21st Cardiology Update, Davos, 8-12/02/15

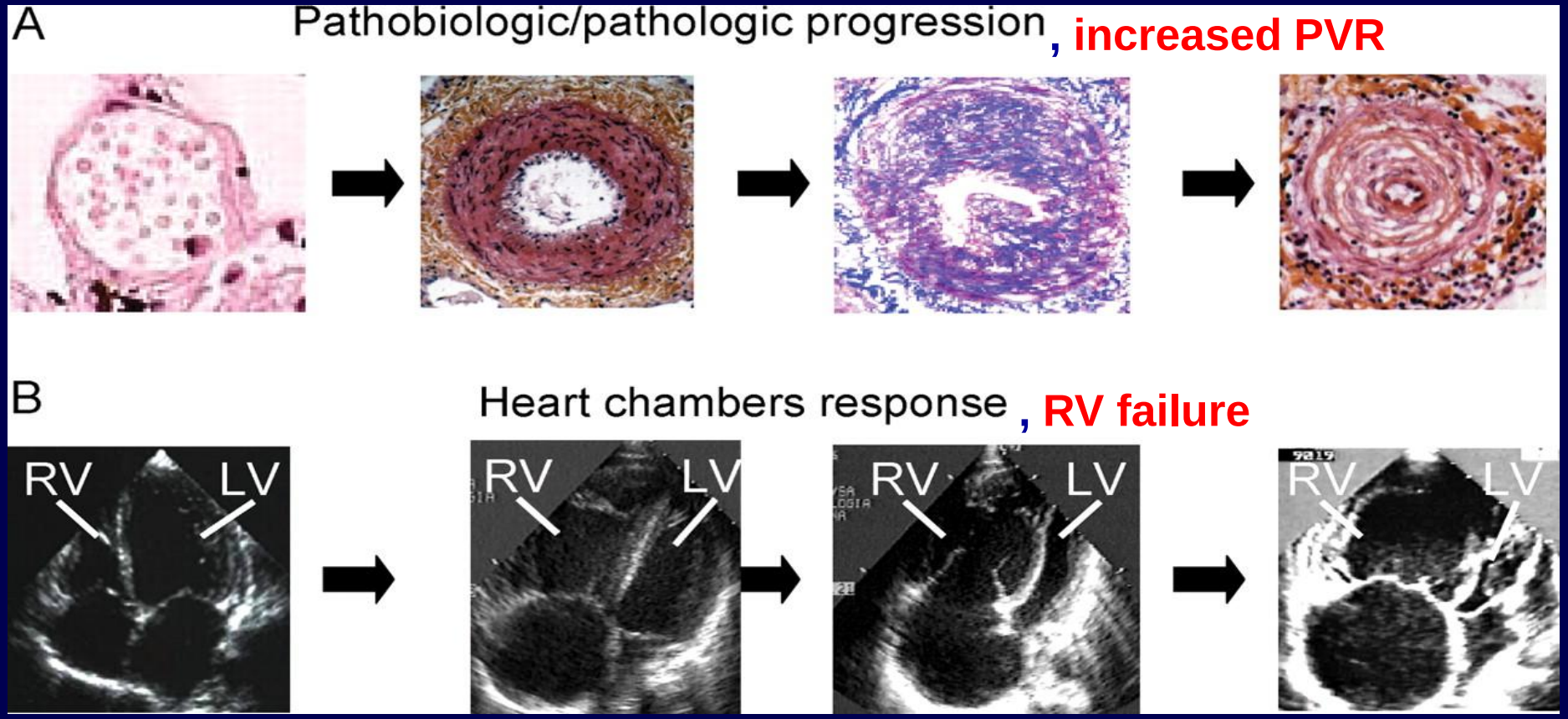
Pathophysiology of PH: the right heart matters

Robert Naeije

Erasme University Hospital

Bruxelles, Belgium

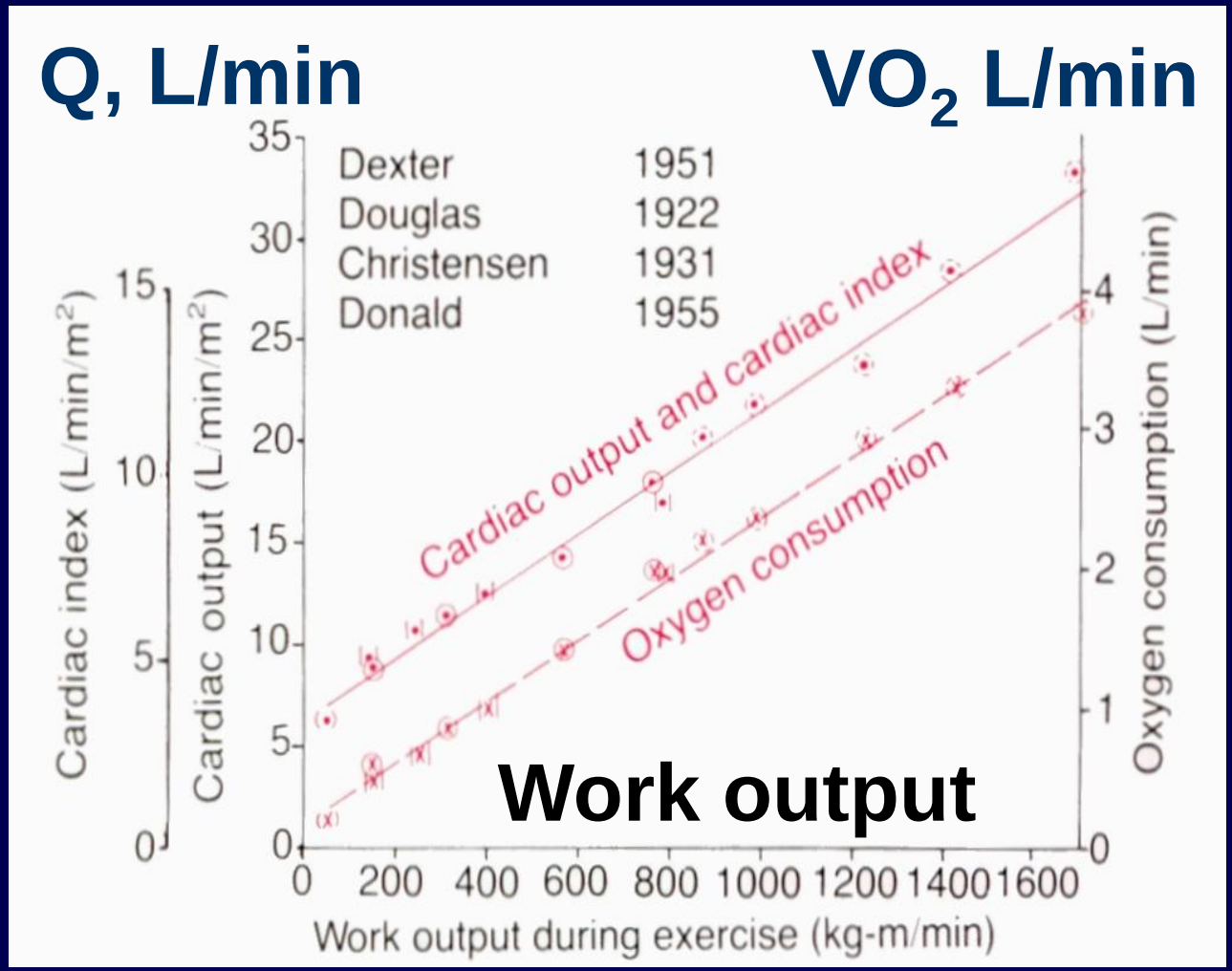
Severe PH: a disease of progressive RV-arterial uncoupling, with RV function determining symptomatology and outcome



Galiè N et al. Eur Heart J 2010; 31: 2080–2086
Vonk Noordegraaf A et al, JACC 2013;62:D22–33.

