The 3rd Indonesia Symposium on Heart Failure and Cardiometabolic Disease 2023

Forgotten No More: Right Ventricular Failure in Pulmonary Arterial Hypertension

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Disclosure

- I have nothing to disclose

Outline

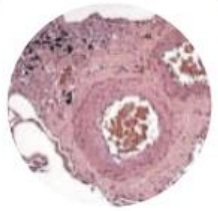
- About Pulmonary Hypertension
- Mechanism of RV Failure
- Evaluation of RV function
- Management of RV failure

Definition

2022 ESC/ERS Guidelines for the diagnosis and treatment of PH

Pulmonary hypertension is defined by a mean pulmonary arterial pressure (mPAP) > 20 mmHg at rest

The general purpose of the clinical classification of PH remains to categorize clinical conditions associated with PH

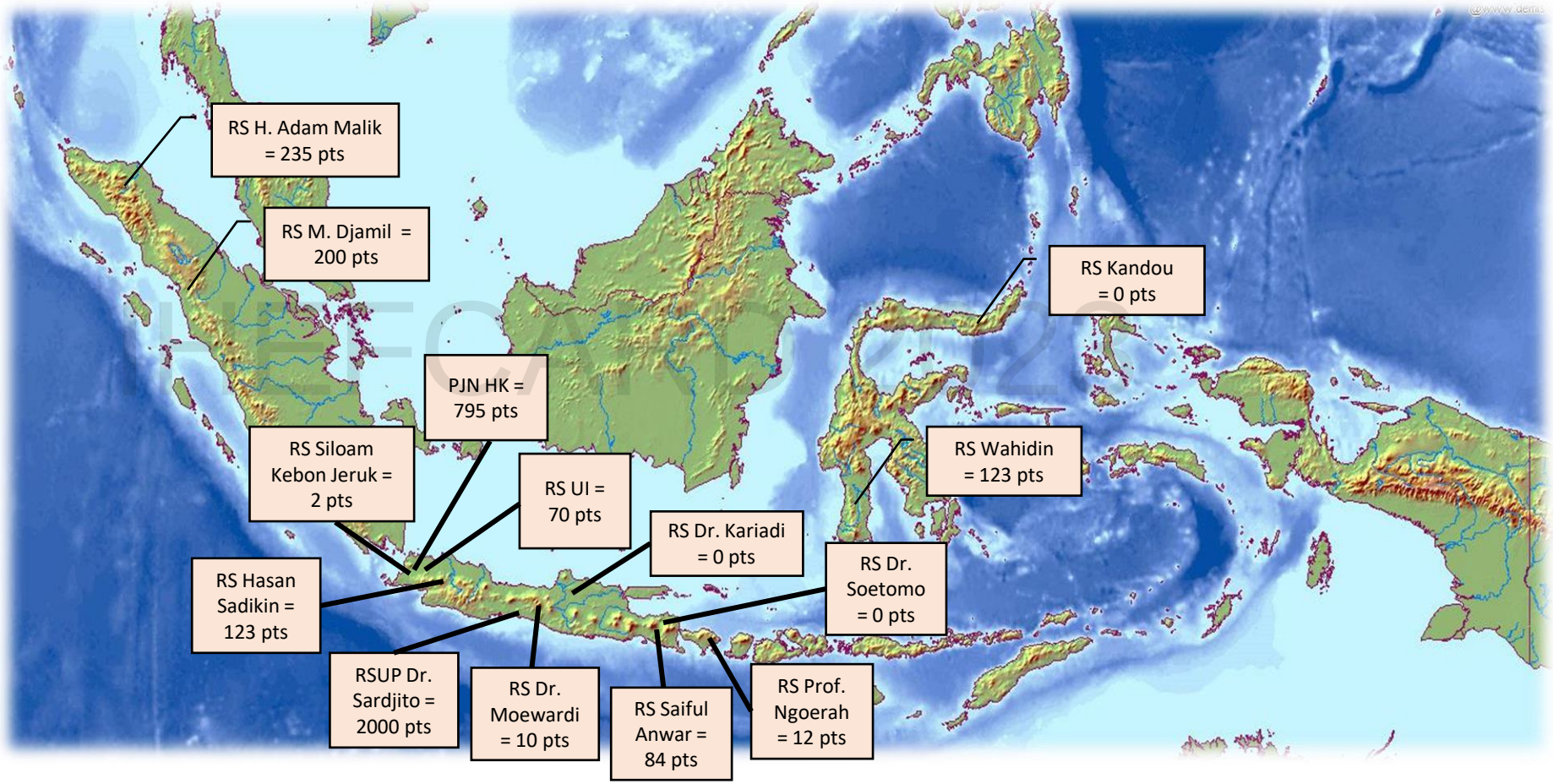
Pulmonary arterial hypertension (PAH)	PH associated with left heart disease	PH associated with lung disease	PH associated with pulmonary artery obstructions	PH with unclear and/or multifactorial mechanisms
				
• Idiopathic/heritable • Associated conditions	• IpcPH • CpcPH	• Non-severe PH • Severe PH	• CTEPH • Other pulmonary obstructions	• Haematological disorders • Systemic disorders

