Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης
Α΄ Καρδιολογική Κλινική ΑΧΕΠΑ
Ιατρείο Πνευμονικής Υπέρτασης

Απεικόνιση στη Πνευμονική Υπέρταση: από το screening στην αξιολόγηση του κινδύνου και την παρακολούθηση των ασθενών

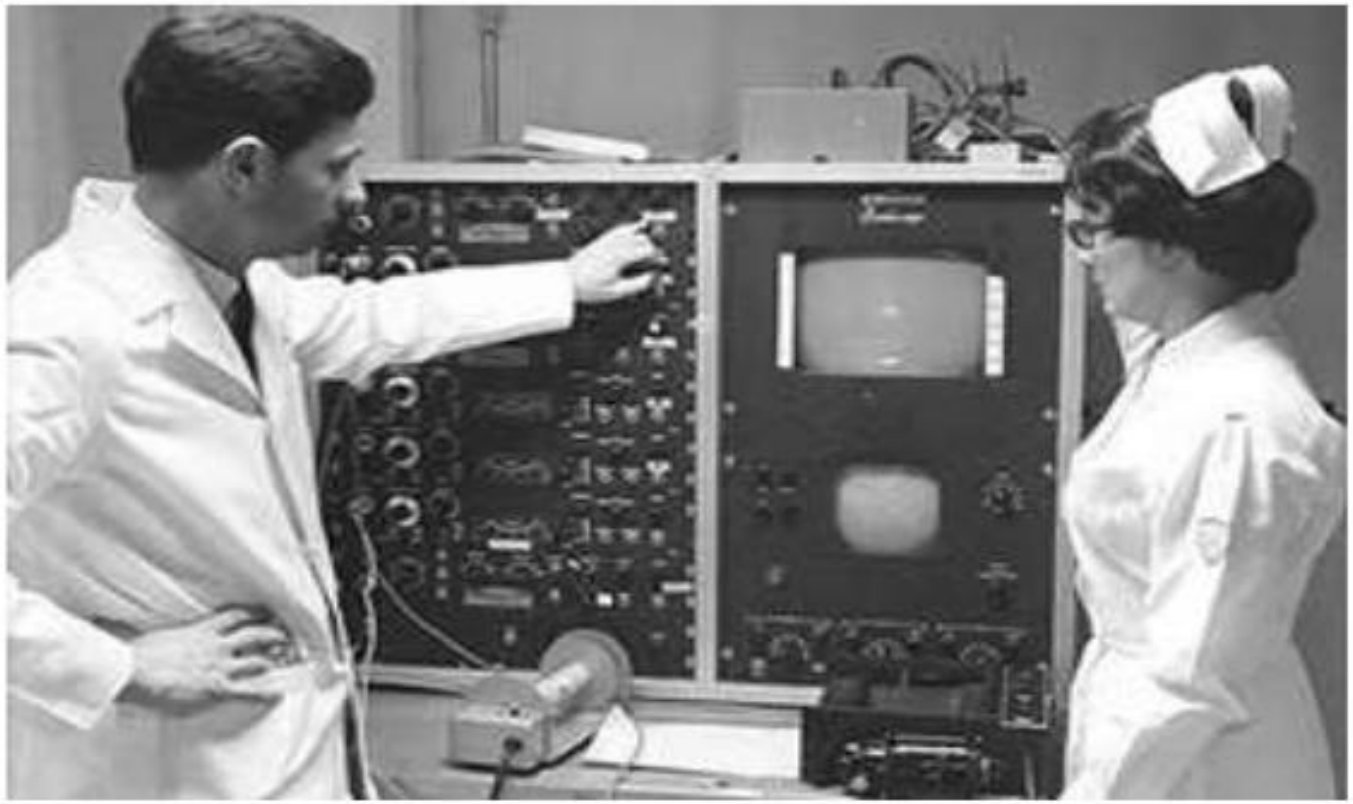
Υπερηχογράφημα καρδιάς

Σοφία Αναστασία Μουράτογλου
Ειδ/νη Καρδιολογίας

Conflict of interest

- None

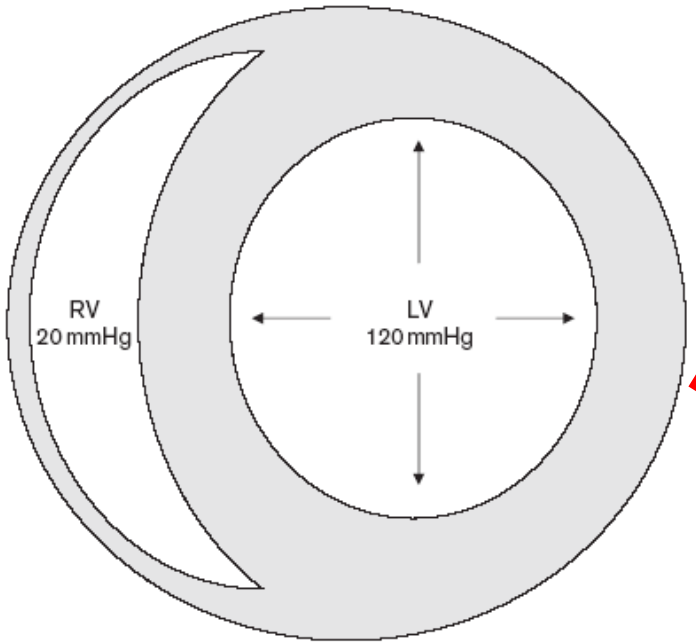
The history of Echocardiography

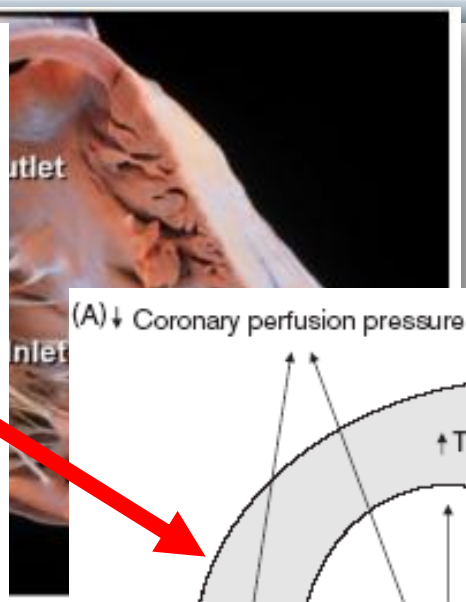


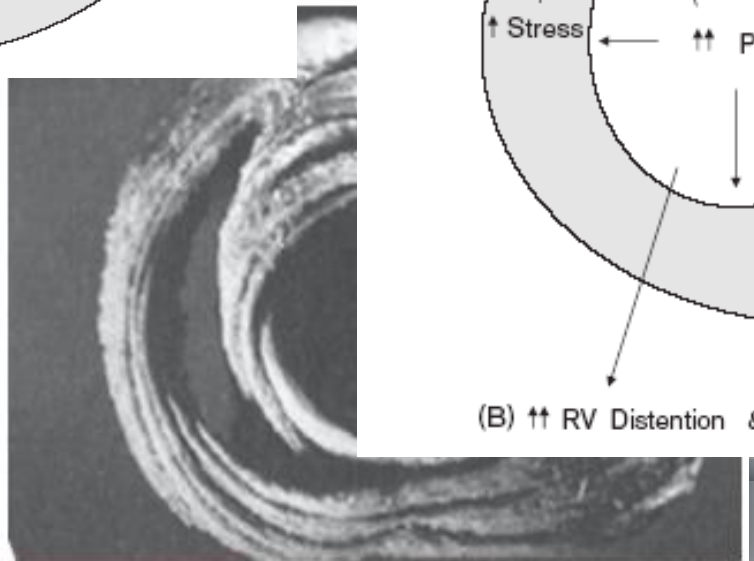
Dr. Feigenbaum with an early echocardiography machine at the IU School of Medicine. | Photo courtesty the Krannert Institute of Cardiology

Edler I and Lindstrom K, Ultrasound Med Biol 2004
Siddharth S and Abha G, Tex Heart Inst J 2007

The effect of PH on the heart…







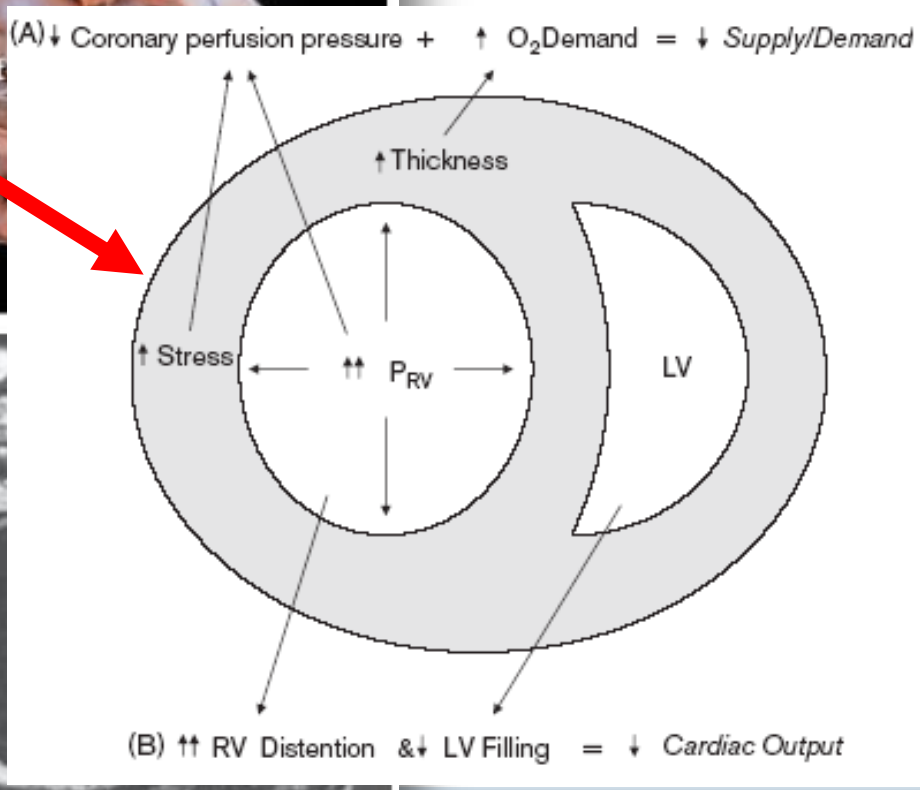
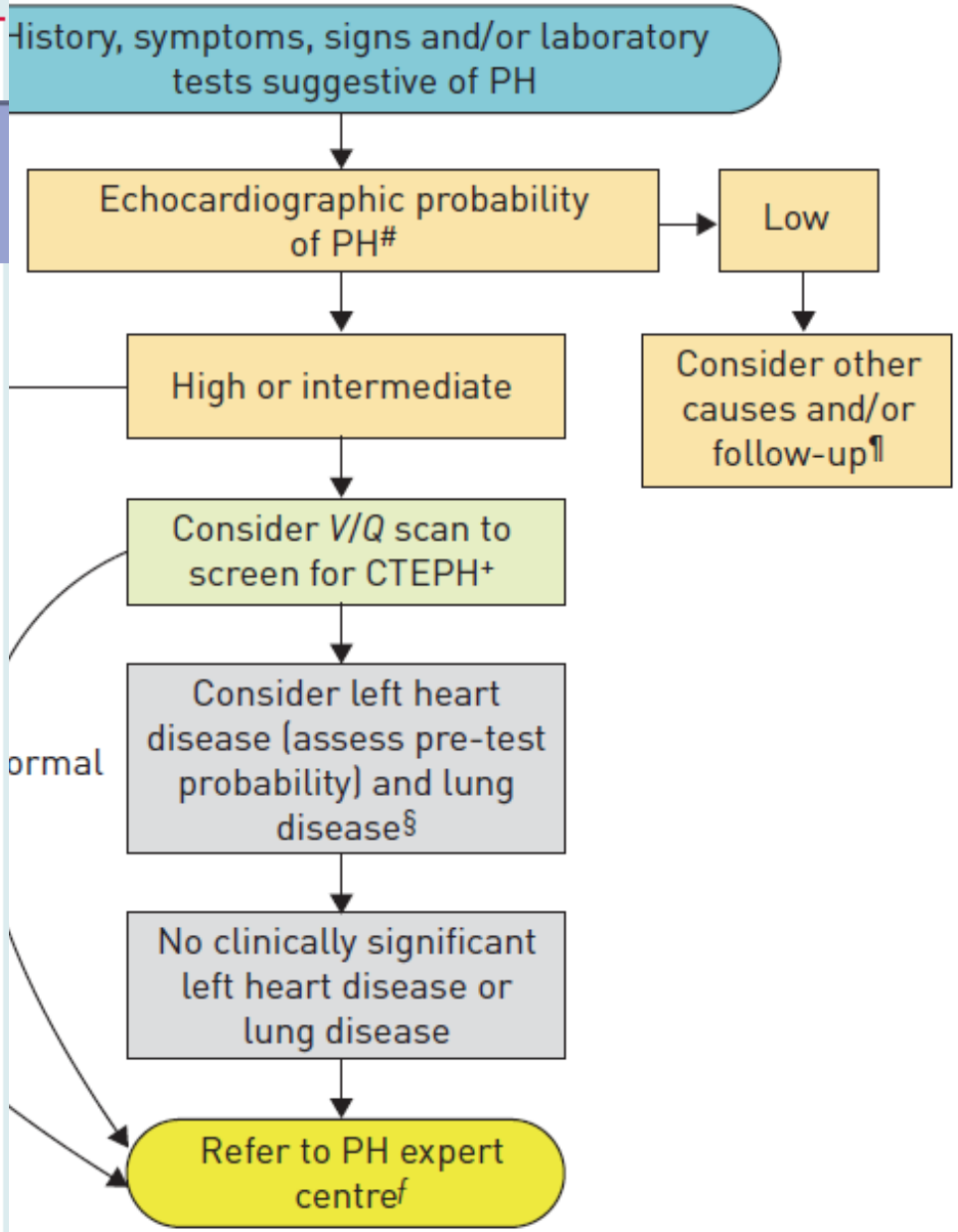