1. RV function in PAH determines maximum cardiac output, aerobic exercise capacity – and survival

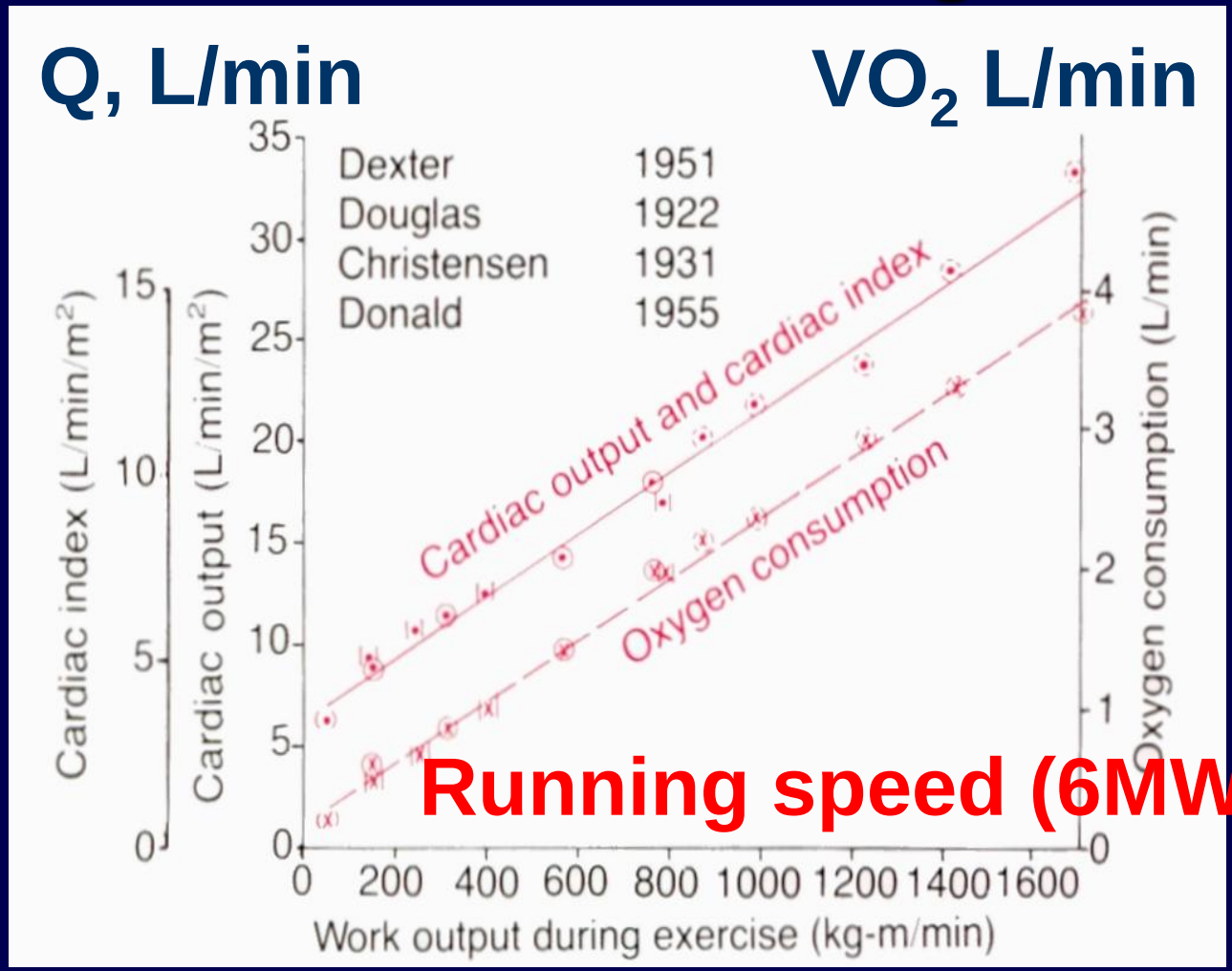
Q and VO_2 are linearly correlated to work output during exercise



Guyton, Texbook of Medical Physiology

Naeije R, Chest 2010; 137: 1259-60

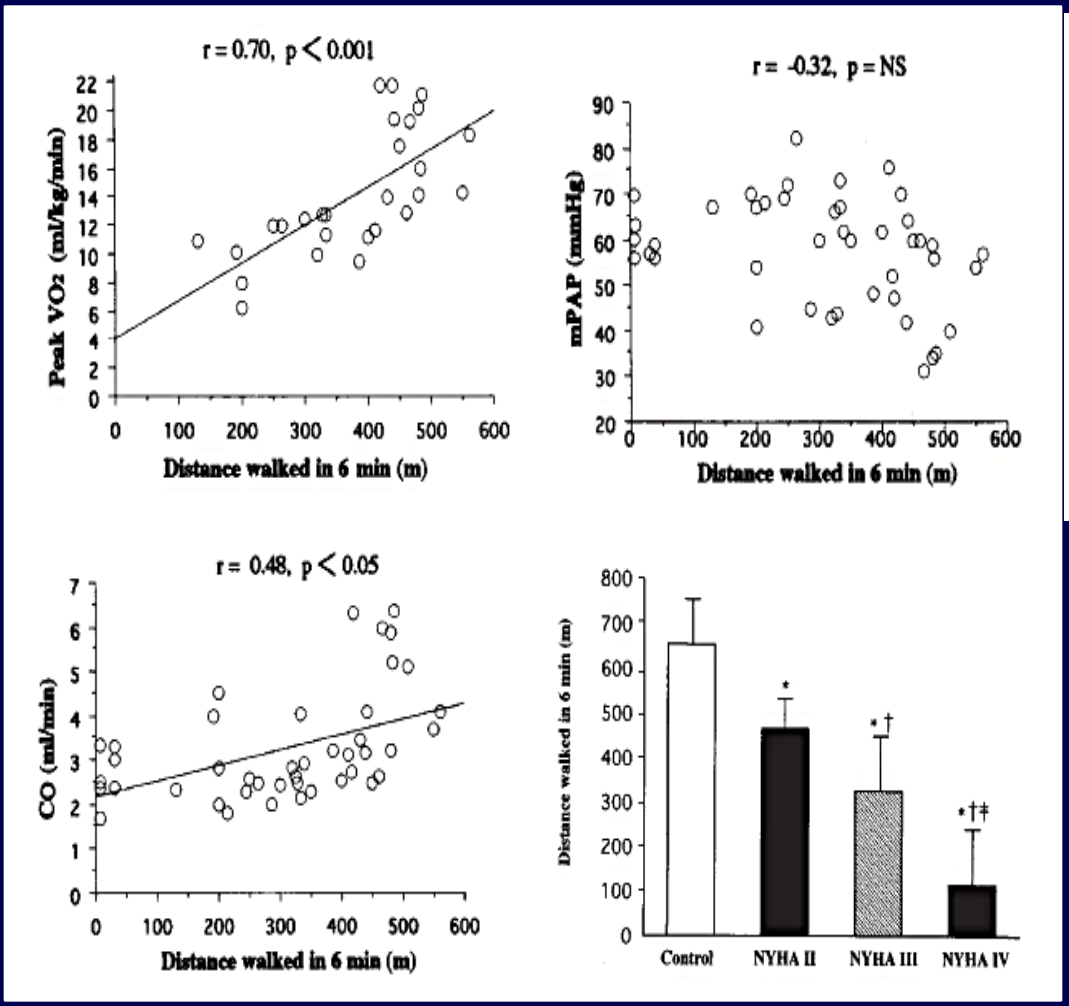
Q and VO_2 are linearly correlated to work output or distance/time during exercise