Indonesian Pulmonary Hypertension Registry

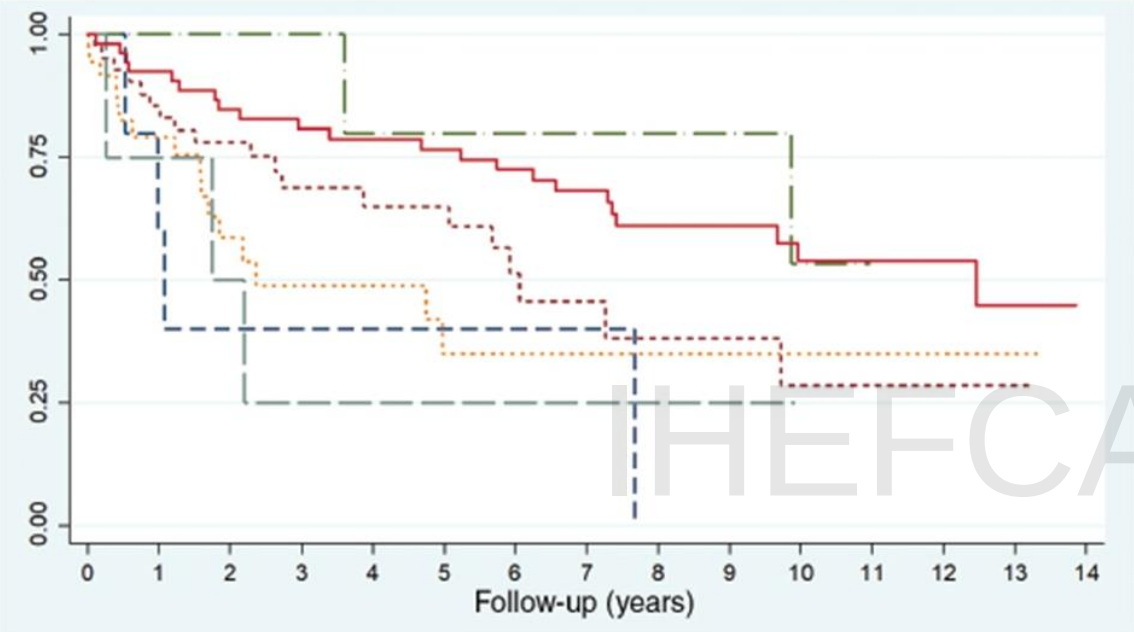
Total National Registry: 3654 patients

- PH Group 1 =
  - PAH-CHD =
  - IPAH =
- PH group 3 =
- PH Group 4 =
- PH group 5 =
  - *Other types =

?

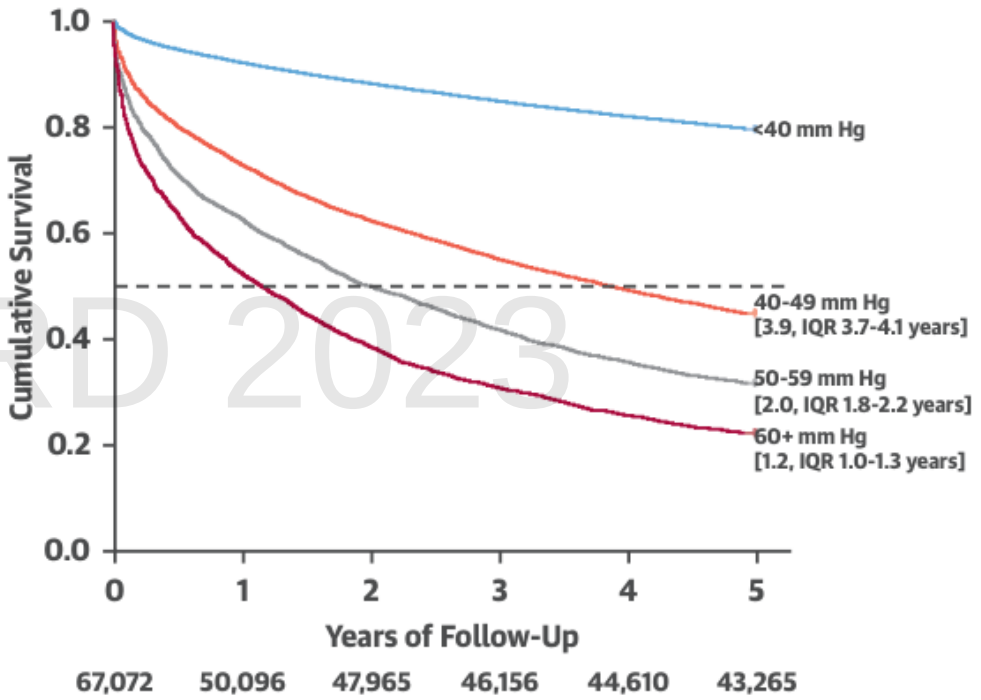


Total population: 261.115.456
Total island: 14.574



No. survived (*n*, %)	Baseline	1 year	3 years	5 years	7 years	10 years
iPAH	44	38 (86.4)	32 (72.7)	31 (70.5)	27 (61.4)	25 (56.8)
CHD	53	49 (92.5)	43 (81.1)	41 (77.4)	37 (69.8)	32 (60.4)
CTD	36	28 (77.8)	21 (58.3)	19 (52.8)	19 (52.8)	19 (52.8)
Hereditary	5	5 (100.0)	5 (100.0)	4 (80.0)	4 (80.0)	3 (60.0)
PVOD	6	4 (66.7)	3 (50.0)	3 (50.0)	3 (50.0)	2 (33.3)
Portal	4	3 (75.0)	1 (25.0)	1 (25.0)	1 (25.0%)	1 (20.0)

FIGURE 3 Five-Year Actuarial Survival According to Increasing Estimated Right Ventricular Systolic Pressure Levels (n = 67,072)



Actuarial survival data derived from 24,227 all-cause deaths during >272,000 patient-years of follow-up. IQR = interquartile range.