Table 12 Recommendations for diagnostic strategy

Recommendations	Class[a]	Level[b]	Ref.[c]
Echocardiography is recommended as a first-line non-invasive diagnostic investigation in case of suspicion of PH	I	C	
Ventilation/perfusion or perfusion lung scan is recommended in patients with unexplained PH to exclude CTEPH	I	C	47
Contrast CT angiography of the PA is recommended in the workup of patients with CTEPH	I	C	93
Routine biochemistry, haematology, immunology, HIV testing and thyroid function tests are recommended in all patients with PAH to identify the specific associated condition	I	C	
Abdominal ultrasound is recommended for the screening of portal hypertension	I	C	67
Lung function test with DLCO is recommended in the initial evaluation of patients with PH	I	C	36
High-resolution CT should be considered in all patients with PH	IIa	C	94
Pulmonary angiography should be considered in the workup of patients with CTEPH	IIa	C	
Open or thoracoscopic lung biopsy is not recommended in patients with PAH	III	C	



Galie N et al, Eur Heart J 2015
Frost A et al, Eur Respir J 2019

A: The ventricles[a]	B: Pulmonary artery[a]	C: Inferior vena cava and right atrium[a]
Right ventricle/ left ventricle basal diameter ratio >1.0	Right ventricular outflow Doppler acceleration time <105 msec and/or midsystolic notching	Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 % with a sniff or <20 % with quiet inspiration)
Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/sec	Right atrial area (end-systole) >18 cm^2
	PA diameter >25 mm.	

Galie N et al, Eur Heart J 2015

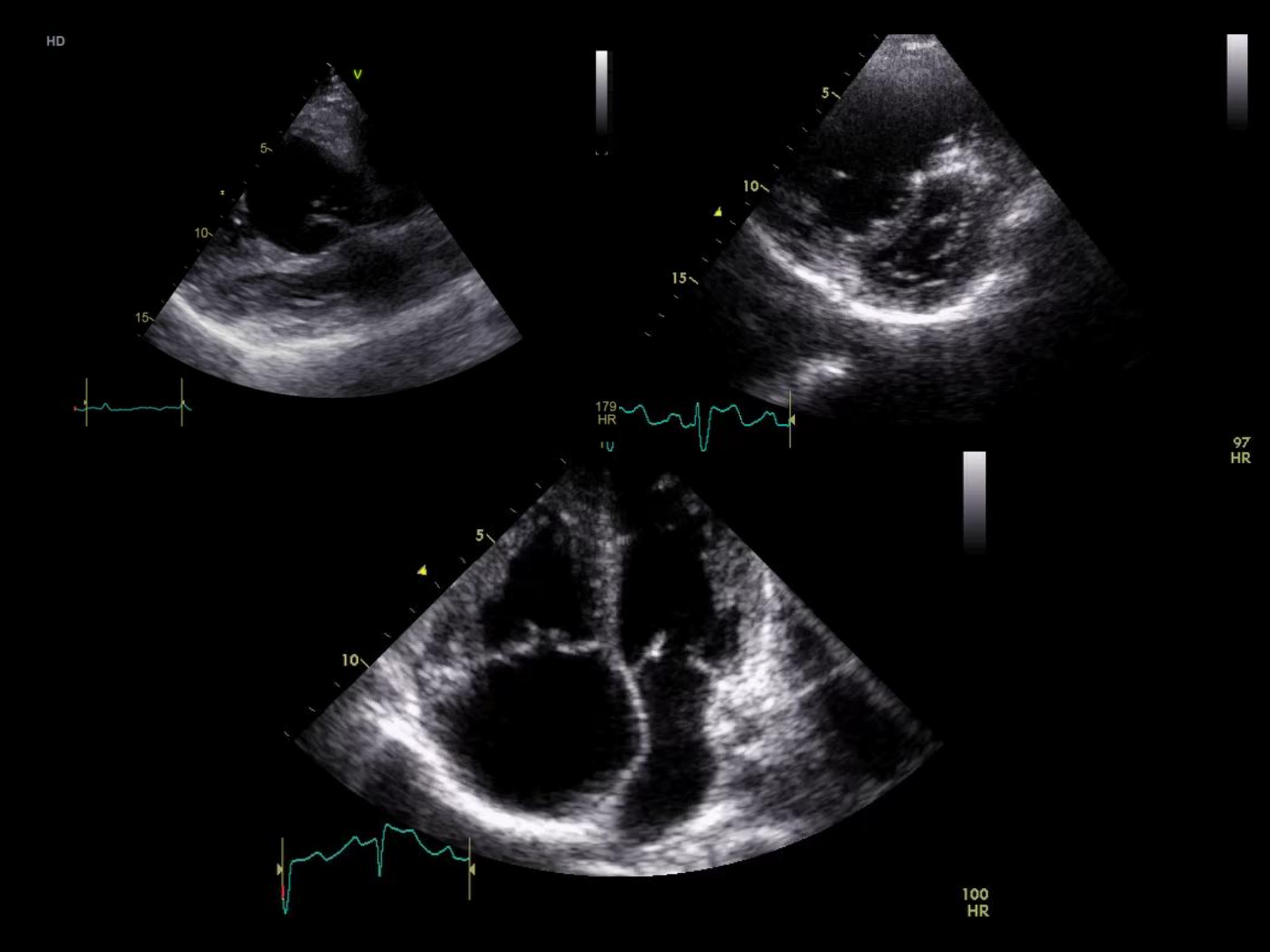
Table 4 Summary of abnormal right heart measurements in pulmonary hypertension [1,8].

Measurement	Abnormal
TR velocity	>2.8 m/s
PASP	>40 mmHg
PR initial velocity	>2.2 m/sec
RV basal diameter	>42 mm
RV mid diameter	>35 mm
RVOT PSAX distal diameter	>27 mm
RA end-systolic area	>18 cm^2
TAPSE	<17 mm
RV S′	<10 cm/s
Pulsed Doppler RIMP	≥0.44
Tissue Doppler RIMP	≥0.55
FAC (%)	<35%
3D right ventricular assessment:	
End diastolic volume	≥87 ml/m^2 (male); ≥74 ml/m^2 (female)
End systolic volume	≥45 ml/m^2 (male); ≥36 ml/m^2 (female)
Ejection fraction	<45%
RV subcostal wall thickness	>0.5 cm

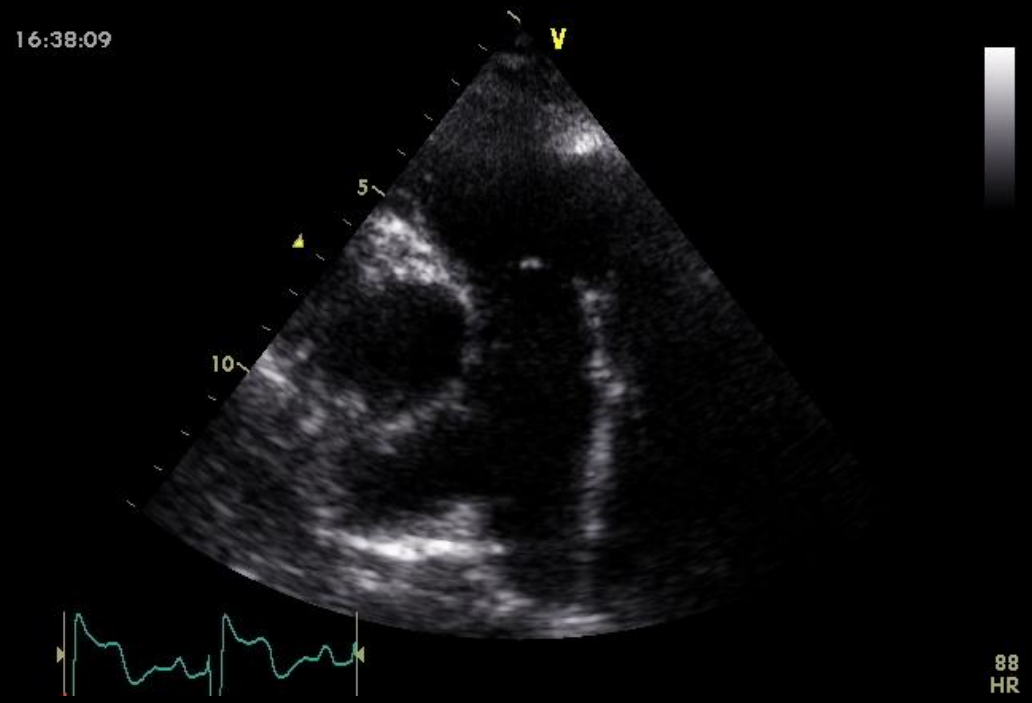
Cordina RL, et al. Heart Lung Circ J 2019

Echo in PAH

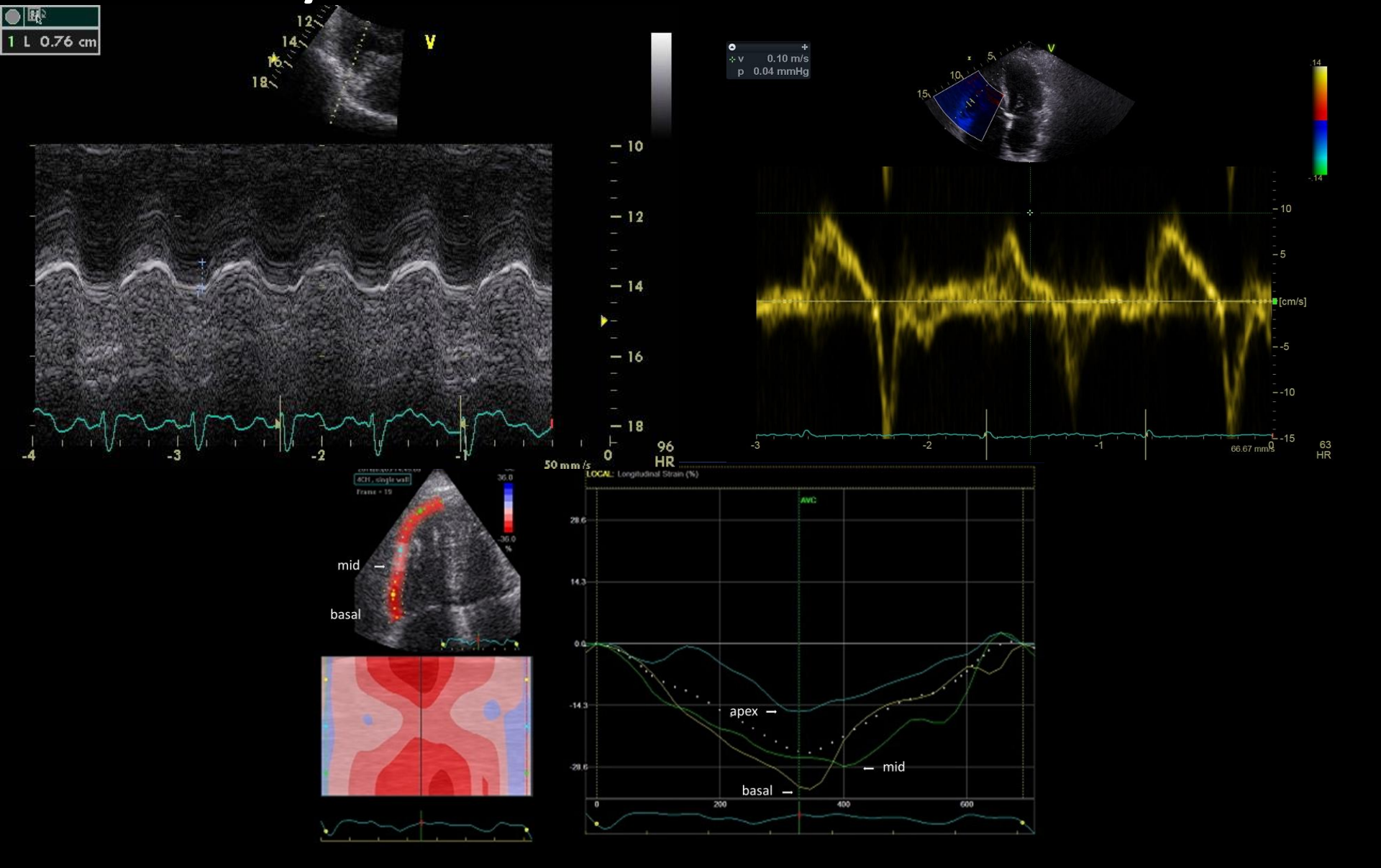
- Echocardiographic techniques can be employed to
  - derive indirect information about right heart structure and function