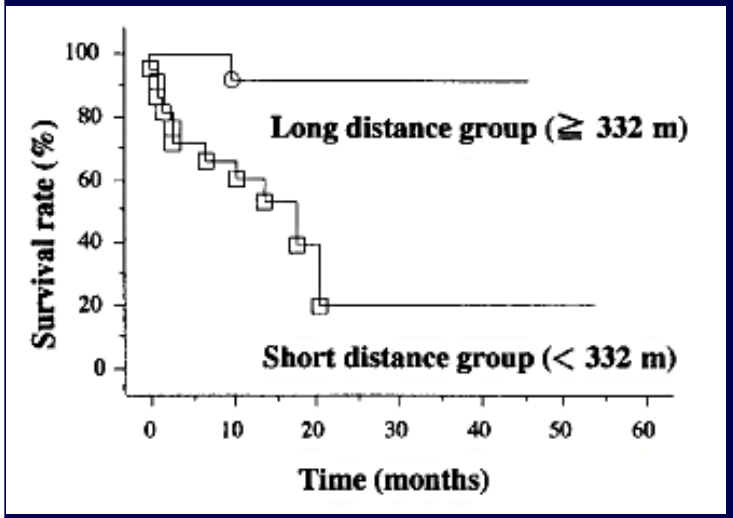


Guyton, Texbook of Medical Physiology

Naeije R, Chest 2010; 137: 1259-60

6-MWD, peak VO_2 , NYHA, resting PAP and cardiac output, and survival in IPAH



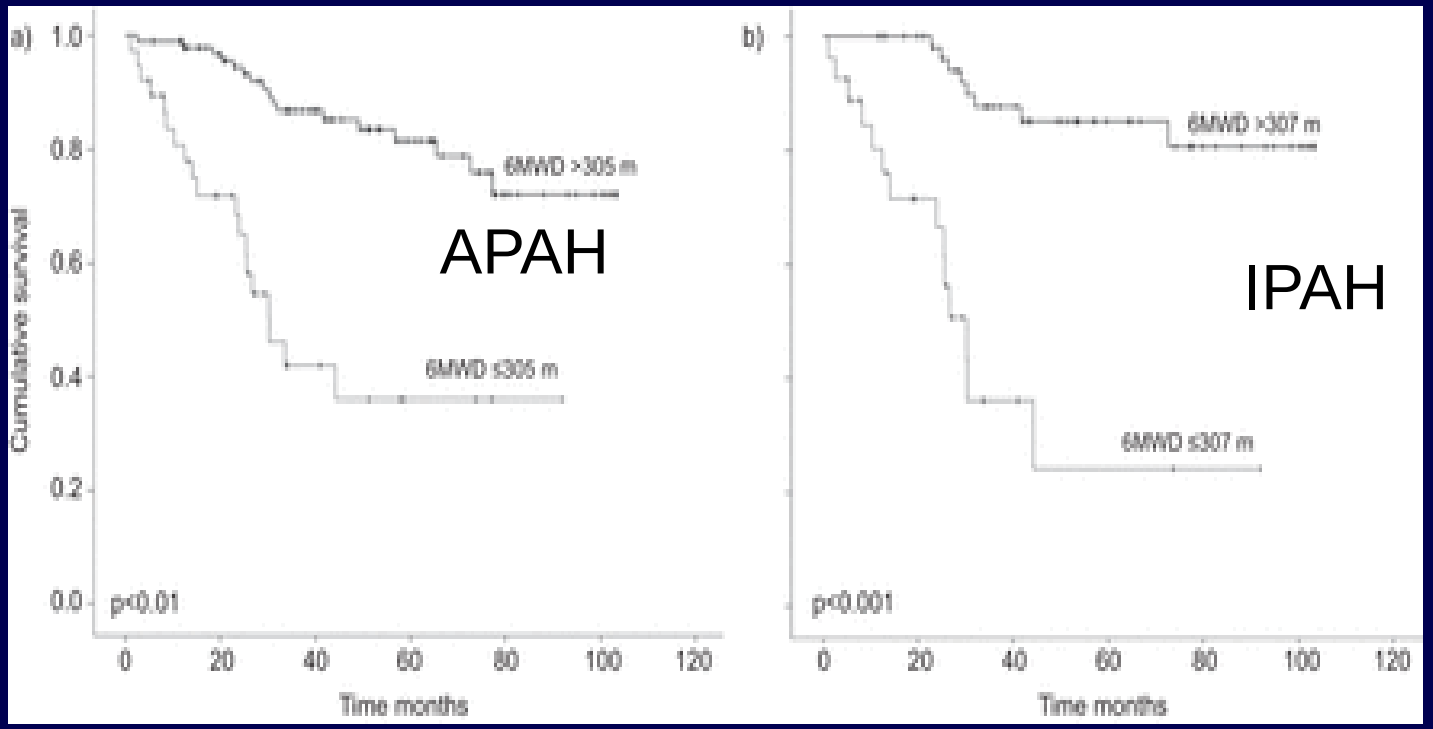


6MWD predicted survival
6MWD was correlated to peak VO_2, NYHA, and resting cardiac output, not to PAP

Miyamoto S, *et al. Am J Respir Crit Care Med* 2000; 161: 487-492

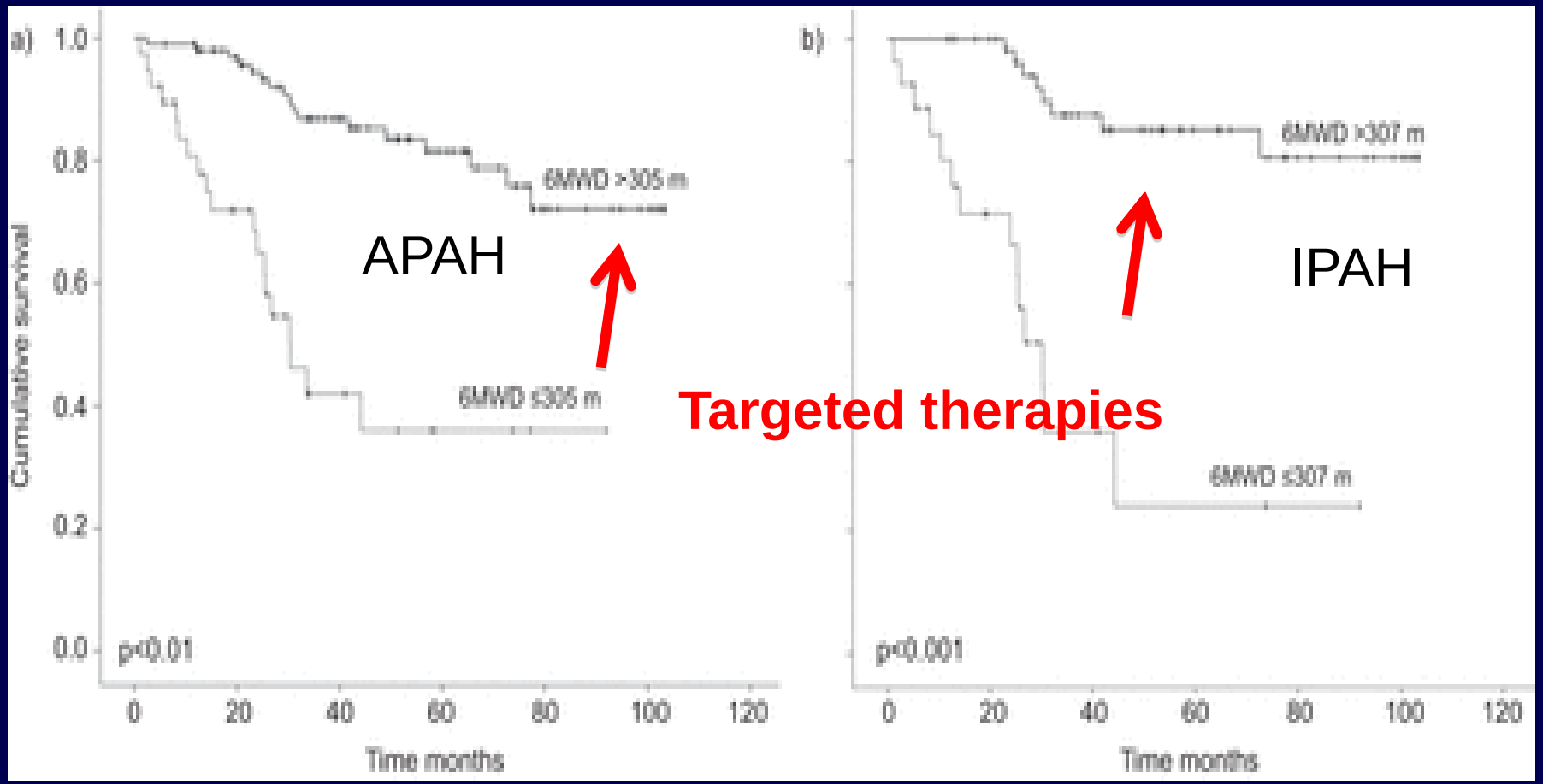
136 prevalent or incident PAH: CPET and 6MWD

Only 6MWD was an independent predictor of survival and clinical stability of all PAH (IPAH or APAH), whether prevalent or incident VE/VCO2 predicted survival only in IPAH, (peak VO2 borderline)



Deboeck et al, Eur Respir J 2012; 40: 1410-9

The notion that targeted therapies would shift PAH patients to better functional state and survival curves



Meta-analysis of RCT of prostacyclins, ERA's and PDE5i's in PAH

Galié et al, Eur Heart J 2009; 30: 394–403
Macchia et al, Am Heart J 2010; 159: 245-257

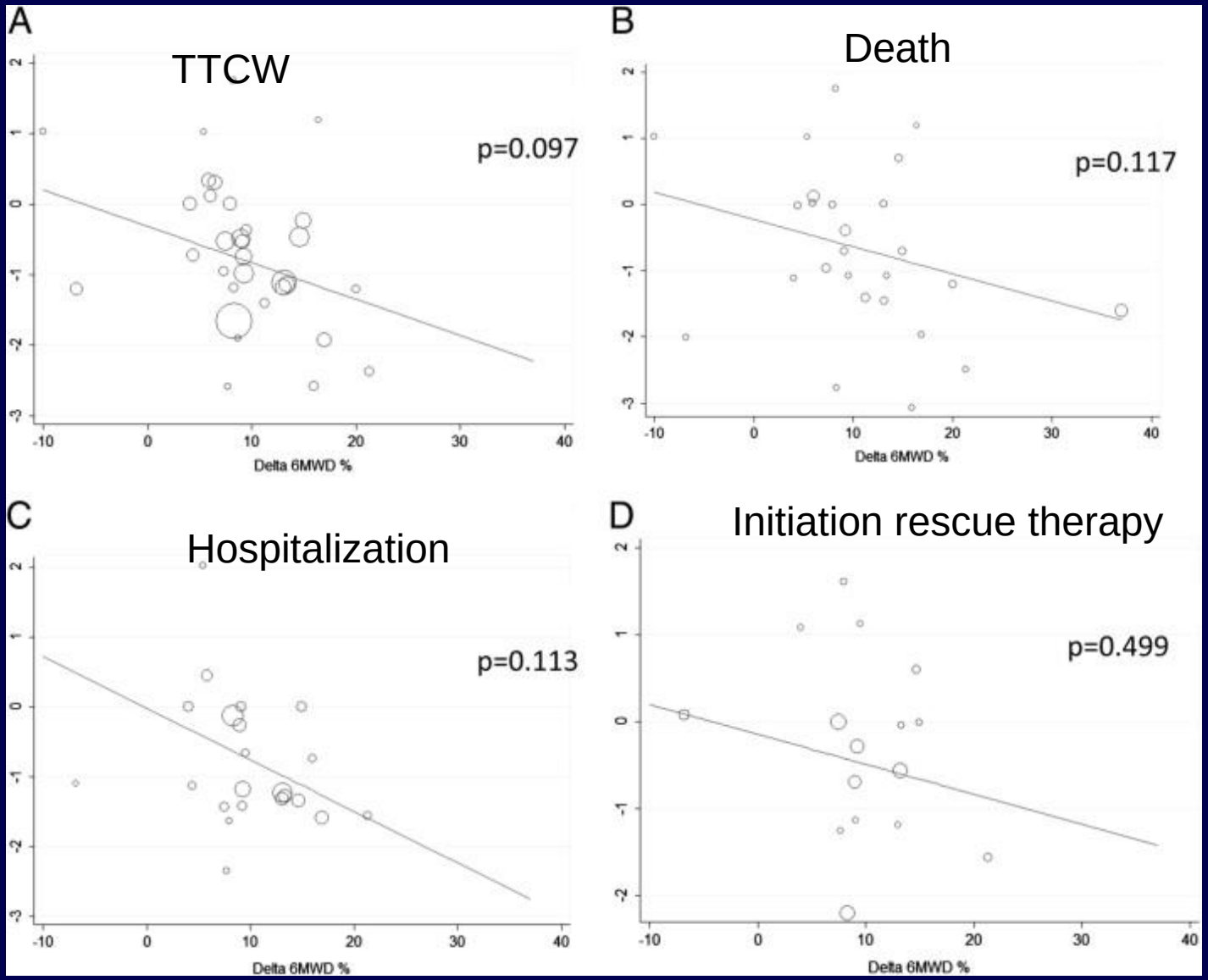
	Galié,2009	Macchia, 2010
Trials, n	21	26
PAH pts, n	3140	3519
6MWD, m	+ 36	+ 38
PAP, mmHg*	- 2.9	- 3.9
PVR, wu*	- 4.1	- 3.5
Mortality	- 43 %	- 39 %

- *** Respectively 11 and 12 trials**

Do changes in the 6MWD predict clinical events in patients with PAH?

