PH)

- Some theoretical basis
- Exercise needs to be standardized
- Further validation required

Thank you

- Backup slide

Post Dana Point Definition of PAH

- Mean PA pressure > 25 mmHg at rest

- In the presence of a normal PCWP
- Mean PA pressure 20 – 25 uncertain

Why was exercise removed?

Why was exercise removed? After Dana point meeting in 2008

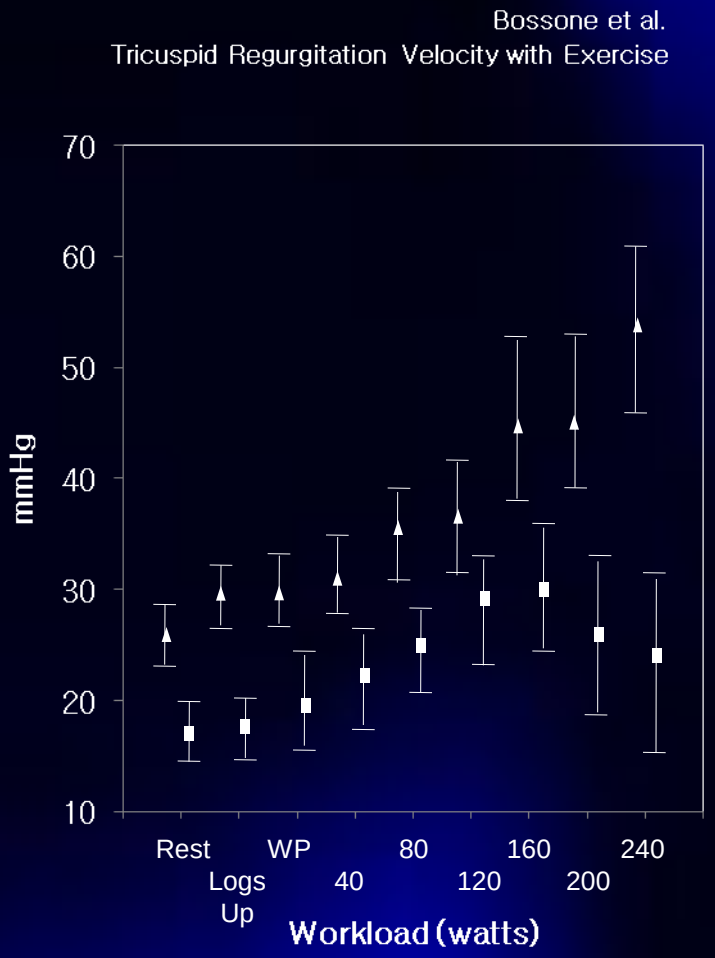
"Potential weaknesses of the current definition include the fact that the level, type, and posture of exercise have not been specified. Furthermore, the normal exercise pulmonary arterial pressure (PAP) varies with age"

Effect of Age on mPAP with Exercise

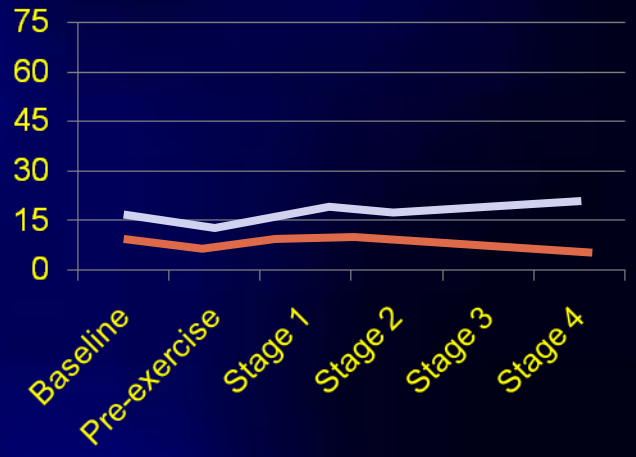
Age	Slight ULN	Submax ULN
< 30	29 mmHg	33 mmHg
30–50	30 mmHg	36 mmHg
>50	45 mmHg	47 mmHg

Exercise Induced Pulmonary Hypertension

In well trained athletes, exercise results in hypoxia and increases in pulmonary pressures