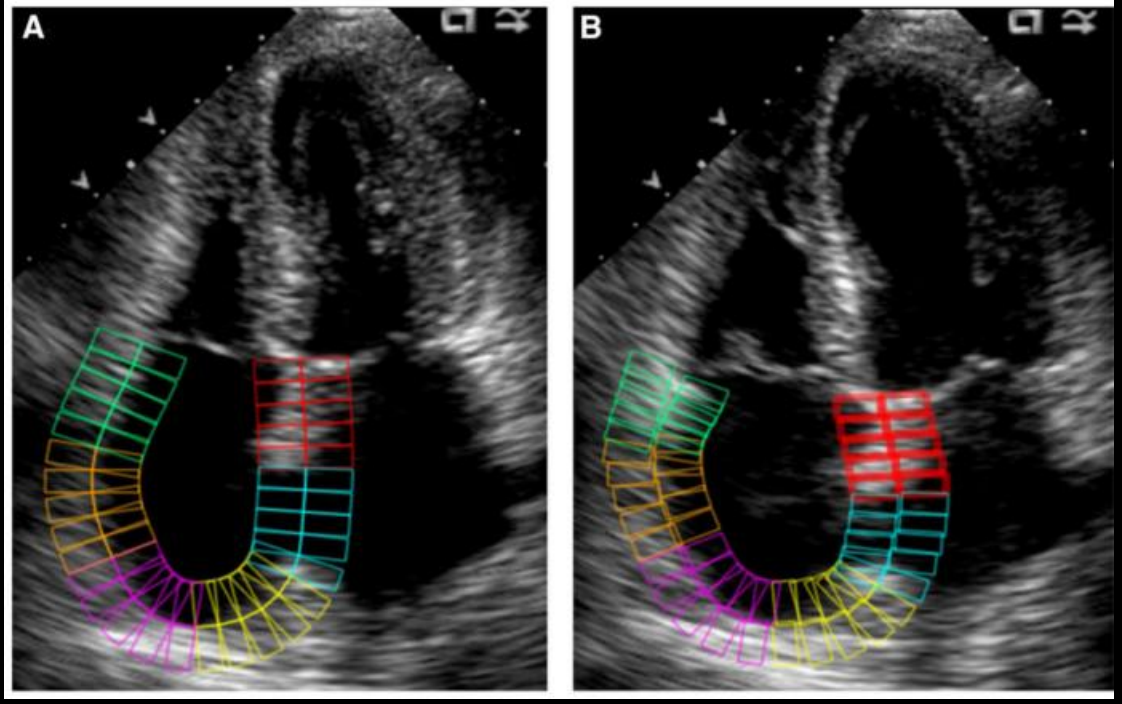

HD
5
10
15
179
HR
97
HR
100
HR


18-03-23-181424
PHILIPS HEALTHCARE
18:23:32
HD
adult GR7
S4-2
MI 1.3
TIS 1.0
H3 Gn 68
232dB/C2
D/2/1
28Hz 21cm
P T R
1.9 3.8


16:38:09
V
5
10
88
HR

RV systolic function assessment

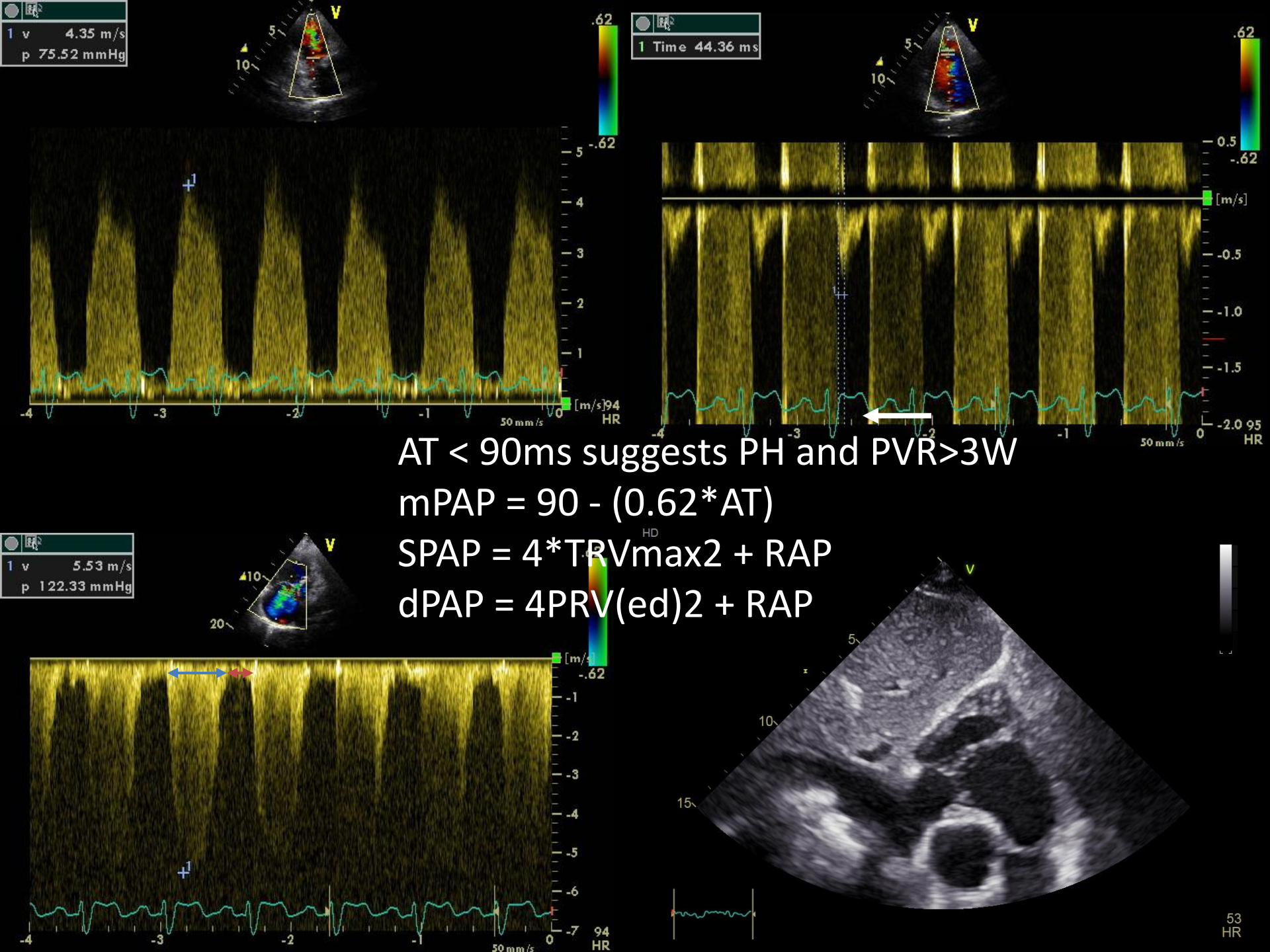




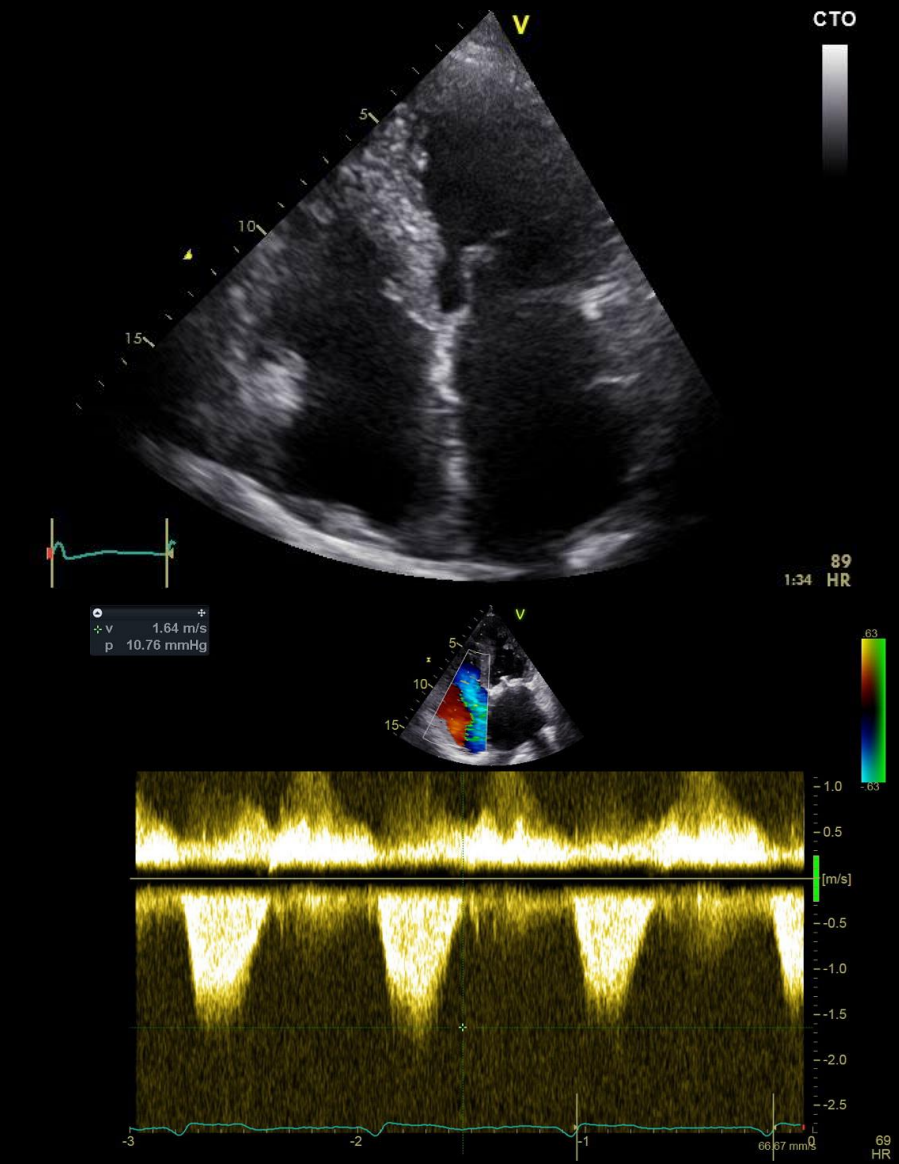
Bhave N et al, Int J Cardiovasc Imaging 2018
Piccinino C et al, J Cardiovasc Med 2017
Weiwei L et al, Heart, Lung Circ 2017
Meng X et al, Int J Cardiol 2017

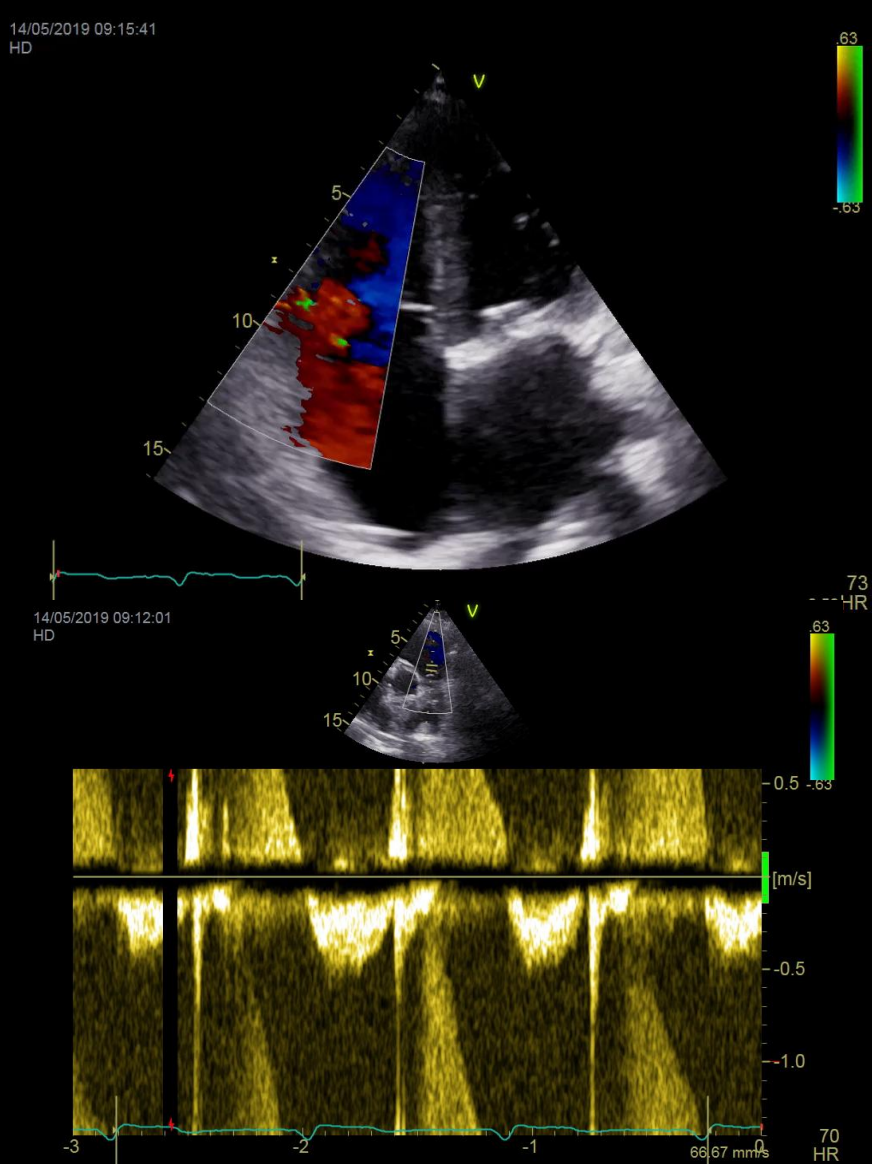
Echo in PAH

- Echocardiographic techniques can be employed to
  - derive indirect information about right heart structure and function
  - estimate PAP, PVR, RAP