Savarese et al, JACC 2012; 60: 1192-1201

- 32 RCT's enrolling 3112 patients
- Active treatments led to significant reductions of mortality and clinical events (> 24 h hospitalisation for PAH, rescue therapies, transplantations and death)
- Δ 6MWD was correlated to Δ PVR, but there was no relationship between Δ6MWD and outcome



Meta-Regression Analysis Meta-regression between (A) Δ6MWD and composite outcome, (B) all-cause death, (C) hospitalization for pulmonary arterial hypertension (PAH) and/or lung or heart-lung transplantation, (D) and initiation of PAH rescue

What is the explanation for this paradox?

Answer: Δs are approximately 1/10 of absolute values while SDs remain the same, thus causing an excessive decrease in signal to noise ratio

Example: A drug increases the 6MWD from 400 ± 40 m to 440 ± 40 m, P < 0.001 while the 6MWD remains at 410 ± 40 m in controls, - F value of analysis of variance P < 0.01

But on Δs: 40 +/- 40 compared to 10 +/- 40 m, P is NS

Haemodynamics, exercise capacity and clinical events in pulmonary arterial hypertension

Savarese et al, Eur Respir J 2013; 42: 414-24

- 16 RCT's enrolling 2353 patients, follow-up 16 ±11 wk
- Active treatments led to significant reductions of mortality and clinical events (> 24 h hospitalisation for PAH, rescue therapies, transplantations and death)`
- There was no relationship between Δ's of PAP, CI, PVR or RAP and outcome

There is no reason for bashing the 6-min walk test, cardiac output, or right atrial pressure, or PVR, in patients with PAH

The 6-min walk distance reflects the capability of the RV to increase flow output in response to peripheral demand

Naeije R, Chest 2010; 137(6):1258-60.

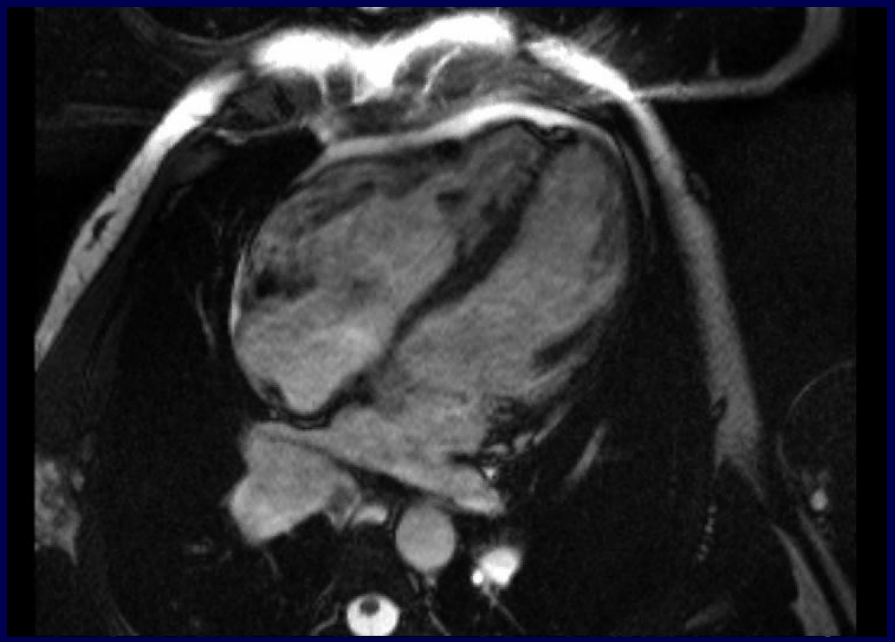
2. How the RV fails in PAH and how to measure it more specifically

RV failure in PAH: from homeometric to heterometric adaptation

Male

Age 25 yr, NYHA II

mPAP = 56 mmHg

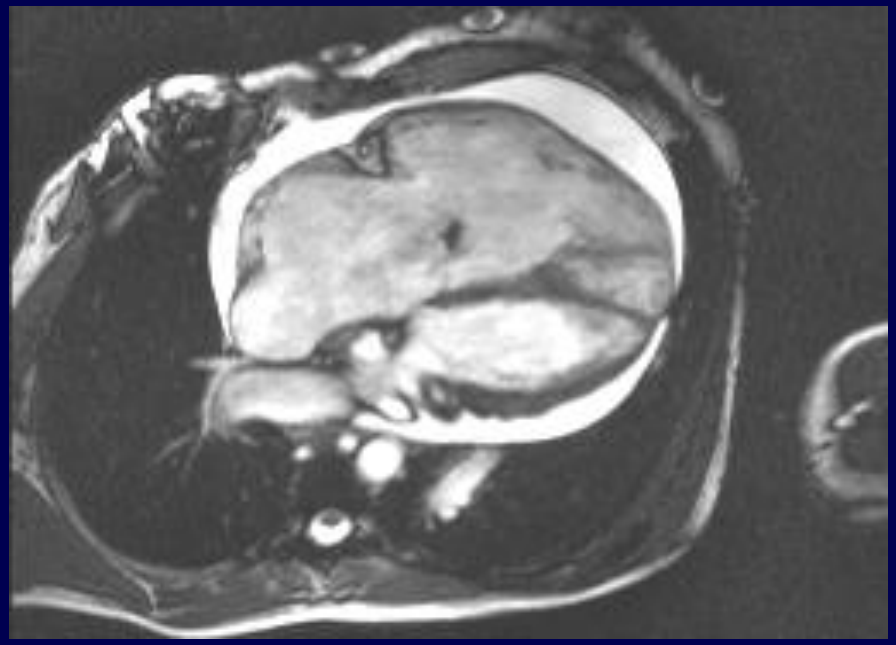


Stroke volume = 90 ml, 6MWD 550 m

Female

Age 24 yr, NYHA III

mPAP = 53 mmHg



Stroke volume = 30 ml, 6MWD 300 m

A Vonk Noordegraaf

Definition of (Right) Heart Failure in Pulmonary Hypertension

Right heart failure is a dyspnea fatigue syndrome with eventual systemic congestion caused by the insufficient adaptation of systolic function (homeometric adaptation, Anrep) to increased afterload and involvement of increased dimensions (heterometric adaptation, Starling) to maintain RV flow output adapted to metabolic demand

After Sagawa et al. Cardiac contraction and the PV relationship, Oxford University Press, 1988, Endorsed by RV summit (Boston, October 2012) and PH World Symposium (Nice, February 2013)
Vonk Noordegraaf et al, JACC 2013;62:D22–33
Naeije et al, Pulm Circ 2014; 4: 395-406

Parameters of RV function

Echocardiography

- Right atrial area[1]
- RV area[1]
- TAPSE[1,2,3]
- Tei index[4]
- Right ventricular fractional area change[3]
- Degree of tricuspid regurgitation[3]
- Pericardial effusion[5,6]
- Inferior vena cava collapsibility[7]
- Left ventricular eccentricity index[3,6]
- 3D RV strain, EF and asynchrony[8]
- RV IVV[9]
- RV dP/dt[10]

MRI

- RV ejection fraction[11,12]
- RV stroke volume[11]
- RV mass[11]
- RV volume[11]

RHC

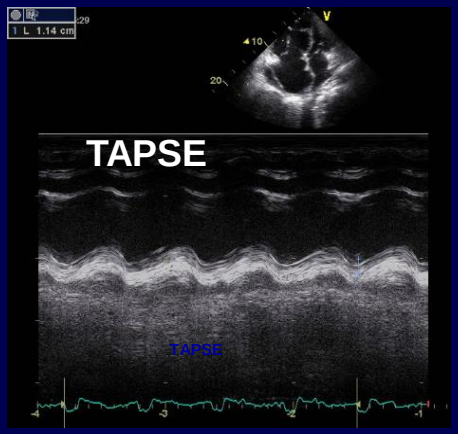
- Right arterial pressure[13,14]
- Cardiac index[14]