Strange et al. JACC. 2019
Zelt et al. Circ Res. 2019

Severe pulmonary hypertension and reduced right ventricle systolic function associated with maternal mortality in pregnant uncorrected congenital heart diseases

Anggoro B. Hartopo[1], Dyah W. Anggrahini[1], Detty S. Nurdiati[2], Noriaki Emoto[3,4] and Lucia K. Dinarti[1]

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Parameters	All subjects n = 48	Survivors n = 42	Nonsurvivors n = 6	*P* value*
Tricuspid transvalvular gradient	71.3 ± 38.2	65.4 ± 36.2	112.2 ± 26.5	0.005
TAPSE	24.7 ± 6.0	25.5 ± 5.9	18.7 ± 2.1	<0.001
RV systolic pressure	79.2 ± 40.3	73.4 ± 38.6	120.0 ± 27.9	0.007
LV ejection fraction	67.8 ± 11.4	67.9 ± 9.6	66.8 ± 21.4	0.828

LV: left ventricle; RV: right ventricle; TAPSE: tricuspid annular plane systolic excursion.
[a]TTE was performed during current admission.
*Comparison between survivors and nonsurvivors.

Pulmonary Circulation 2019; 9(4) 1–9

Dinarti *et al. BMC Cardiovascular Disorders* (2020) 20:163
https://doi.org/10.1186/s12872-020-01434-z

BMC Cardiovascular Disorders

RESEARCH ARTICLE Open Access

The COngenital HeARt Disease in adult and Pulmonary Hypertension (COHARD-PH) registry: a descriptive study from single-center hospital registry of adult congenital heart disease and pulmonary hypertension in Indonesia

Lucia Kris Dinarti*, Anggoro Budi Hartopo*, Arditya Damar Kusuma, Muhammad Gahan Satwiko, Muhammad Reyhan Hadwiono, Aditya Doni Pradana and Dyah Wulan Anggrahini*

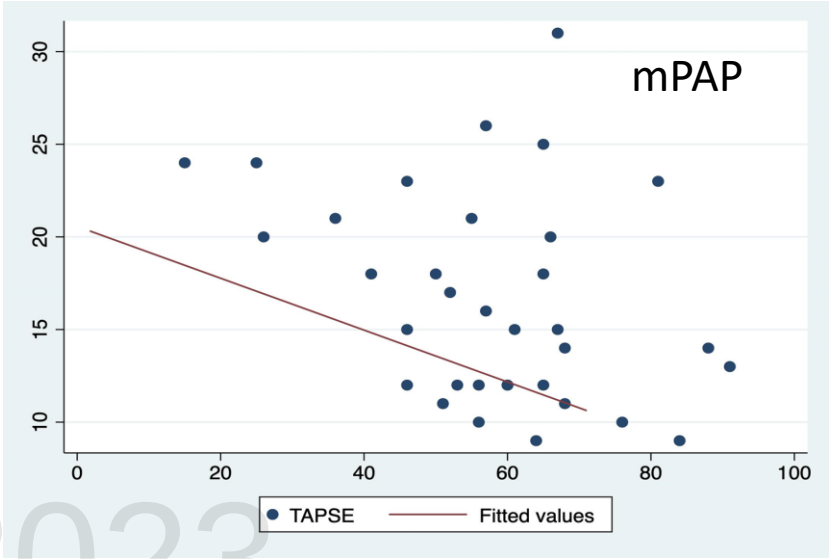
Table 6 Characteristics of Patients based on the WHO Functional Class ($n = 602$)