1 v 4.35 m/s
p 75.52 mmHg
1 Time 44.36 ms
AT < 90ms suggests PH and PVR>3W
mPAP = 90 - (0.62*AT)
SPAP = 4*TRVmax2 + RAP
dPAP = 4PRV(ed)2 + RAP
1 v 5.53 m/s
p 122.33 mmHg
HD
50 mm/s
HR

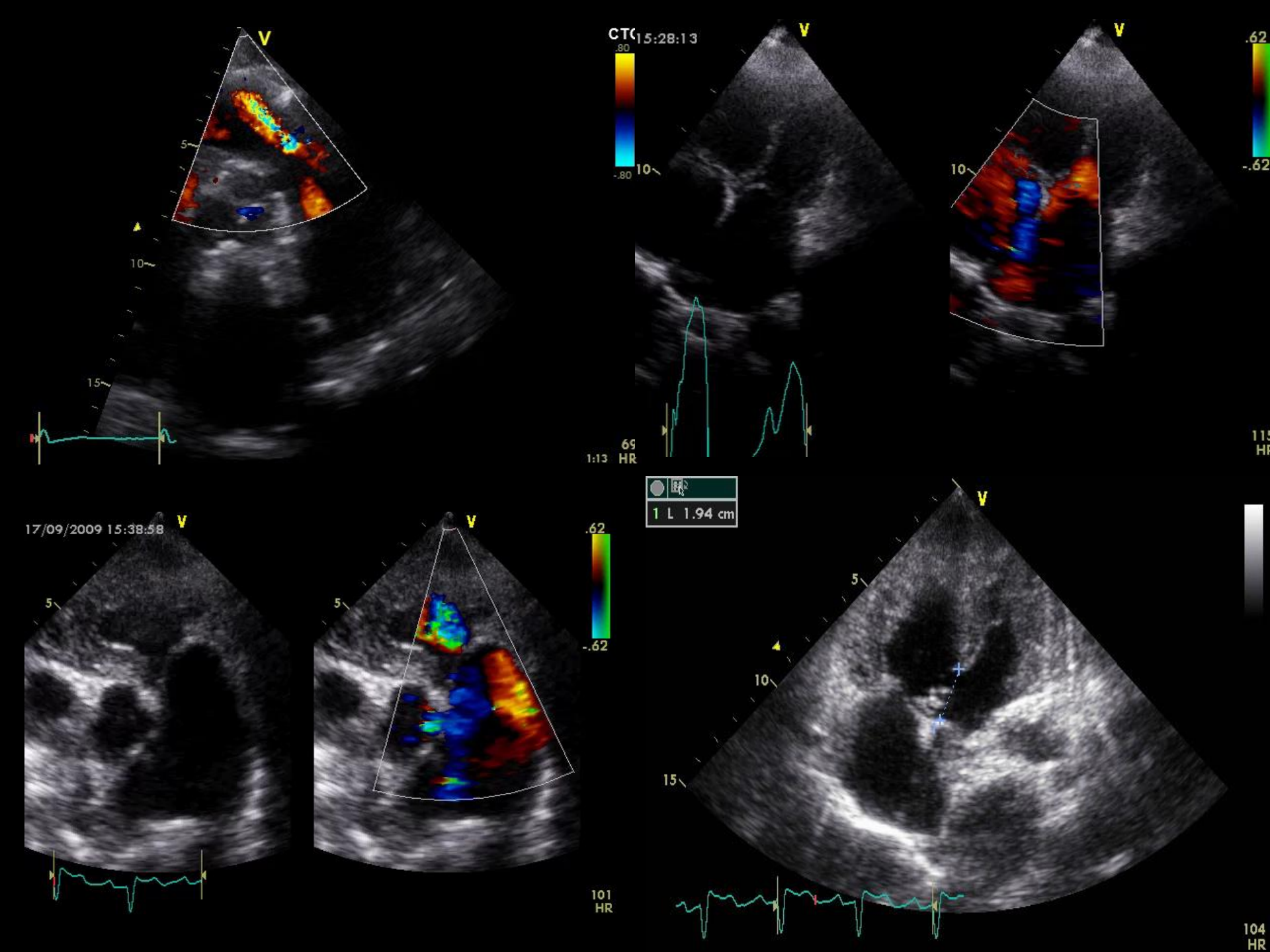
TRV estimation CAVES



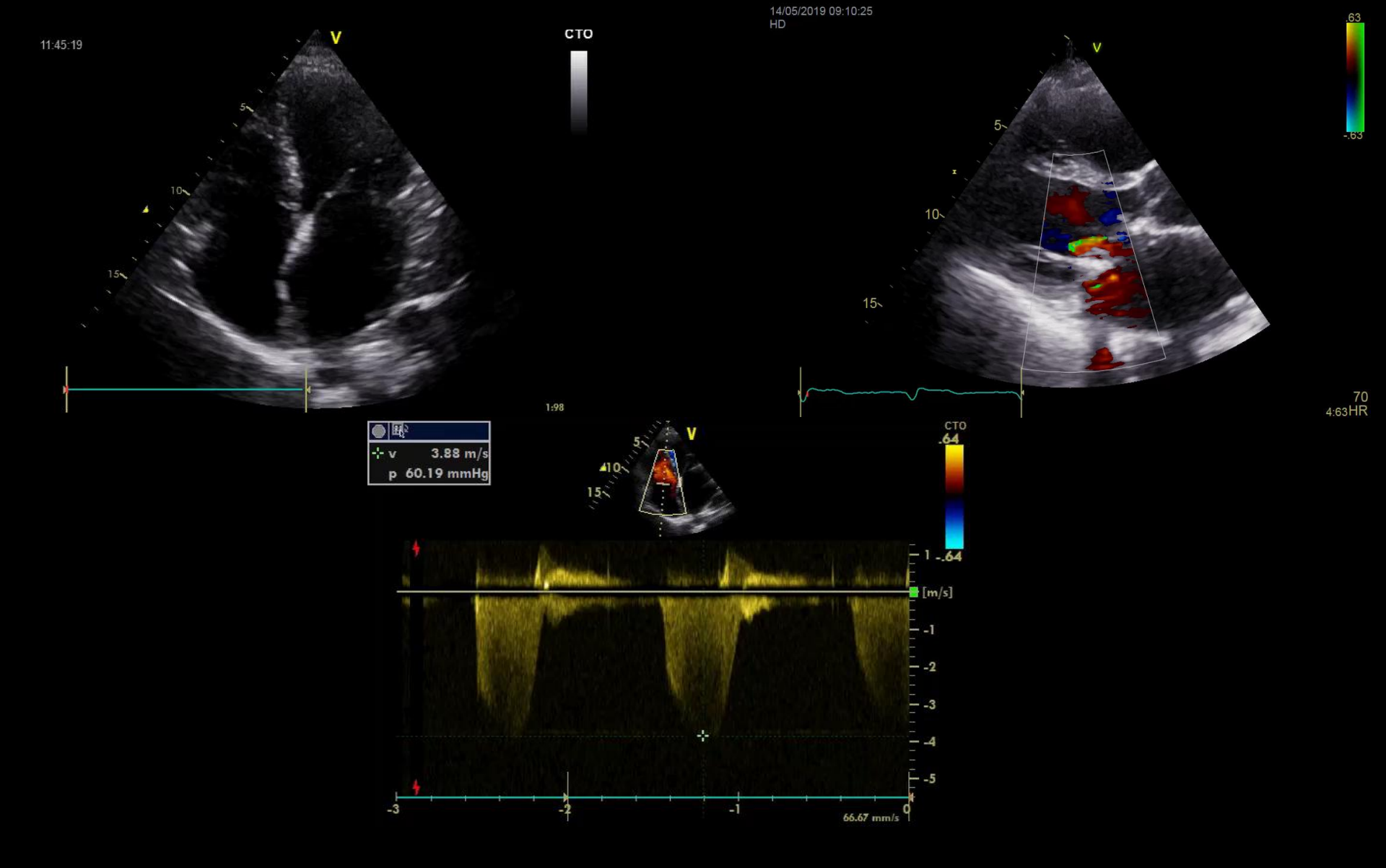


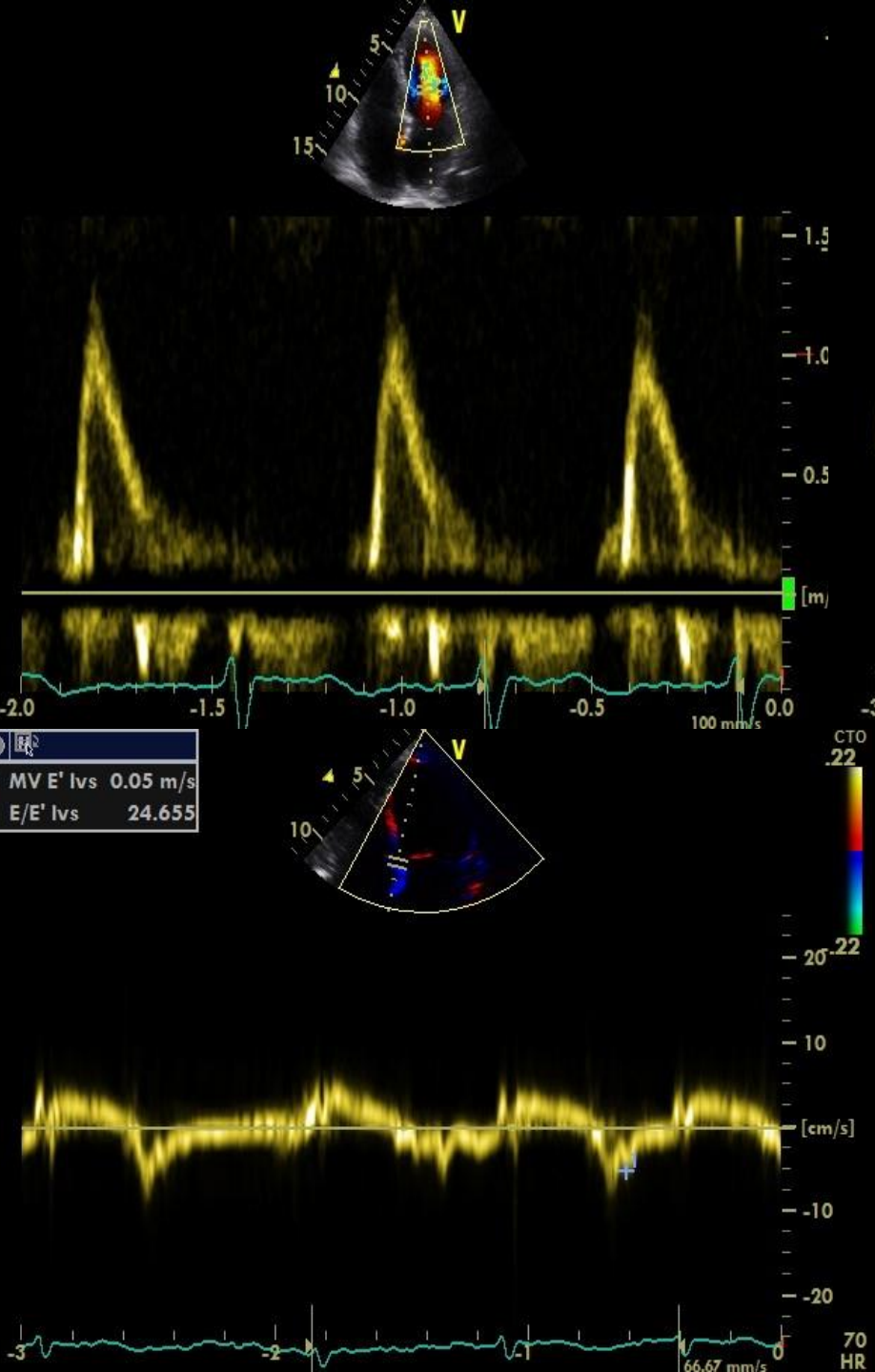
Echo in PAH

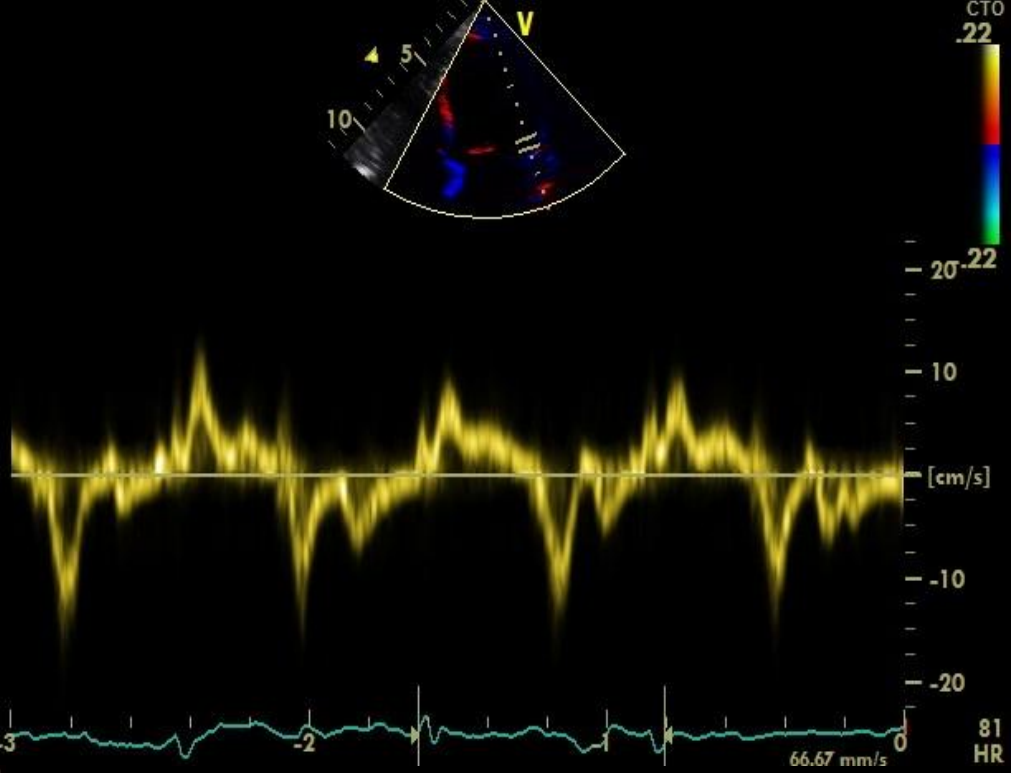
- Echocardiographic techniques can be employed to
  - estimate PAP, PVR, RAP
  - derive indirect information about right heart structure and function
  - identify possible causes such as left heart or congenital heart disease


V
5
10
15
.80
-.80
15:28:13
1 L 1.94 cm
.62
-.62
17/09/2009 15:38:58
101
HR
104
HR

Echo LHD


11:45:19
14/05/2019 09:10:25
HD
CTO
.63
-.63
70
4:63HR
v 3.88 m/s
p 60.19 mmHg
CTO
.64
-.64
[m/s]
66.67 mm/s





- E= 1.25 m/s
- E septal= 0.05 m/s
- E lateral= 0.14m/s

Echo in PAH

- Echocardiographic techniques can be employed to
  - estimate PAP, PVR, RAP
  - derive indirect information about right heart structure and function
  - identify possible causes such as left heart or congenital heart disease
  - monitor treatment response

TABLE 2 Association of PAH Therapy and Echocardiographic RV Parameters

Medication	Specific Drug (Ref. #)	Imaging Tool	Study Design	n	Parameter
Prostacyclins and prostanoids	Parenteral prostacyclin analogues (32)	Echo	1 year follow-up Not placebo controlled	48	Significant improvement in: RVEDA, RVED mid-cavity, TAPSE, RAA, PVR
	Epoprostenol (9)	Echo	12 weeks	81	
	Epoprostenol (43)	Echo	1 year	7	Significant changes in: RA size, diastolic eccentricity index, pericardial effusion score
	Epoprostenol (53)	Echo	Follow-up 5.9 ± 4.6 months	16	Significant change in MPI ($p = 0.05$). RV size and TR severity did not significantly change
Endothelin receptor antagonist	Bosentan	Echo			Significant change in RV size (qualitatively assessed) No significant change in MPI and TR Vmax
	Bosentan BREATH-1 study (19)	Echo	16 weeks of treatment	85 (56 treated)	Change in RV systolic eccentricity ($p = 0.03$) No change in TRV, RVEDA, RV diastolic eccentricity