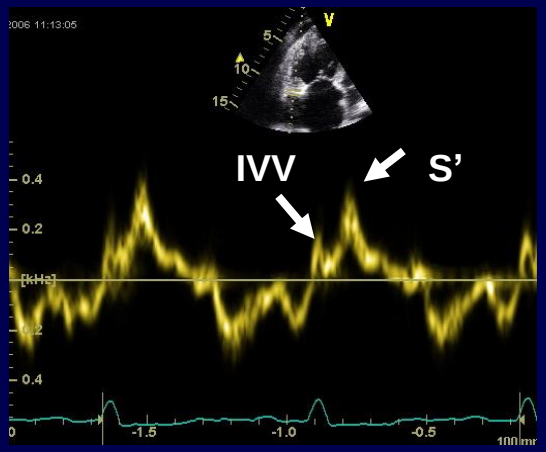
Biomarkers

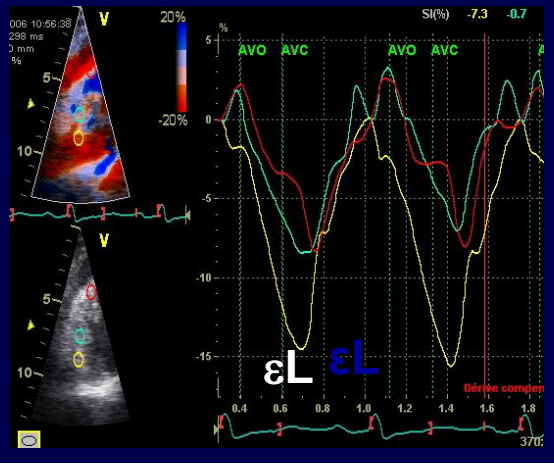
- N-terminal pro-brain natriuretic peptide[15]
- Troponin T[16]

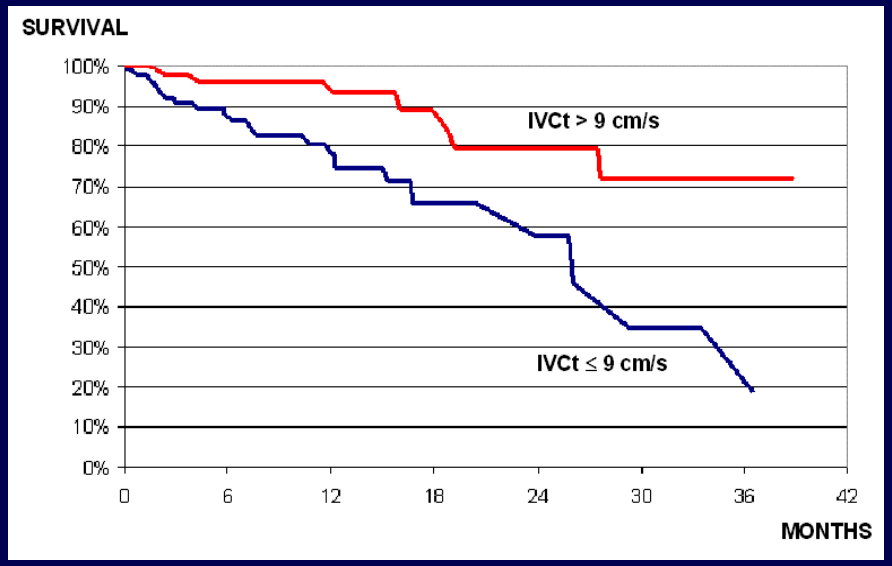
TAPSE: tricuspid annular plane systolic excursion

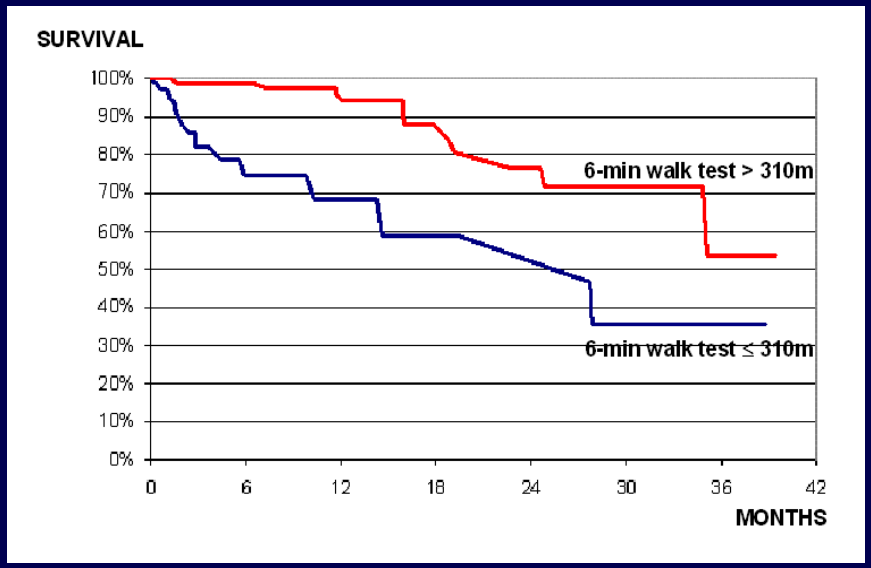
1. Grünig. *DMW* 2010. 2. Forfia lAJRCCM 2006, 3. Ghio IJC 2010. 4. Tei *J ASE* 1996. 5. ,Eysmann Circ 1989. 6. Raymond *JACC* 2002. 7. Utsunomiya *JASE* 2009. 8. Smith JACC 2014; 9. Ernande JASE 2013; 10. Ameloot EHJCI 2014, 11 van Wolferen EHJ 2007, 12. van de Veerdonk *JACC* 2011, 13. McLaughlin 2002. 14. D'Alonzo . *Ann Intern Med* 1991. 15. Nagaya. *JACC* 1998. 16. Torbicki . *Circulation* 2003.











142 pts with severe PAH (n=105) or CTEPH (n=37)

Univariate analysis: 6MWD, NYHA, EI, RA area, S, TAPSE, IVRT, εL ,IVV

Multivariate analysis: 6MWD (P<0.05) and IVV (P<0.005)

RV isovolumic contraction velocity predicts survival in PH

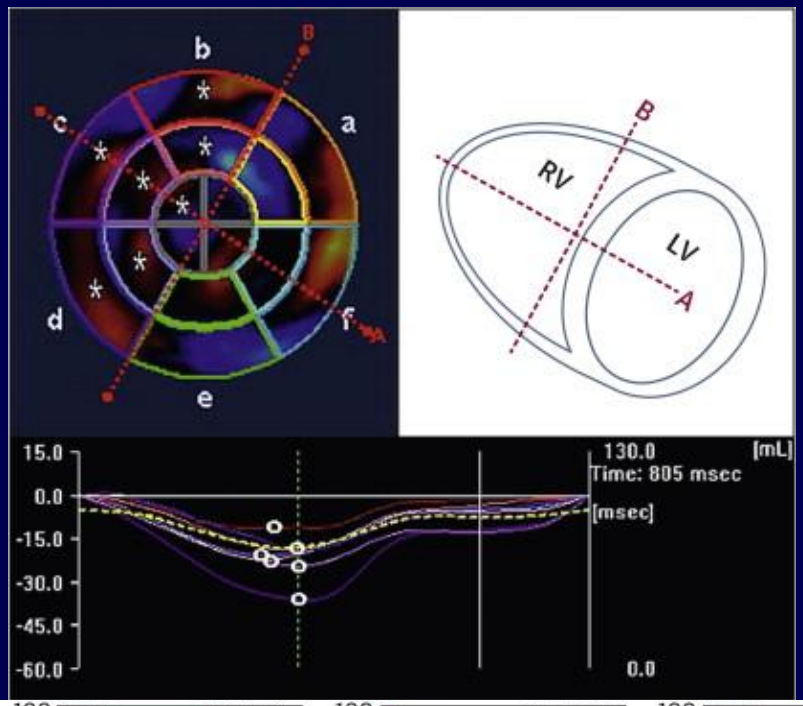
Ernande, Huez, Naeije, Derumeaux et al, JASE 2013;26:297-306

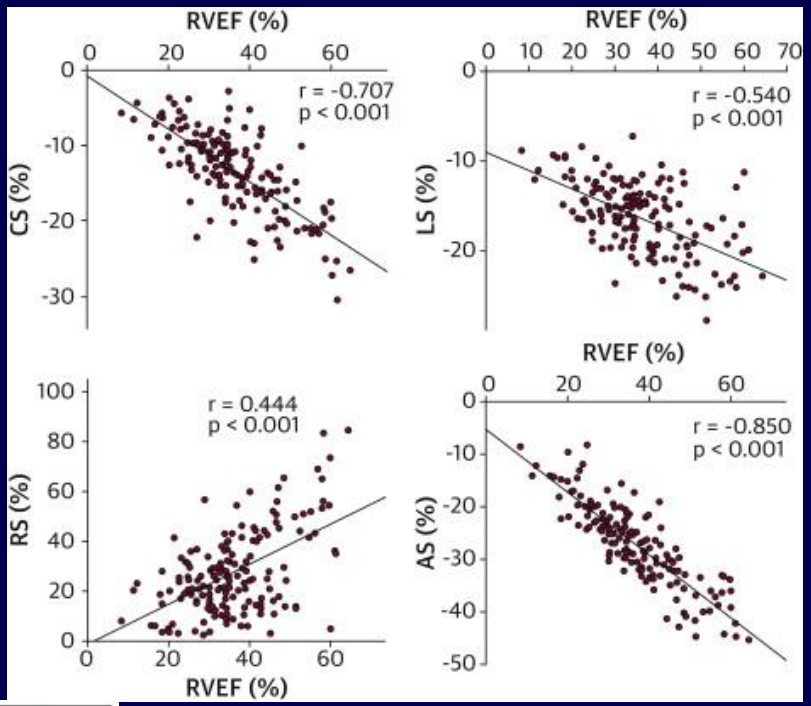
3D speckle tracking of the RV
Smith BCF et al, JACC 2014; 64: 41-51