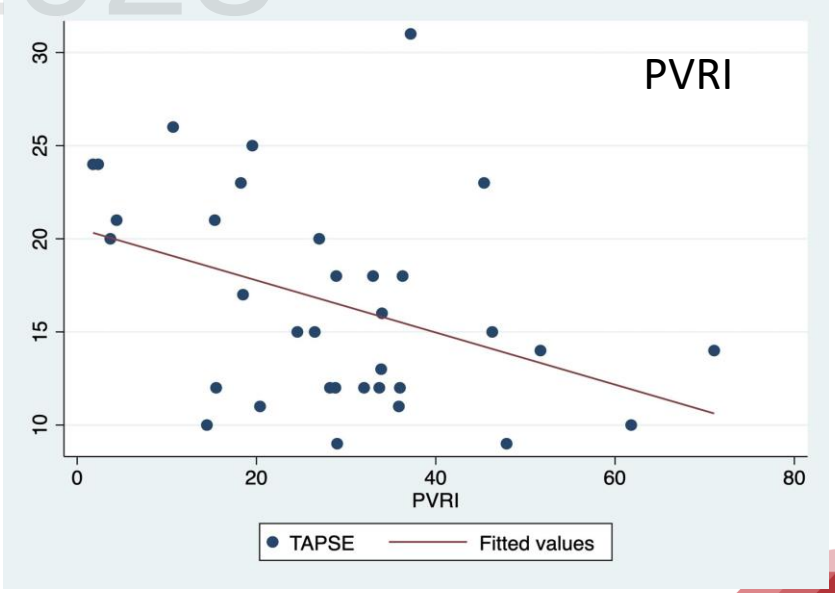
Characteristics	WHO class I (***n*** = 258)	WHO class II (***n*** = 277)	WHO class III-IV (***n*** = 67)	***P*** value
Age at Enrollment (years) [mean ± SD]	34.5 ± 12.9	34.9 ± 12.8	36.6 ± 12.2	0.498
Gender [n (%)]				
Males	55 (21.3)	53 (19.1)	7 (10.4)	0.131
Females	203 (78.7)	224 (80.9)	60 (89.6)	
Body Mass Index [mean ± SD]	19.9 ± 3.4	19.2 ± 3.9	20.9 ± 14.7	0.064
Oxygen Saturation (%)[mean ± SD][a]	96.9 ± 3.2	95.4 ± 5.2	92.6 ± 8.1	< 0.001
6 Minute Walk Distance (meter)[mean ± SD][b]	403.9 ± 80.2	333.1 ± 88.4	276.6 ± 104.6	< 0.001
Hemoglobin (g/dL) [mean ± SD][c]	13.8 ± 2.0	13.9 ± 2.1	14.0 ± 2.5	0.569
Hematocrit (%) [mean ± SD][d]	41.4 ± 5.3	41.6 ± 6.4	41.9 ± 7.6	0.783
NTproBNP (pg/mL) [median (IQR)][e]	178.0 (91.9–718.6)	556.9 (159.6–1687.0)	929.1 (383.0–2882.0)	0.022
Congenital Anomaly [n (%)]				0.001
ASD ($n = 523$)	207 (80.2)	252 (91.0)	64 (95.5)	
VSD ($n = 41$)	29 (11.2)	9 (3.2)	3 (4.5)	
PDA ($n = 31$)	21 (8.1)	10 (3.6)	0 (0)	
Others ($n = 7$)	1 (0.5)	6 (2.2)	0 (0)	
Echocardiography parameters				
mPAP (mmHg) [mean ± SD][f]	32.6 ± 14.7	37.3 ± 15.2	43.5 ± 15.0	< 0.001
TVRG (mmHg) [mean ± SD][g]	50.7 ± 32.7	66.5 ± 34.1	80.8 ± 35.4	< 0.001
RA diameter (mm) [mean ± SD][h]	44.8 ± 7.5	46.6 ± 8.1	47.4 ± 8.6	0.017
RV diameter (mm) [mean ± SD][i]	39.8 ± 7.7	44.4 ± 8.4	45.4 ± 7.5	< 0.001
TAPSE (mm) [mean ± SD][j]	25.4 ± 5.3	25.2 ± 5.8	22.7 ± 5.4	0.002
Left ventricle EF (%)[mean ± SD][k]	68.9 ± 7.4	69.7 ± 9.1	66.1 ± 11.6	0.011
RHC parameters				
mPAP (mmHg) [median (IQR)][l]	28.0 (20.3–46.0)	40.0 (26.0–58.0)	52.5 (32.8–68.5)	< 0.001
PVRi (Wood Unit.m^2) [median (IQR)][m]	2.2 (1.4–5.3)	3.8 (1.5–13.5)	10.2 (2.1–21.6)	< 0.001
Flow Ratio [median (IQR)][n]	2.5 (1.7–3.6)	2.4 (1.5–3.4)	1.8 (1.0–3.1)	0.115

COHARD-PH Registry data:

High mPAP and PVRI are associated with low RV function in Idiopathic PAH

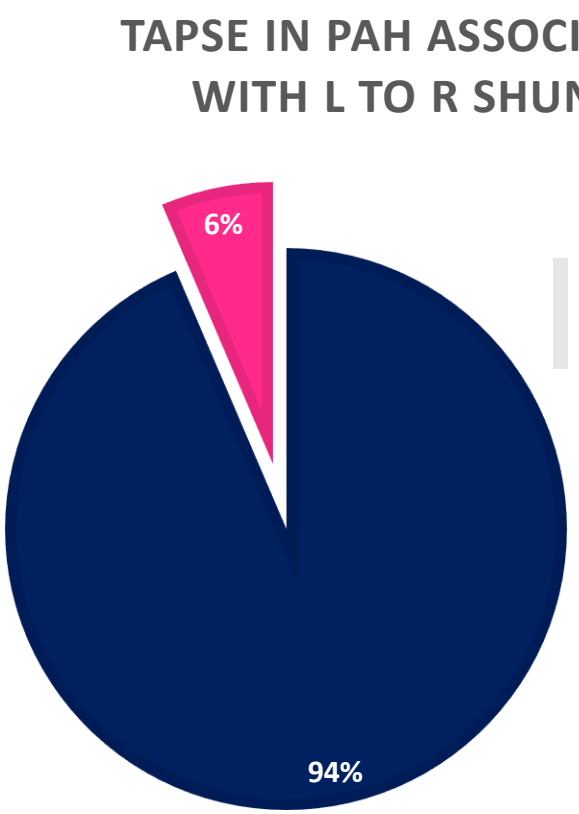
Baseline characteristics	All (median)	TAPSE ≥ 17 mm n=14	TAPSE < 17 mm n=19
Sex			
Male	6	3	3
Female	27	11	16
Age	35 (20-64)	38 (23-64)	31 (20-55)
Weight	52 (35-86)	49.5 (39-86)	54 (35-72)
Height	156 (144-174)	155.5 (145-172)	156 (144-174)
BSA	1.5 (1.2-2)	1.5 (1.3-2)	1.6 (1.2-1.8)
TAPSE (median)	15 (9-31)		
mPAP	60 (25-91)	53.5 (25-81)	61 (46-91)
PVRI	28.9 (2.3-71.1)	19 (2.3-45.4)	33.7 (14.5-71.1)