Combined therapy	Bosentan & prostanoid (54)	Echo	8 ± 3 months Not placebo controlled	37	Significant changes in TAPSE, RV strain, RV strain rate, MPI
	Conventional therapy+ prostacylcine (40)	Echo	12 weeks	N = 81, N = 40 on combined therapy	Significantly greater change in RVEDA, systolic and diastolic eccentricity index in combined arm. No comment on combined group changes between baseline and follow-up
	Sildenafil versus bosentan (47)	CMR and echo	16 weeks	25 (13 sildenafil, 12 bosentan)	Significant change in RV mass with sildenafil, not shown with bosentan No significant change in Tei index
	Predominantly ERA (35)	CMR and echo	12 months	91	Significant change in ejection fraction ($p = 0.0001$). No significant change in RVEDVI ($p = 0.22$) or RVmass ($p = 0.68$)

CMR = cardiac magnetic resonance; ERA = endothelin receptor antagonist; MPI = myocardial performance index; PAH = pulmonary artery hypertension; PVR = pulmonary vascular resistance; RAA = right atrial appendage; RV = right ventricular; RVED = right ventricular end-diastolic dimension; RVEDA = right ventricular end-diastolic area; RVEDVI = right ventricular end-diastolic volume index; RVmass = right ventricular mass; TAPSE = tricuspid annular systolic excursion; Tei = total ejection isovolume; TR = tricuspid regurgitation; TRV = tricuspid regurgitation velocity; VTI = velocity time integral.

Wright L et al, JACC: Cardiovasc Imaging 2016

Echo in PAH

- Echocardiographic techniques can be employed to
  - estimate PAP, PVR, RAP
  - derive indirect information about right heart structure and function
  - identify possible causes such as left heart or congenital heart disease
  - monitor treatment response
  - predict clinical outcomes

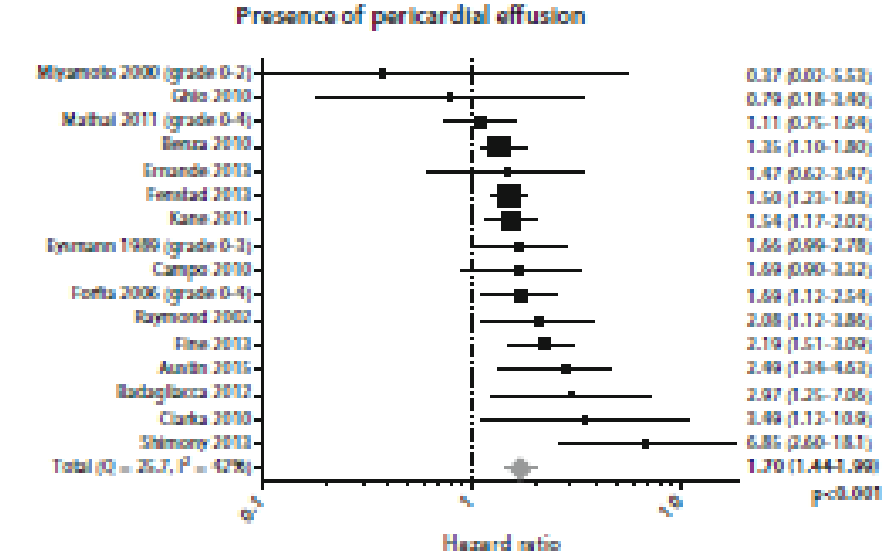
Echocardiography I

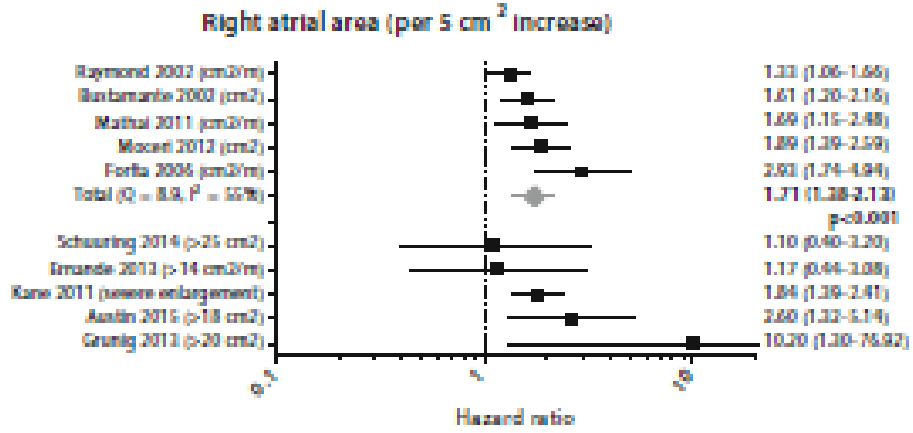
- >50 echo prognostic indexes described in literature
- The majority examines baseline findings
- Composite end-points (death, hospitalization, clinical deterioration, treatment uptitration etc)