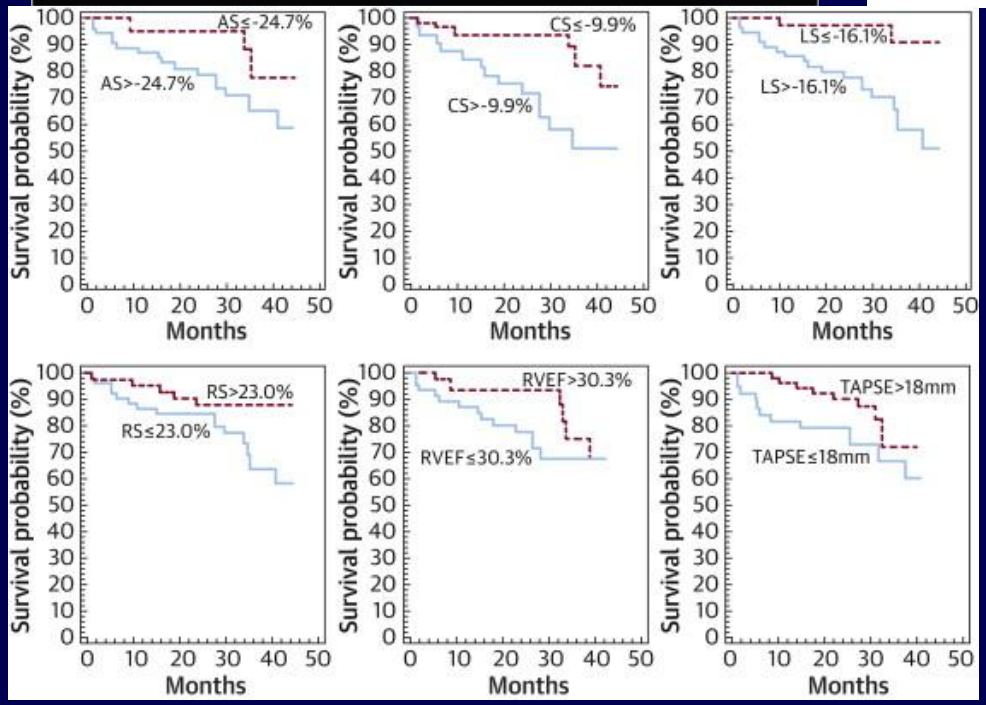
- 3D-ST > 2D-ST because it is not slice-plane limited and delivers vectorial data in 3 orthogonal planes
- 3D ST allows for optimal measurement of dyssynchrony
- 3D echo allows for RV volume measurements

- 97 patients with PH
- Area strain, circumferential strain and indices of systolic dyssynchrony (SD of mean time to peak systolic strain for 7 RV segments) strongly correlated with RVEF

- Only area strain independently predicted survival







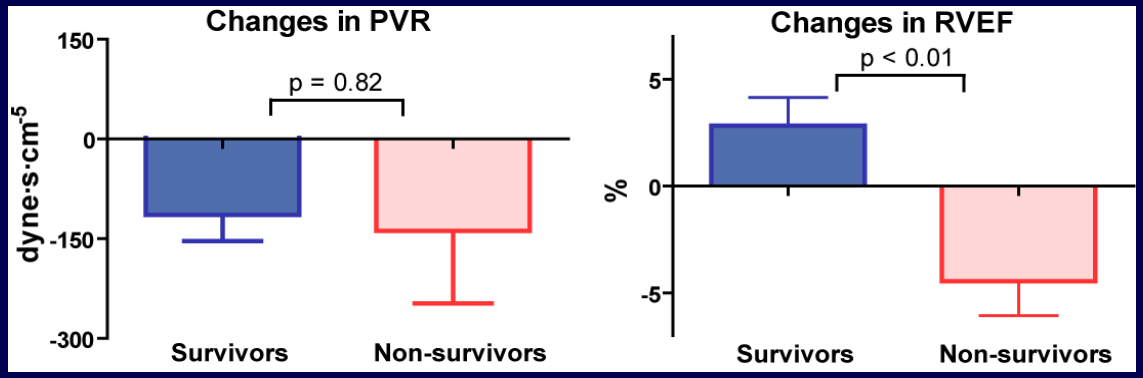
Measurements of dyssynchrony (strain/time), correlations with RVEF, and prediction of survival

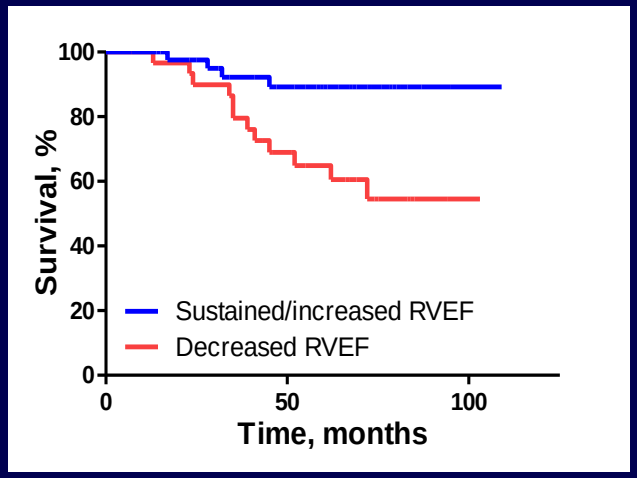
Only AS was an independent predictor of survival

Smith et al, JACC 2014; 64: 41-51

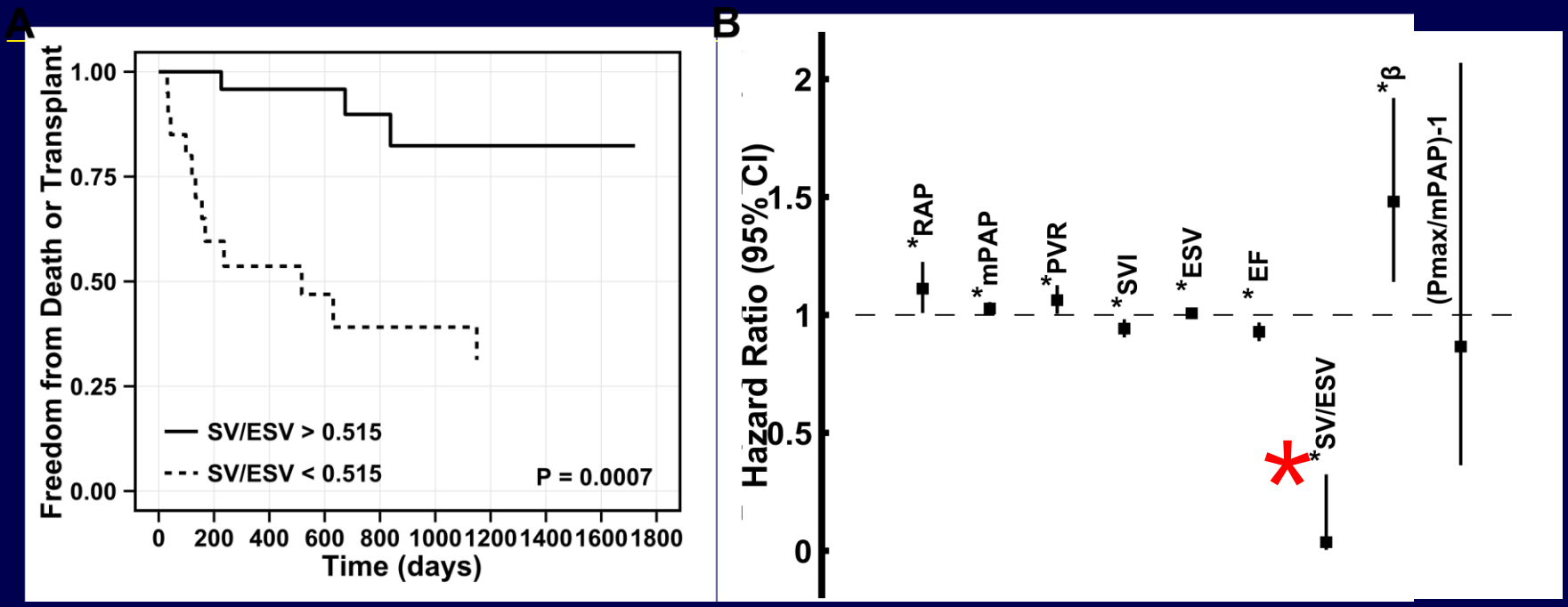
RVEF as predictor of survival in patients with PAH Van de Veerdonk et al, JACC 2011;58:2511-9

- 110 patients with incident PAH
- Baseline RVEF (hazard ratio [HR]: 0.938; p = 0.001) and PVR (HR: 1.001; p = 0.031) were predictors of mortality
- Changes in RVEF were associated with survival





RV function to predict survival in patients referred for PH Vanderpool, Naeije et al, Heart 2015; 101: 37-43