Aji RP, et.al, InaHF (abstract), 2023

Increase in mPAP in Patients with low TAPSE in CHD- PAH : result of COHARD-PH registry



Parameters	TAPSE (mean ± SD)		*Mean difference (p-value)*
	Low (<17 mm)	High (≥17 mm)	
TAPSE (mm)	13.91 ± 1.92	25.16 ± 4.92	
LVEF	66.03 ± 11.27	68.82 ± 8.30	0.020
RA diameter (mm)	50.22 ± 11.02	38.52 ± 13.33	<0.01
RV diameter (mm)	48.48 ± 8.15	42.79 ± 9.37	<0.01
TVG (mmHg)	87.40 ± 33.58	59.22 ± 33.32	<0.01
mPAP (mmHg)	56.55 ± 22.72	39.60 ± 22.63	<0.01
Flow ratio	2.00 ± 1.43	3.07 ± 4.64	0.095

Anggrahini DW, et.al, unpublished data

Decreased RV function was associated with death in patients with acute decompensated PH

Parameter	Survive (n = 6)	Death (n = 7)
Age (y.o)	36.3 ± 17.1	37 ± 14.6
Sex (female), n (%)	6 (100)	4 (57.1)
Cause of PH (grup 1)		
IPAH, n (%)	-	2 (28.5)
CHD, n (%)	6 (100)	5 (71.4)
Comorbidities		
Pneumonia, n (%)	3 (50)	5 (71.4)
UTI, n (%)	1 (16.6)	3 (42.8)
Sepsis, n (%)	-	2 (28.5)
Use of Inotropic	4 (66.7)	5 (71.4)
Use of prostanoid inhalation	7 (100)	7 (100)
Use of vasopressor	2 (33.3)	7 (42.9)
ECHO at admission in CVCU		
EF (%)	64.66 ± 19.67	68.85 ± 15.19
TAPSE (mm)	19.33 ± 4.5	15.42 ± 4.03
CO (L/min)	3.03 ± 0.88	2.7 ± 1.34
CI (L/min/m2)	2.32 ± 0.81	1.81 ± 0.79
TVG (mmHg)	88.63 ± 25.82	77.98 ± 31.7
PASP (mmHg)	95.8 ± 25.4	90.98 ± 31.03
RAP (mmHg)	7.16 ± 2.04	13 ± 3.41
Lactate at admission in CVCU	2.15 ± 0.83	3.22 ± 4.29
Use of NIV, n (%)	2 (33.3)	5 (71.4)
Use of MV, n (%)	1 (16.7)	3 (42.9)
Use of RRT, n (%)	-	1 (14.2)
LOS, day	15.5 (3 – 44)	4 (1 – 13)

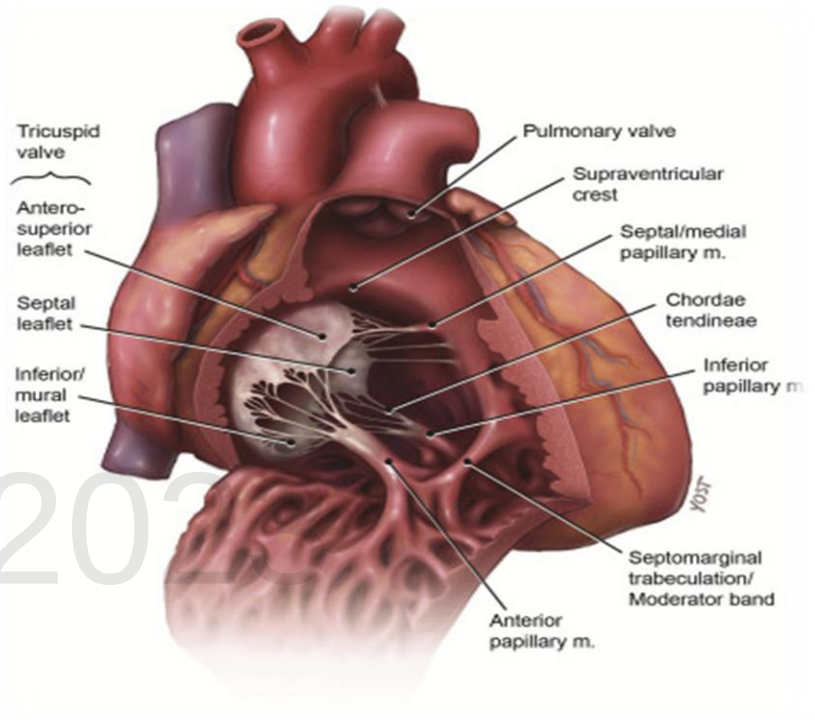
Sardjito Cardiovascular Intensive Care (SCIENCE) registry (Jan 2021 – 2022)