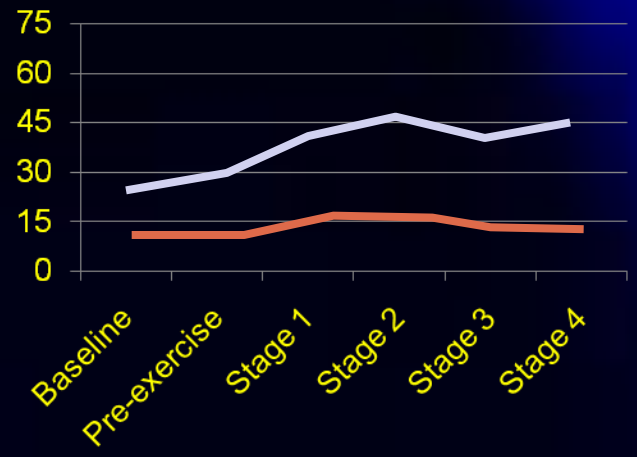
Incremental increases in PA mean and PCW over exercise stages



Normal, young

PA mean

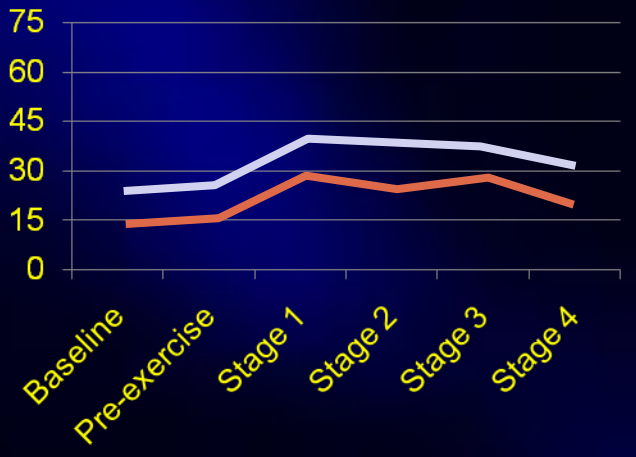
PCW



PAH

PA mean

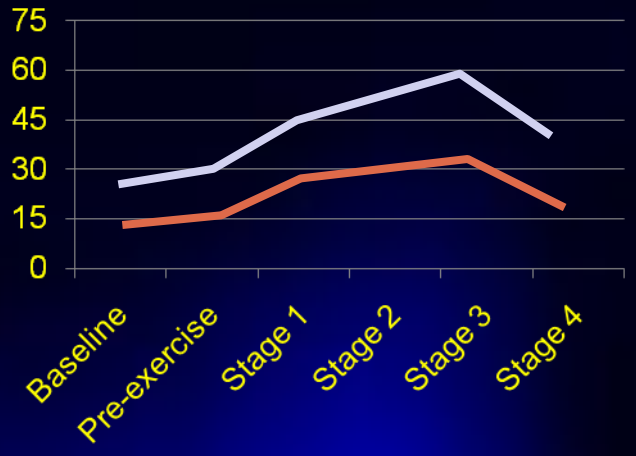
PCW



DHF

PA mean

PCW



DHF+PH

PA mean

PCW

Improve technique in exercise echo.

- Need IV access for contrast
- Modify stress echo protocol on machine for additional measures
  - Apical RV view
  - CW of tricuspid regurgitation
  - Mitral inflow
  - E’
  - ?LVOT VTI
- May only need low level stress

Downside of Exercise Rt HC

- Exercise to fatigue
- Measure C.O. immediately before exercise ceases
- Measure PAP and PCWP immediately after removing load, but with legs still spinning
- Thermodilution cardiac output may be inaccurate with severe TR

Can we use exercise to identify PAH?

You need to know:

- Amount of exercise
- Pulmonary pressures at that level of exercise
- Perhaps the slope of the CO – PA pressure curve provides information
- More work required for this to be a reliable modality

PAH: classification

1. PAH
   - Idiopathic PAH
   - Familial PAH
   - Associated with:
     - Connective tissue disease
     - CHD (shunts)
     - Portal hypertension
     - HIV infection
     - Sickle cell disease
     - Drugs and toxins
     - Other
   - Associated with significant venous or capillary involvement
   - Persistent pulmonary hypertension of the newborn
2. PH associated with left heart dise ase
3. PH associated with respiratory dis ease
   - COPD
   - Interstitial lung diseases
4. PH due to chronic thrombotic and/ or embolic disease
5. Miscellaneous

1. Simonneau G *et al. JACC* 2004