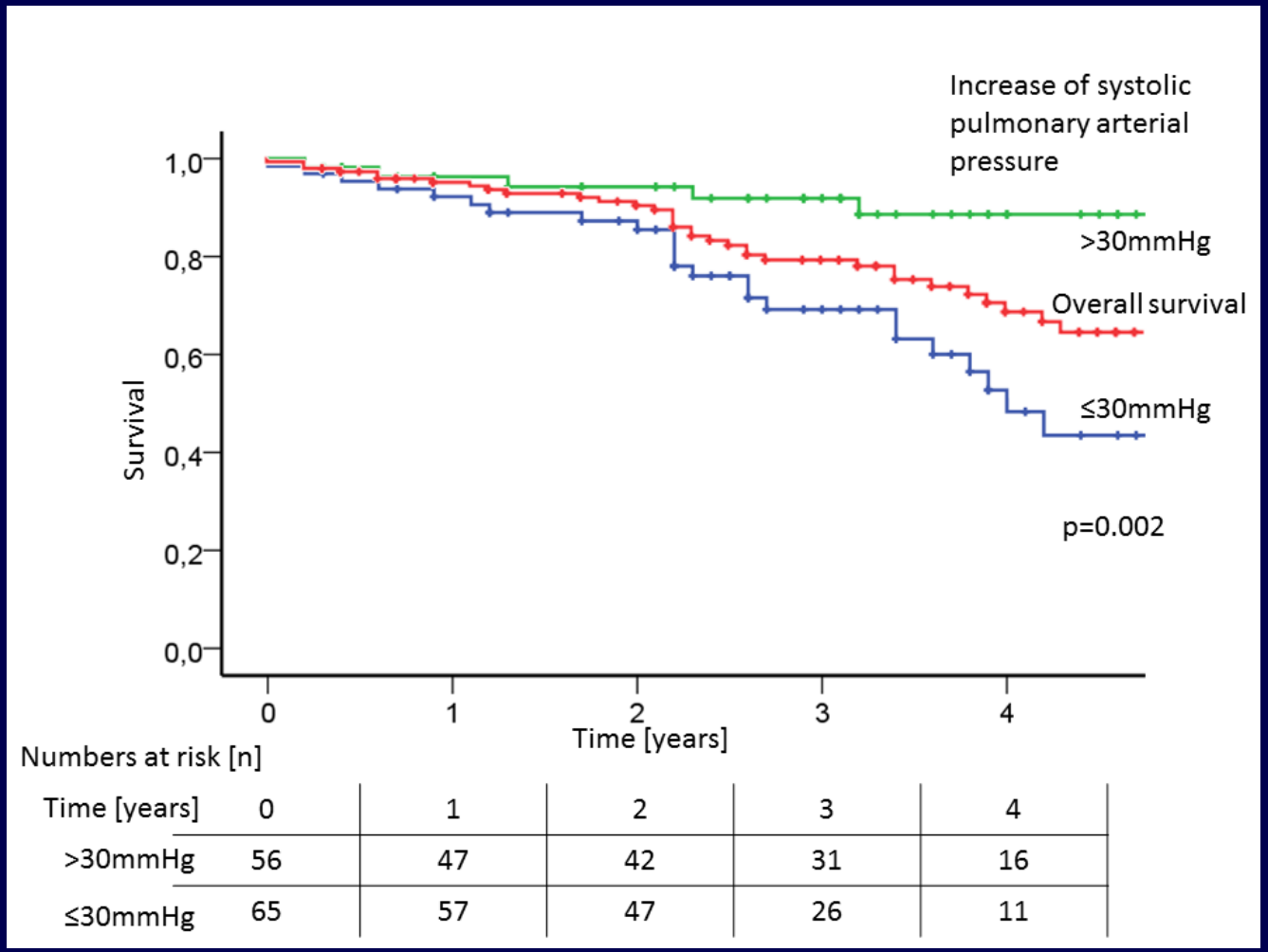


-50 patients referred for severe severe PH

-Higher RAP, mPAP, PVR and β, and lower SV, EF and Ees/Ea all predicted outcome at univariate analysis – at multivariable analysis, **SV/ESV (not SV/EDV) was the only independent predictor**

3. The emerging importance of RV contractile reserve

Prognostic relevance of RV contractile reserve in patients with PH Grunig, Naeije et al, Circulation 2013; 128:2005-15



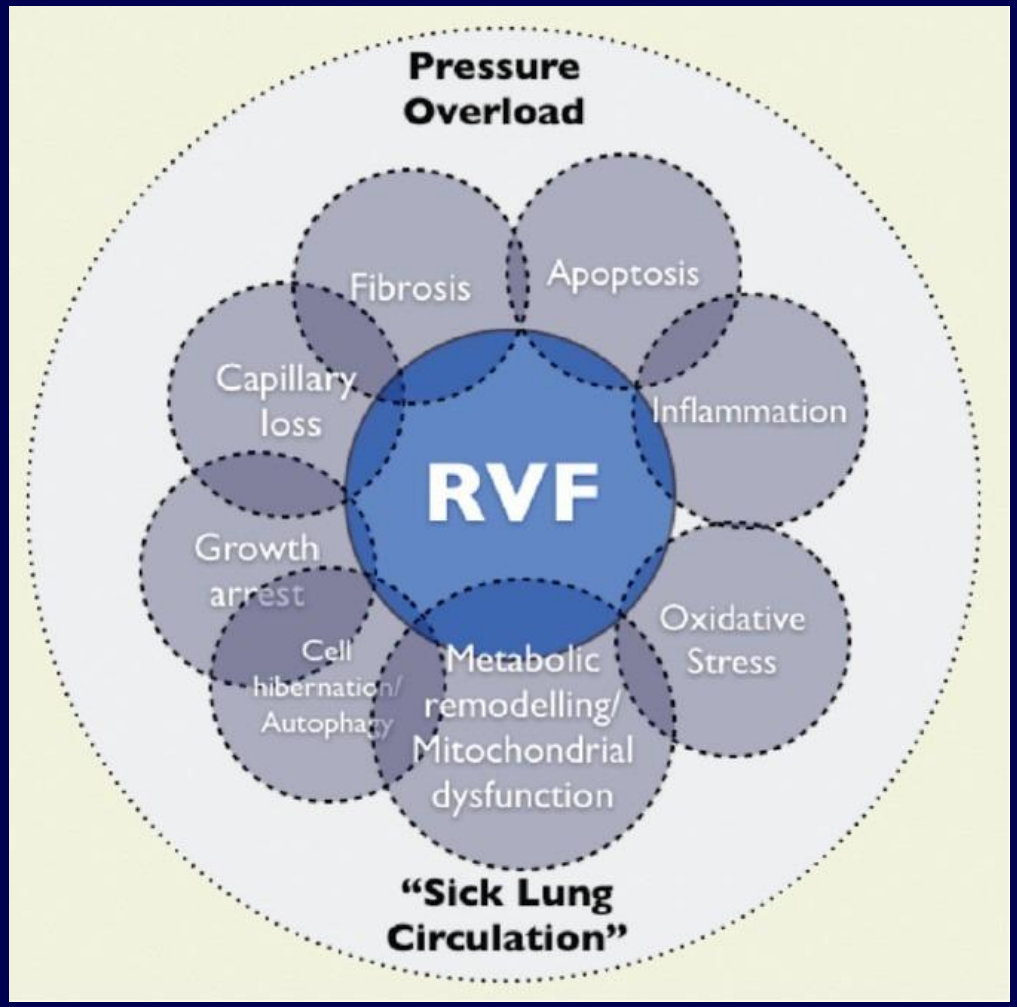
Numbers at risk [n]

Time [years]	0	1	2	3	4
>30mmHg	56	47	42	31	16
≤30mmHg	65	57	47	26	11

N=124, stress echo , contractile reserve defined by exercise-induced increase in SPAP

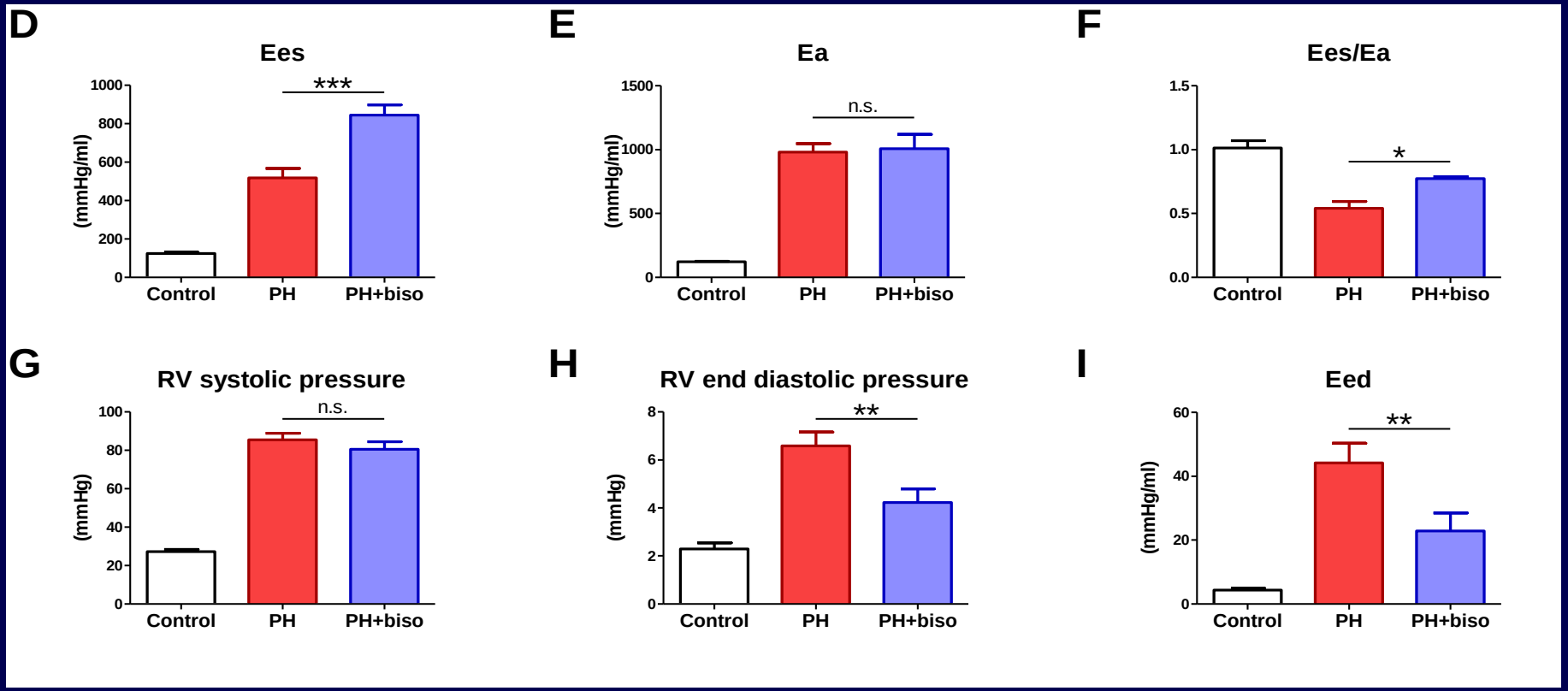
4. What is the therapeutic relevance of improved measurements of RV function?