Admission to CVCU (hypoxemia, hypotension) ≈ **13 patients**

IPAH: *idiopathic pulmonary artery hypertension*; **CHD:** *congenital heart disease*; **UTI:** *urinary tract infection*; **EF:** *ejection fraction*; **TAPSE:** *tricuspid annular plane systolic excursion*; **CO:** *cardiac output*; **CI:** *cardiac index*; **TVG:** *tricuspid valve gradient*; **PASP:** *pulmonary artery systolic pressure*; **RAP:** *right atrial pressure*; **NIV:** *non-invasive ventilation*; **MV:** *mechanical ventilation*; **RRT:** *renal replacement therapy*; **LOS:** *length of hospital stay*

Courtesy by Purnasidha HP, 2023

Right Ventricle

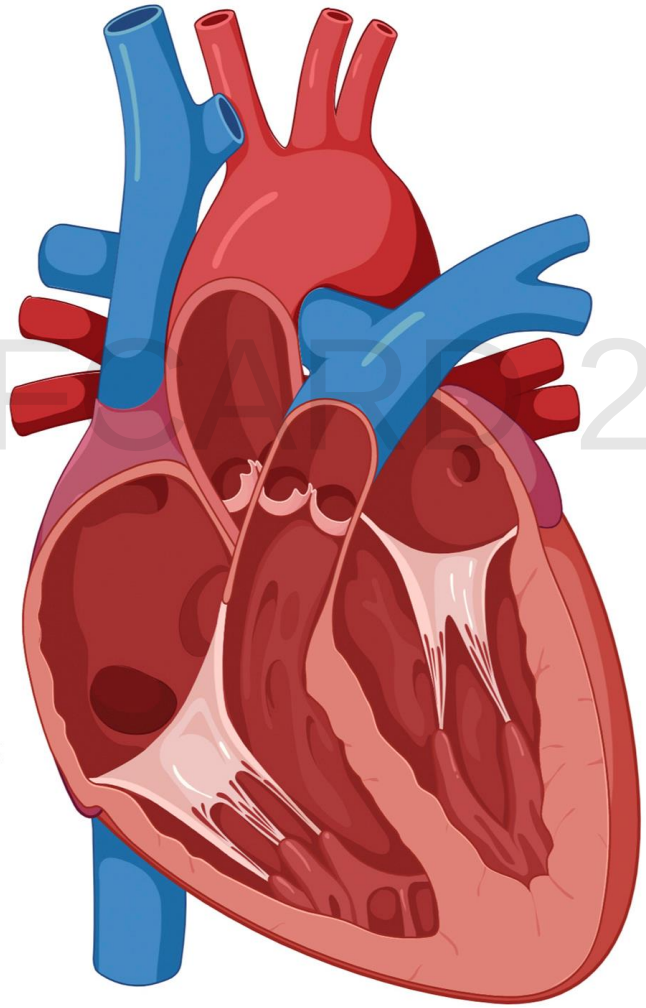


- ✓ *typically a **thin-walled structure***
- ✓ *can **accommodate** large changes in volume, or preload, but acutely has a **limited contractile reserve** to tackle increased impedance to ejection, or afterload [tolerates acute increases in afterload poorly]*

Wilcox SR, Kabrhel C, Channick RN, 2015. Pulmonary Hypertension and Right Ventricular Failure in Emergency Medicine, *American College of Emergency Physicians*

Different characterizations between RV vs LV

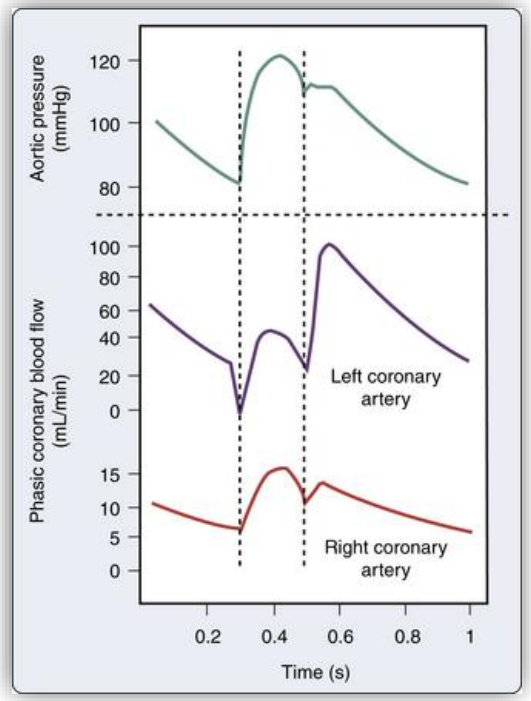
Right Ventricle
- Derived from secondary heart field
- 2 cell layers with most contractility leading to longitudinal shortening
- Thin walled, crescent shaped chamber
- Low pressure system
- Better adapted to volume overload
- Perfusion occurs during systole and diastole
- α1-receptor signaling decreases inotropy in pressure overload
- Does not develop hypertrophy following norepinephrine infusion
- Lower β-MHC content
- Higher macrophage and dendritic cell content
- Higher ECM content
- ER-α stimulation most beneficial