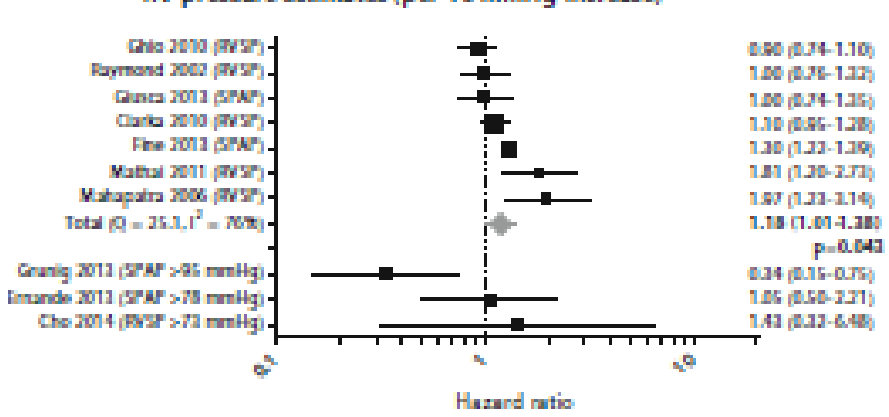
Baggen VJM et al, Neth Heart J 2016

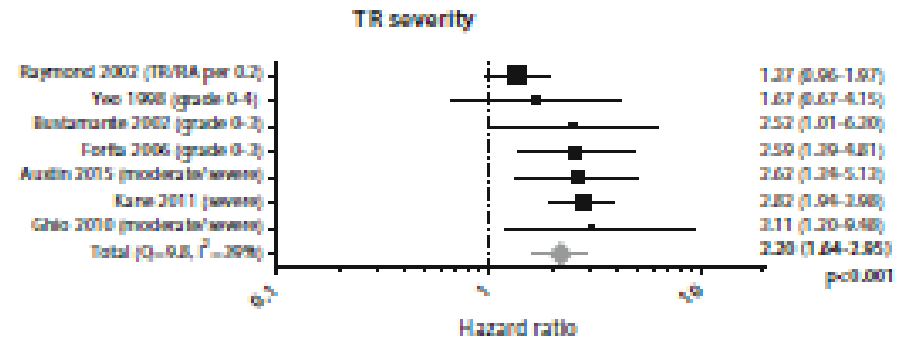
Λειτουργικότητα δεξιάς κοιλίας	Ογκομετρικές και ανατομικές μετρήσεις
• TAPSE • Επιμήκης μέγιστη συστολική παραμόρφωση της δεξιάς κοιλίας • Κλασματική μεταβολή της επιφάνειας της δεξιάς κοιλίας • Tei index • Χρόνος εξώθησης της δεξιάς κοιλίας • Διάρκεια της ανεπάρκειας της τριγλώχινας βαλβίδας • Λόγος κύματος S:D • Χρόνος ισοογκοτικής χάλασης • Χρόνος ισοογκοτικής επιτάχυνσης • Ρυθμός παραμόρφωσης του ελεύθερου τοιχώματος της δεξιάς κοιλίας • Χρόνος μέχρι τη μέγιστη συστολική παραμόρφωση του ελεύθερου τοιχώματος της δεξιάς κοιλίας • Ρυθμός πρώιμης διαστολικής παραμόρφωσης του ελεύθερου τοιχώματος της δεξιάς κοιλίας • Κυκλοτερής παραμόρφωση της δεξιάς κοιλίας • Ακτινική παραμόρφωση της δεξιάς κοιλίας • Παραμόρφωση της επιφάνειας της δεξιάς κοιλίας	• Επιφάνεια του δεξιού κόλπου • Λόγος επιφάνειας του δεξιού προς τον αριστερό κόλπο • Δείκτης εκκεντρότητας της αριστερής κοιλίας • Ανώμαλη διαμόρφωση του μεσοκοιλιακού διαφράγματος κατά τη τελοδιαστολή • Επιφάνεια της δεξιάς κοιλίας στη τελοδιαστολή και τη τελοσυστολή • Διάμετρος της δεξιάς κοιλίας κατά τη τελοδιαστολή • Λόγος διαμέτρου της δεξιάς προς την αριστερή κοιλία κατά τη τελοδιαστολή • Διάμετρος της δεξιάς κοιλίας στη μεσότητα αυτής • Επιμήκης διάμετρος της δεξιάς κοιλίας • Πάχος του ελεύθερου τοιχώματος της δεξιάς κοιλίας • Τελοδιαστολικός όγκος της αριστερής κοιλίας • Διάμετρος της αριστερής κοιλίας κατά τη τελοσυστολή και τη τελοδιαστολή • VTI_{RVOT}
Λειτουργικότητα αριστερής κοιλίας	**Παράμετροι μέτρησης της πίεσης**
• Καρδιακή παροχή και καρδιακός δείκτης της αριστερής κοιλίας • Κλάσμα εξώθησης της αριστερής κοιλίας • Επιμήκης μέγιστη συστολική παραμόρφωση της αριστερής κοιλίας • Κυκλοτερής παραμόρφωση της αριστερής κοιλίας • Δυσλειτουργία της αριστερής κοιλίας	• Συστολική πίεση της δεξιάς κοιλίας • Συστολική πίεση στην πνευμονική αρτηρία • Μέγιστη ταχύτητα παλίνδρομης ροής στην τριγλώχινα βαλβίδα • Βαρύτητα της ανεπάρκειας της τριγλώχινας βαλβίδας • Πίεση του δεξιού κόλπου • Χρόνος επιτάχυνσης ροής στην πνευμονική αρτηρία • Χρόνος επιτάχυνσης ροής στον χώρο εξόδου της δεξιάς κοιλίας

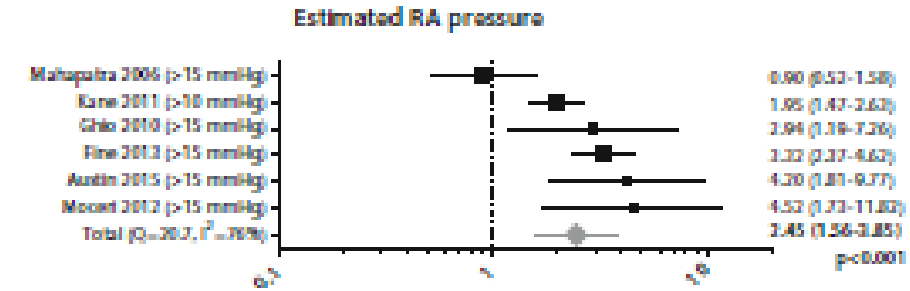
Baggen VJM et al, Neth Heart J 2016

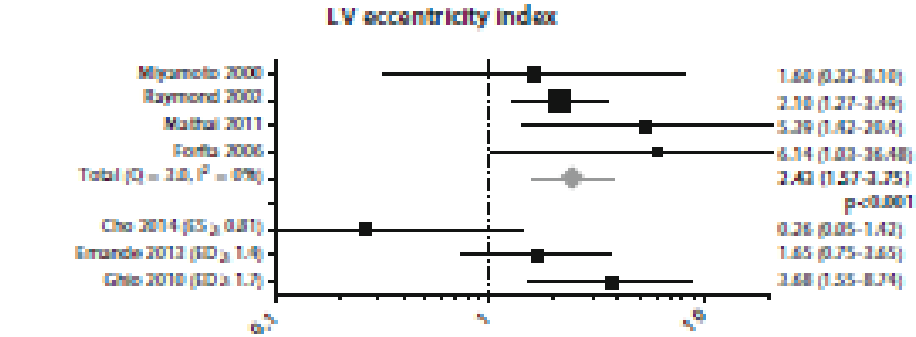




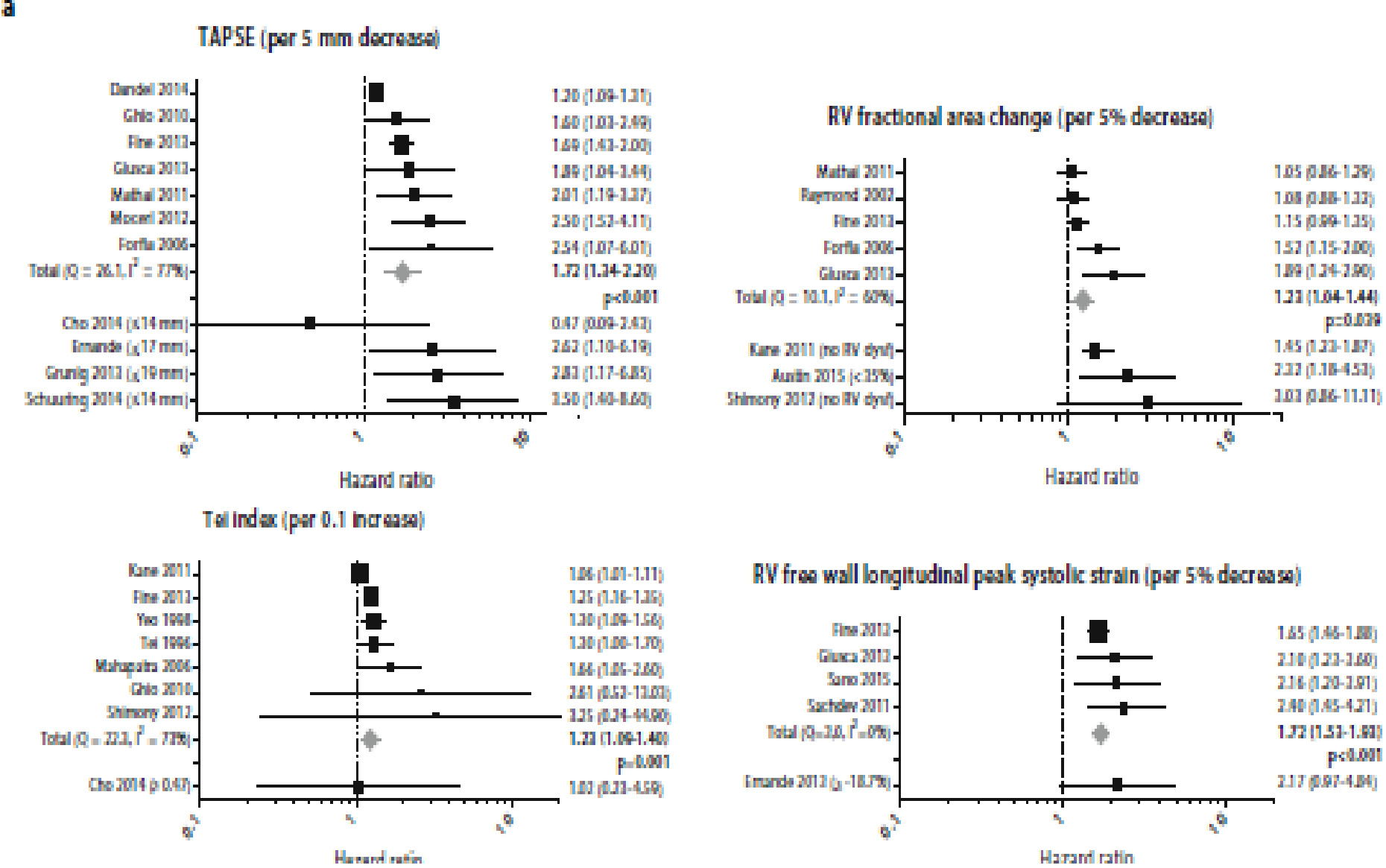






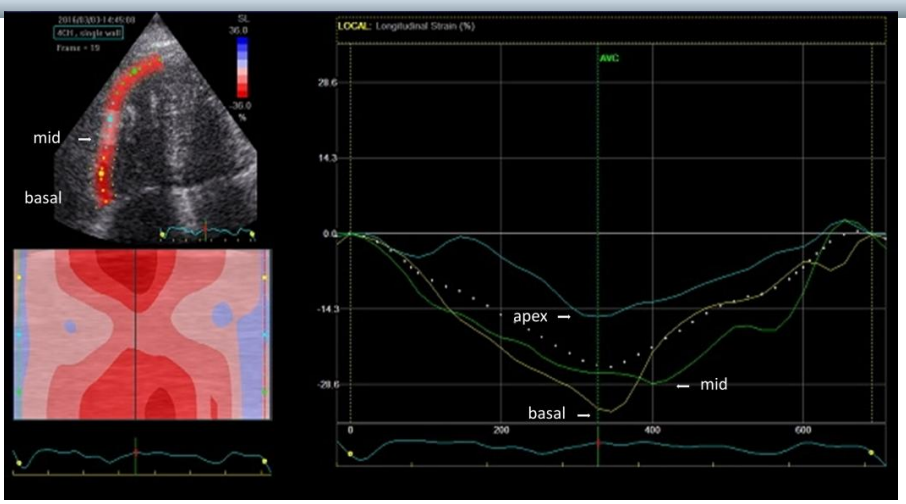


Baggen VJM et al, Neth Heart J 2016



Baggen VJM et al, Neth Heart J 2016

Echocardiography – modern technologies



	Multivariable analysis			Model comparison			
	HR	95%≤ CI	P value	-2 LL	χ^2	p-value	c-statistic
Model A (6MWD)	3.769	1.204-11.795	0.023	56.381	16.997	<0.0001	0.712
Model A + RV-LPSS				54.288	17.762	<0.0001	0.796
6MWD	2.928	1.001-9.226	0.011				
RV-LPSS	5.391	1.467-19.814	0.014				
Model B (NT-proBNP)	5.817	1.297-26.100	0.021	65.901	5.420	0.02	0.704
Model B + RV-LPSS				61.808	8.525	0.014	0.760
NT-proBNP	1.001	1.001-1.003	0.043				
RV-LPSS	1.133	1.004-1.279	0.042				
Model C (WHO class)	10.01	2.931-34.190	<0.0001	62.862	6.961	0.008	0.705
Model C + RV-LPSS				60.153	9.662	0.008	0.780
WHO class	4.193	1.119-15.721	0.033				
RV-LPSS	1.102	1.002-1.235	0.045				

- In PAH RV strain (area, longitudinal, radial and circumferential) is
  - Reduced
  - Predictive of functional capacity
  - Predictive of survival
- Serial assessment of RV free wall systolic strain predicts
  - Clinical deterioration
  - Mortality
- Serial assessment of RV longitudinal strain improves the prediction of long-term outcomes for PH patients over standard hemodynamic indices.