Investigation of the mechanisms of right heart failure Voelkel et al, Pulm Circ 2013;3:137-143



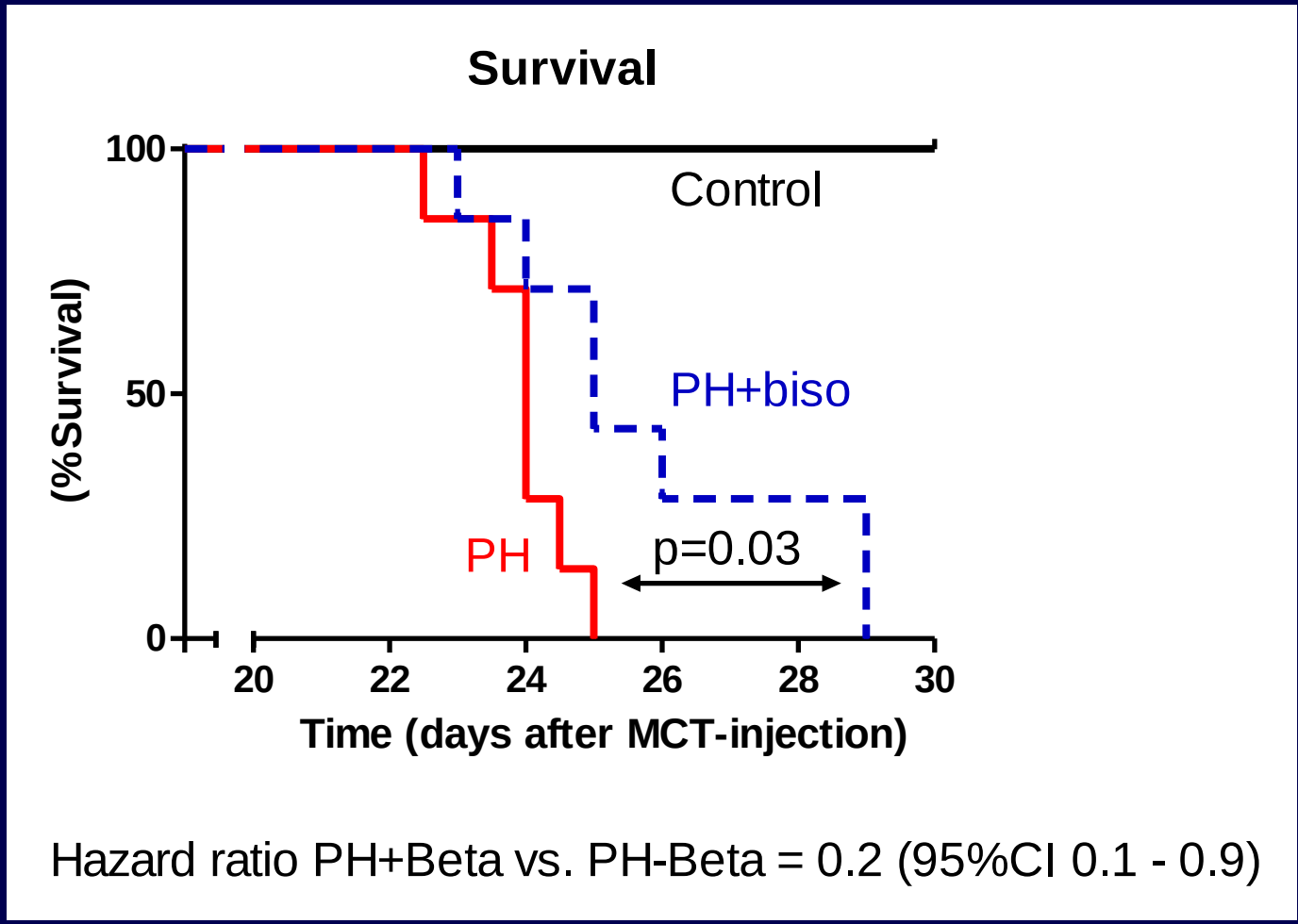
The RV between a rock and a hard place

Improved in RV-arterial coupling with bisoprolol in rats with monocrotaline-induced PH



De Man et al, Circ Heart Fail 2012;5:97-105

Improved survival with low dose bisoprolol



Hazard ratio PH+Beta vs. PH-Beta = 0.2 (95%CI 0.1 - 0.9)

De Man et al, Circ Heart Fail 2012;5:97-105

Intensify targeted therapies: upfront triple combo in PAH Sitbon O et al, Eur Respir J 2014; 43: 1691-7

- Upfront triple combo Rx i.v. epoprostenol + bosentan + sildenafil
- 18 newly diagnosed (i.e. incident) Idiopathic (11) /Heritable (7) PAH patients
- Mean age 40 ± 14 years (17 – 63)
- NYHA III (7) or IV (11) / 6MWD = 228 ± 164 m (0 – 415)

RAP, *mmHg*	13 ± 4
mPAP, *mmHg*	69 ± 16
wPAP, *mmHg*	9 ± 3
CI, $L.min^{-1}.m^{-2}$	1.7 ± 0.3
PVR, $dyn.s.cm^{-5}$	1716 ± 605
SvO_2, *%*	48 ± 10

Up-front triple combo Rx: first follow-up

- Two patients died before starting any treatment
- One patient failed and underwent urgent HLT (D118) before reassessment
- Dramatic improvement in the remaining 15 patients

N = 15	Baseline	First f-up (4 ± 1 mo.)		P-value
NYHA FC I : II : III : IV, *n*	0 : 0 : 7 : 8	1 : 13 : 1 : 0		<.001
6-min walk distance, *m*	248 ± 168	451 ± 83		<.0003
Haemodynamics				
RA pressure, *mmHg*	13 ± 5	5 ± 5		<.0002
Mean PAP, *mmHg*	67 ± 14	46 ± 14		<.0005
Cardiac index, *L/min/m²*	1.7 ± 0.3	3.6 ± 0.7		<.00001
PVR, *dyn.s.cm⁻⁵*	1604 ± 469	537 ± 228		<.00001
Mean BP, *mmHg*	92 ± 13	81 ± 12		<.002
Heart rate, *bpm*	92 ± 11	85 ± 10		.052
SvO_2, *%*	50 ± 9	70 ± 5		<.00007
Epoprostenol dose, *ng/kg/min*	0	16 ± 2		

Courtesy O Sitbon

Up-front triple combo Rx: last follow-up

- Mean follow-up = 24 ± 12 months (range: 6 - 52 mo.)
- All 15 patients alive, in NYHA class I-II
- 12 patients reassessed after 9 - 51 months

N = 12	Baseline	First f-up (4 ± 1 mo.)	Last f-up (23 ± 12 mo.)	P-value
NYHA FC I : II : III : IV, *n*	0 : 0 : 5 : 7	0 : 12 : 0 : 0	2 : 10 : 0 : 0	<.001
6-min walk distance, *m*	242 ± 160	449 ± 52	490 ± 39	<.01
Haemodynamics				
RA pressure, *mmHg*	13 ± 5	5 ± 5	6 ± 5	<.001
Mean PAP, *mmHg*	65 ± 15	46 ± 14	43 ± 12	<.05
Cardiac index, *L/min/m²*	1.7 ± 0.3	3.6 ± 0.6	3.7 ± 0.7	<.01
PVR, *dyn.s.cm^{-5}*	1603 ± 505	534 ± 206	475 ± 233	<.01
Mean BP, *mmHg*	92 ± 14	80 ± 10	85 ± 20	NS
Heart rate, *bpm*	95 ± 11	85 ± 11	81 ± 13	<.01
SvO_2, *%*	51 ± 9	70 ± 4	72 ± 6	<.01
Epoprostenol dose, *ng/kg/min*	0	16 ± 1	18 ± 4	

Courtesy O Sitbon

Conclusions

1. The WSPH 2013 in Nice underscored that P(A)H is a RVF syndrome

2. Measurements of RV function best include volumes and indices of systolic function and dyssynchrony – optimal method likely to become 3D echo – or MRI

3. Better measurements of the RV will likely improve current therapeutic approaches to patients with PAH