Left Ventricle
- Originates from primary heart field
- 3 cell layers and most contractility is circumferential
- Thick walled, bullet shaped chamber
- High pressure chamber
- Better adapted to pressure overload
- Perfusion occurs during diastole
- Higher afterload reserve
- α1-receptor signaling increases inotropy in pressure overload
- Develops hypertrophy following norepinephrine infusion
- Higher β-MHC content
- ER-β stimulation most beneficial

Coronary perfusion of RV

- ✓ Unlike the LV, which is fed by the coronaries during diastole, the RV is **perfused during both diastole and systole** because of low RV wall tension
- ✓ In pulmonary hypertension, RV perfusion by the coronary arteries decreases in proportion to increases in RV pressure
- ✓ PA pressure >>> the systemic pressures, the RV cannot be well perfused and will become ischemic → diminishing RV contractility and worsening RV overload → **catastrophic spiral**



Wilcox SR, Kabrhel C, Channick RN, 2015. Pulmonary Hypertension and Right Ventricular Failure in Emergency Medicine, *American College of Emergency Physicians*

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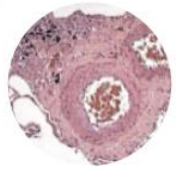
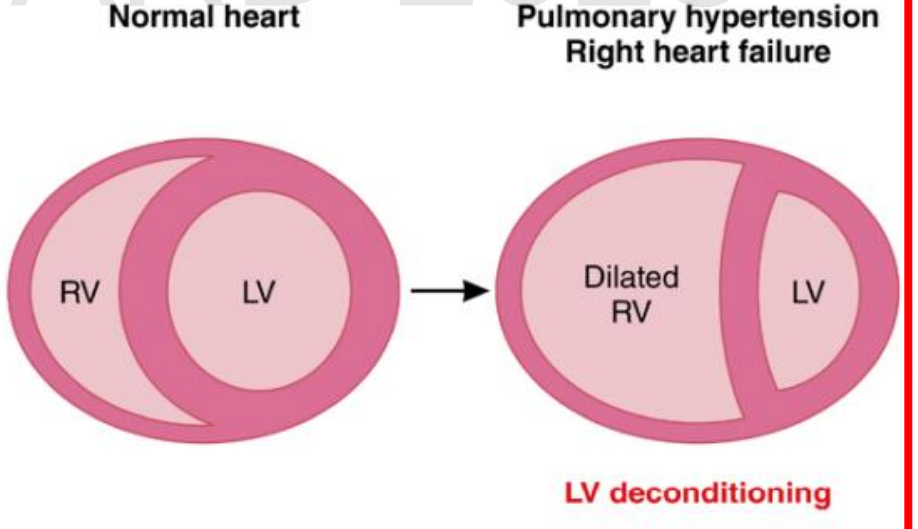
				?
• Idiopathic/heritable • Associated conditions	• IpcPH • CpcPH	• Non-severe PH • Severe PH	• CTEPH • Other pulmonary obstructions	• Haematological disorders • Systemic disorders

- Progressive changes to the pulmonary vasculature
- Increased right ventricular (RV) afterload
- Lead to right-sided heart failure (HF)



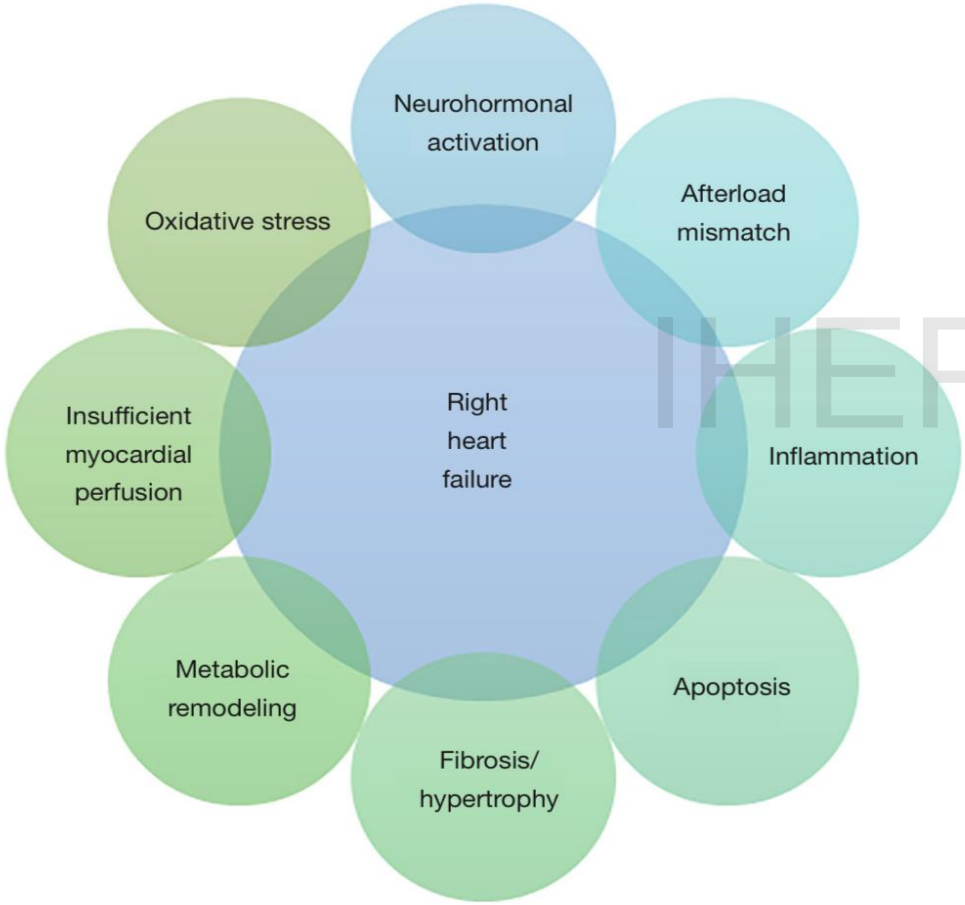
Mechanical:
- LV compression
- Septal leftward shift
- Impaired filling
- Left main compression