Smith BC et al, Am J Coll Cardiol 2014
Rajagopal S er al, J Am Soc Echocardiogr 2014
Hardegree EL, Am J Cardiol 2013
Sano H et al, Can J Cardiol 2015
Okumura K et al, J Am Soc Echocardiogr 2014
Mouratoglou SA et al, ESC Annual Congress 2016

Author	Relative reduction of RVLS (%)	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Murata *et al*. 2016	5%	0.04879	0.04342	25.8%	1.05 [0.96, 1.14]
Giusca *et al*. 2012	6%	0.19885	0.14434	12.6%	1.22 [0.92, 1.62]

Author	Relative reduction of RVLS (%)	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Vitarelli *et al*. 2015	10%	1.52606	0.28056	31.4%	4.60 [2.65, 7.97]
Haeck *et al*. 2012	19%	1.22378	0.53577	11.9%	3.40 [1.19, 9.72]
Kessel, van *et al*. 2016	19%	1.45861	0.69022	7.6%	4.30 [1.11, 16.63]
Park *et al*. 2015	31%	0.73716	0.35059	23.3%	2.09 [1.05, 4.15]
Sachdev *et al*. 2011	33%	0.69315	0.32446	25.9%	2.00 [1.06, 3.78]
Total (95% CI)				**100%**	**2.96 [2.00, 4.38]**

Heterogenity: $Tau^2 = 0.05$; $Chi^2 = 5.27$, df = 4 ($P = 0.26$); $I^2 = 24\%$
Test for overall effect: Z = 5.45 ($P < 0.00001$)

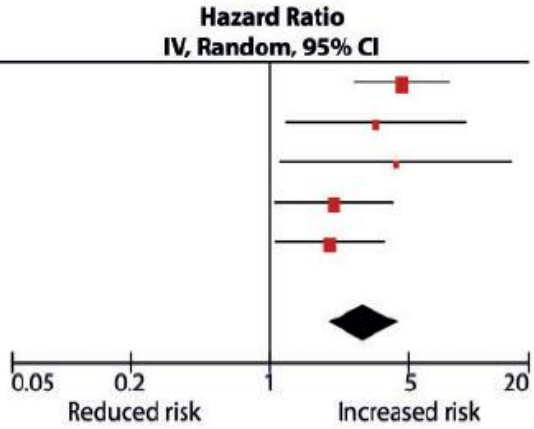
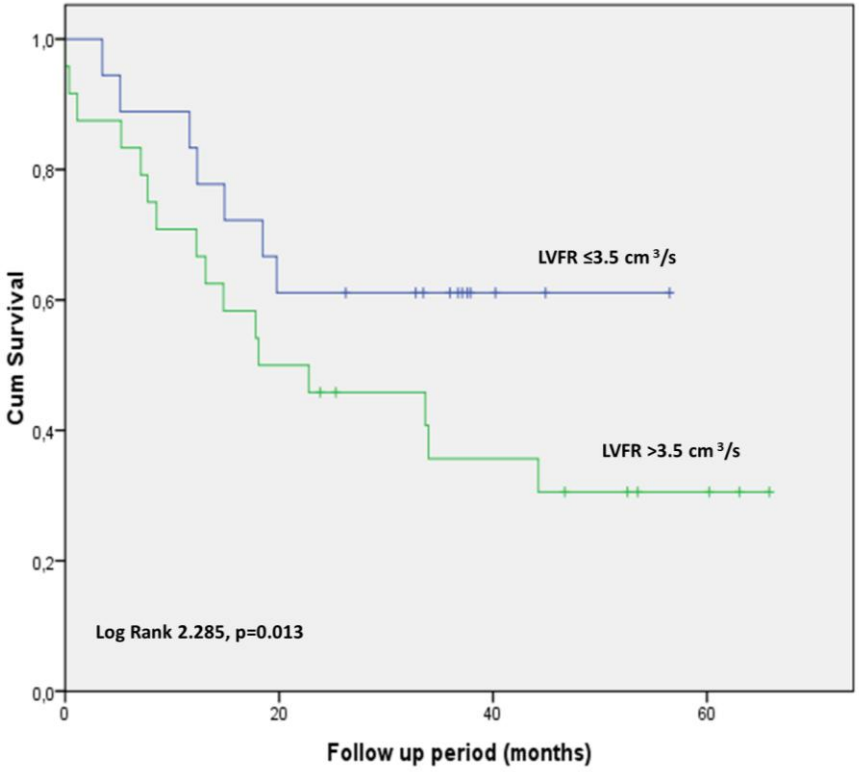


Figure 3 Forrest plot summarising the effect of a (relative) reduction of RVLS on all-cause mortality in PH patients. The red squares present the weighted effect size and the black lines the 95% CIs. The size of the red squares indicate the weight of the study. The black diamond presents the mean weighted HR.

LV in PAH prognosis



$$LVFR = E\ wave * 3.14 * (MAd/2)^2$$

	Multivariable analysis			Model comparison			
	HR	**95%≤ CI**	**P value**	**-2 LL**	**χ^2**	**p-value**	**c-statistic**
Model A (6MWD)	0.995	0.992-0.998	<0.0001	43.8	8.3	0.004	0.835
Model A + LVFR				33.37	5.978	<0.0001	0.876
6MWD	0.987	0.977-0.996	0.007				
LVFR	1.044	1.040-1.091					
Model B (NT-proBNP)	1.002	1.001-1.004	0.008	41.0	6.961	<0.0001	0.836
Model B + LVFR				32.9	6.060	<0.0001	0.868
NT-proBNP	1.002	1.001-1.004	0.011				
LVFR	1.034	1.010-1.076					
Model C (WHO class)	22.086	2.641-180.726	<0.004	41.0	16.801	<0.0001	0.791
Model C + LVFR				33.7	17.347	<0.0001	0.847
WHO class	17.256	2.013-147.947	0.006				
LVFR	1.033	1.030-1.080					

Table 4. Additive prognostic value of left ventricular filling rate in patients with precapillary pulmonary hypertension
NT-proBNP: N-terminal pro B-natriuretic peptide, 6MWD: distance walked in six minute walk test, WHO: world health organization, LVFR: left ventricular filling rate

Giannakoulas G, Mouratoglou S et al, ACC Annual Congress 2017

Right atrial function index

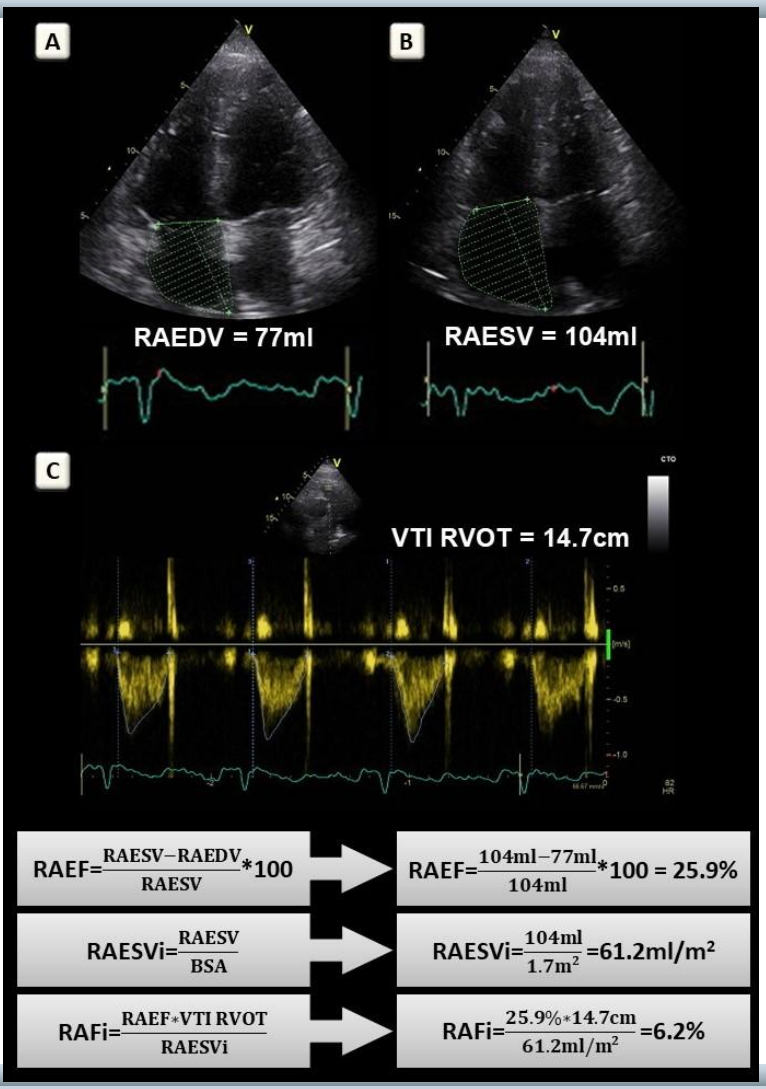
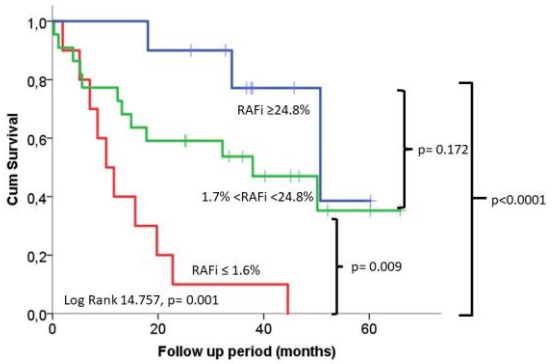
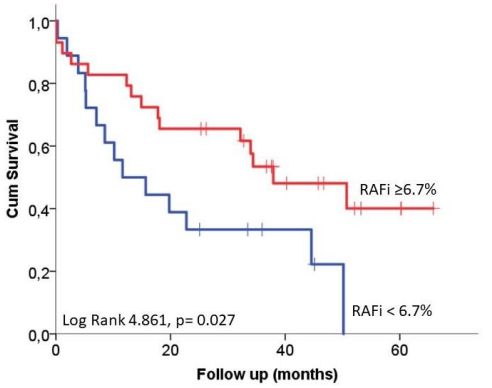


Table 6 Additive value of RAFi (≥6.7%) over known survival predictors

Parameter	HR	C statistic	*P*
6-min walk distance	0.994	0.822	
6-min walk distance + RAFi	0.952	0.844	<.0001
NT-proBNP	1.000	0.737	
NT-proBNP + RAFi	0.964	0.814	<.0001
RA area	1.104	0.764	
RA area + RAFi	1.099	0.845	<.001



	Month 0	Month 10	Month 20	Month 30	Month 40	Month 50
RAFi ≤ 1.6%	15	6	2	1	1	0
1.7% <RAFi <24.8%	22	17	13	12	11	10
RAFi ≥24.8%	10	10	9	8	8	8



	Month 0	Month 10	Month 20	Month 30	Month 40	Month 50
RAFi <6.7%	18	11	7	5	3	0
RAFi≥ 6.7%	29	24	22	20	19	18

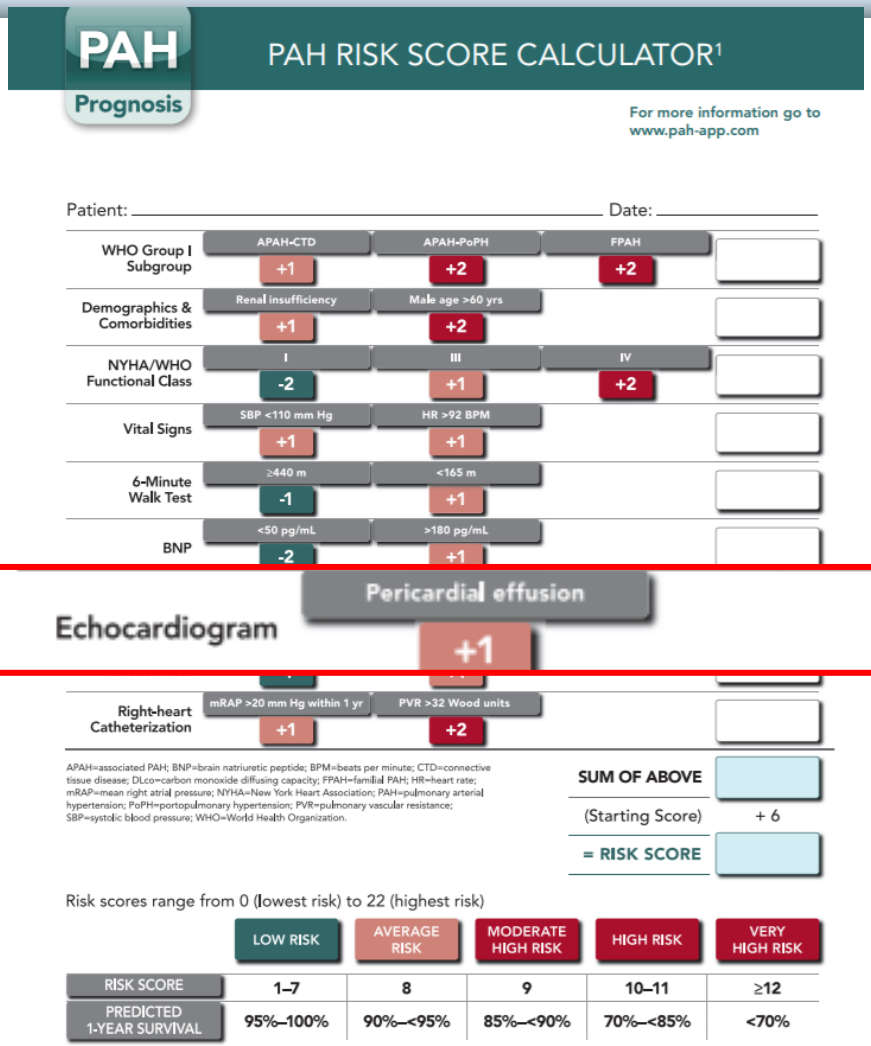
Mouratoglou SA et al, JASE 2018

Risk assessment of PAH

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 slope ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

Galie N et al, Eur Heart J 2015

The REVEAL risk assessment calculator



PAH Prognosis

PAH RISK SCORE CALCULATOR[1]

For more information go to www.pah-app.com

Patient: _____ Date: _____

WHO Group I Subgroup	APAH-CTD +1	APAH-PoPH +2	FPAH +2	
Demographics & Comorbidities	Renal insufficiency +1	Male age >60 yrs +2		
NYHA/WHO Functional Class	I -2	III +1	IV +2	
Vital Signs	SBP <110 mm Hg +1	HR >92 BPM +1		
6-Minute Walk Test	≥440 m -1	<165 m +1		
BNP	<50 pg/mL -2	>180 pg/mL +1		
Echocardiogram	Pericardial effusion +1			
Right-heart Catheterization	mRAP >20 mm Hg within 1 yr +1	PVR >32 Wood units +2		

APAH=associated PAH; BNP=brain natriuretic peptide; BPM=beats per minute; CTD=connective tissue disease; DLco=carbon monoxide diffusing capacity; FPAH=familial PAH; HR=heart rate; mRAP=mean right atrial pressure; NYHA=New York Heart Association; PAH=pulmonary arterial hypertension; PoPH=portopulmonary hypertension; PVR=pulmonary vascular resistance; SBP=systolic blood pressure; WHO=World Health Organization.

SUM OF ABOVE

(Starting Score) + 6

= RISK SCORE

Risk scores range from 0 (lowest risk) to 22 (highest risk)

	LOW RISK	AVERAGE RISK	MODERATE HIGH RISK	HIGH RISK	VERY HIGH RISK
RISK SCORE	1–7	8	9	10–11	≥12
PREDICTED 1-YEAR SURVIVAL	95%–100%	90%–<95%	85%–<90%	70%–<85%	<70%

Benza et al, Chest 2012

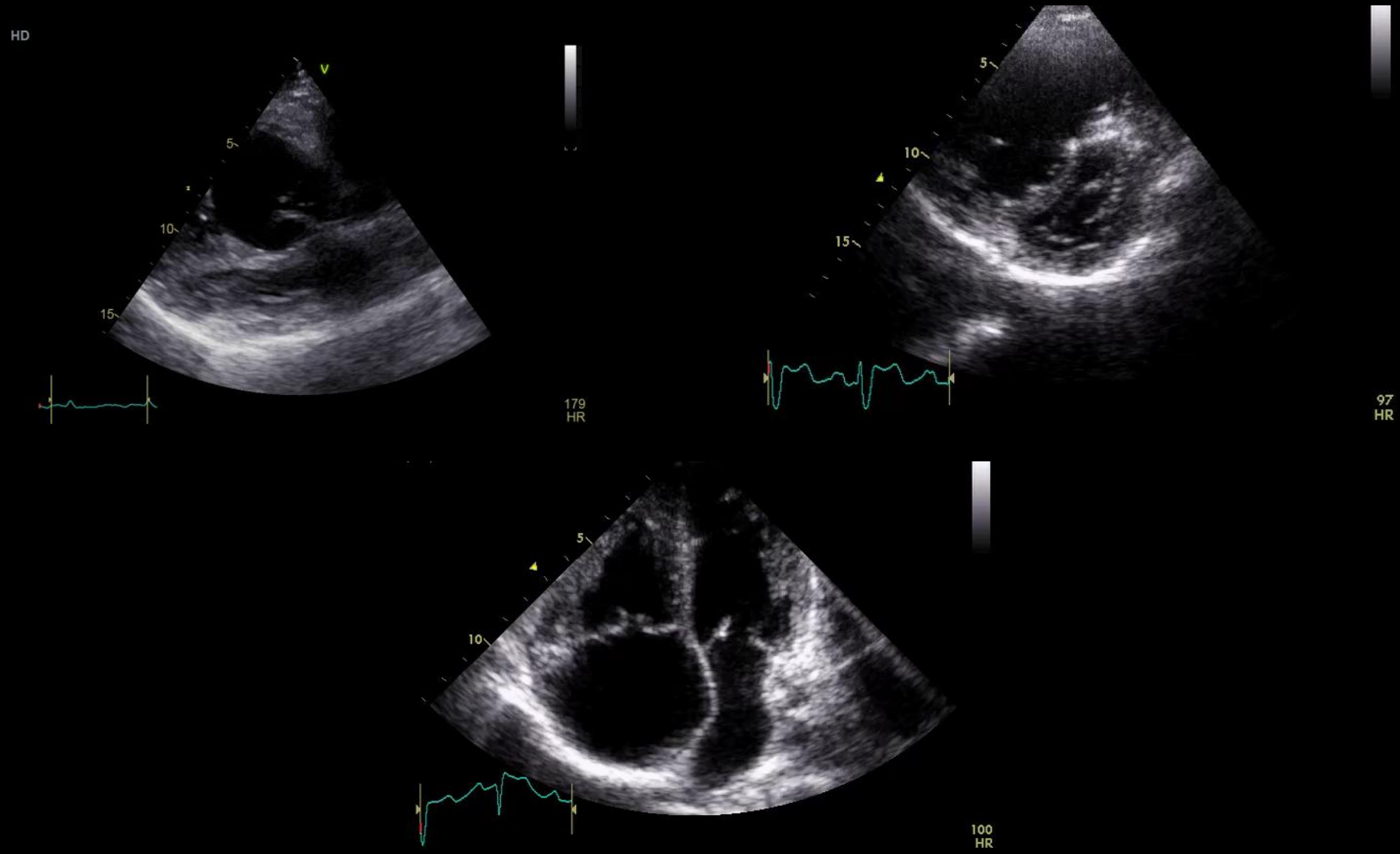
6th World Symposium on PH

	Prognostic criteria	Low risk	Intermediate risk	High risk
A	WHO FC	I/II	III	IV
B	6MWD	>440m	165-440m	<165m
C	NT-proBNP Or RAP	<300ng/ml Or <8mmHg	300-1400ng/ml Or 8-14mmHg	>1400ng/ml Or >14mmHg
D	CI Or SvO_2	≥ 2.5 Or >65%	2.0-2.4 Or 60-65%	<2.0 Or <60%

Where is echo?

Adapted from McLaughlin V, 6th World Symposium on PH, 2018

Who has doubts about prognosis here?



Take home messages

- Echocardiography is the most studied imaging modality in PAH providing useful information on diagnosis, clinical classification, risk stratification and prognosis in PAH patients
- Right heart function and dimensions and pericardial effusion are the most studied main determinants of prognosis in PAH
- Right atrial function is an emerging field in the assessment of PAH prognosis
- Novel imaging techniques may be proved of prognostic significance in PAH

Acknowledgements

AHEPA University Hospital

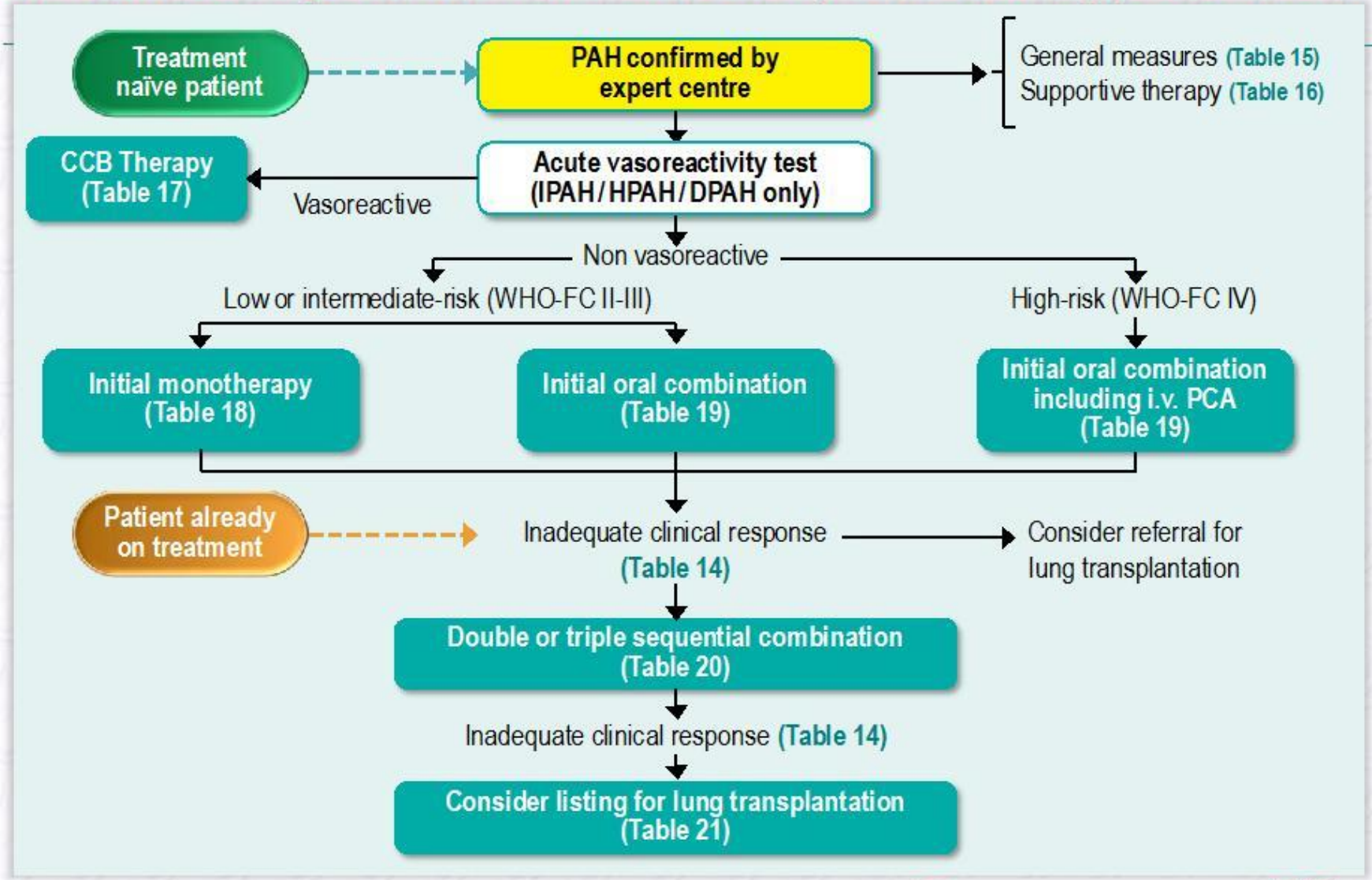
Pulmonary Hypertension Unit

Thank you

Does RV works alone?

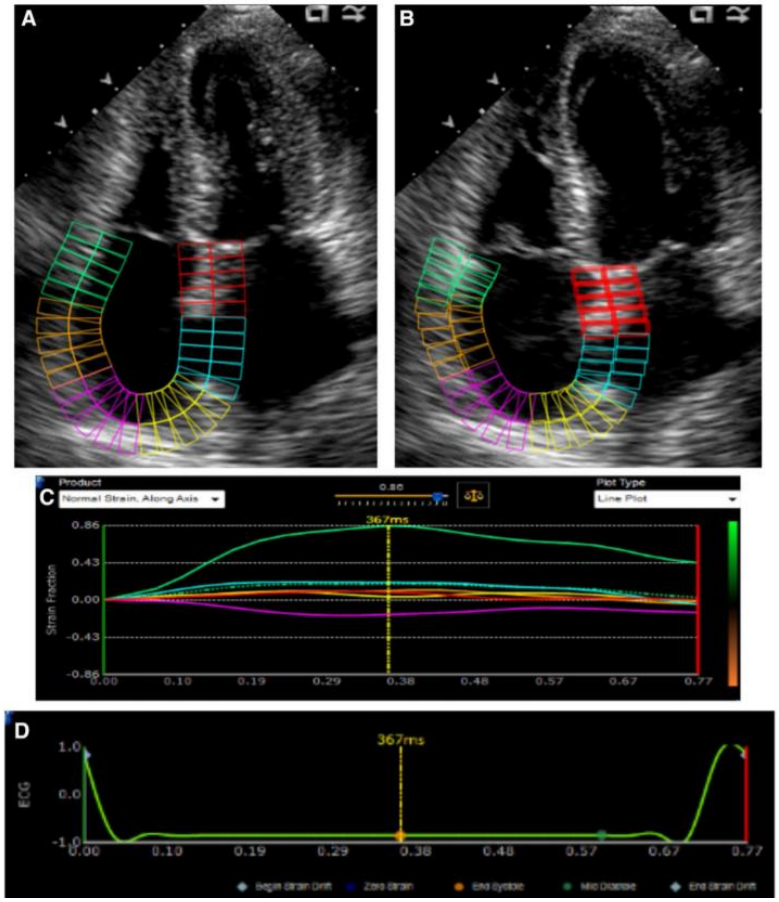
It takes two to tango…

Treatment Algorithm for Pulmonary Arterial Hypertension



European Heart Journal 2016:37;67–119 -doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015 46: 903-975;

Echocardiography – modern technologies II



- Peak RA strain represents the reservoir function of the right atrium
- In PAH, RA strain
  - Is lower compared to normal controls
  - Is predictive of invasive hemodynamic parameters in group I PAH
  - Predicts clinical outcomes

Bhave N et al, Int J Cardiovasc Imaging 2018
Piccinino C et al, J Cardiovasc Med 2017
Weiwei L et al, Heart, Lung Circ 2017
Meng X et al, Int J Cardiol 2017

The RAFi

Low risk criteria:
WHO FC I/II
6MWD >440 m,
RAP <8 mmHg,
CI>2.5 L·min−1·m−2
NT-proBNP <300pg/dl