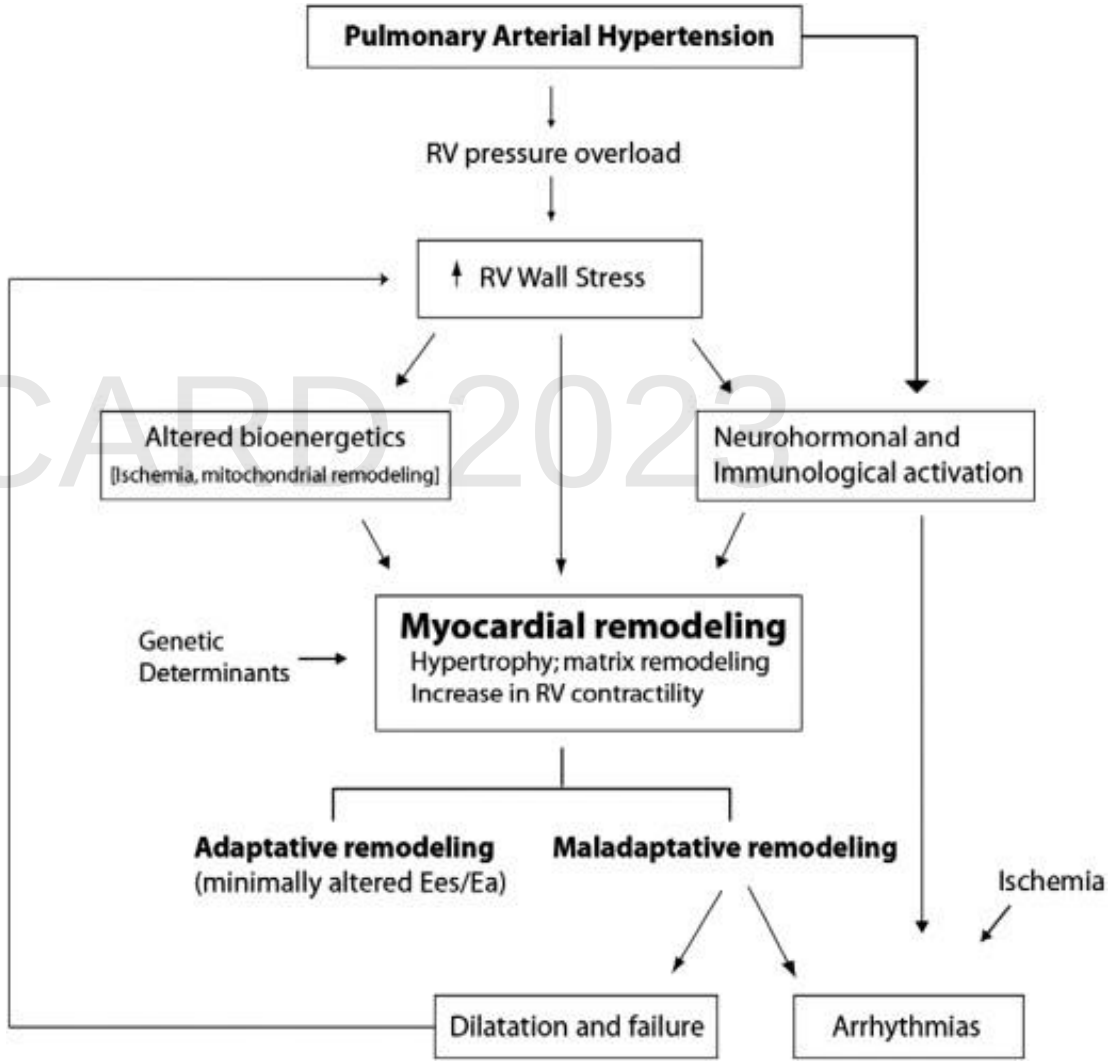
Functional:
- Diastolic dysfunction
- Systolic dysfunction
- Ischemia

Cellular/molecular:
- Cardiomyocyte atrophy
- Reduced myosin
- Impaired force generation

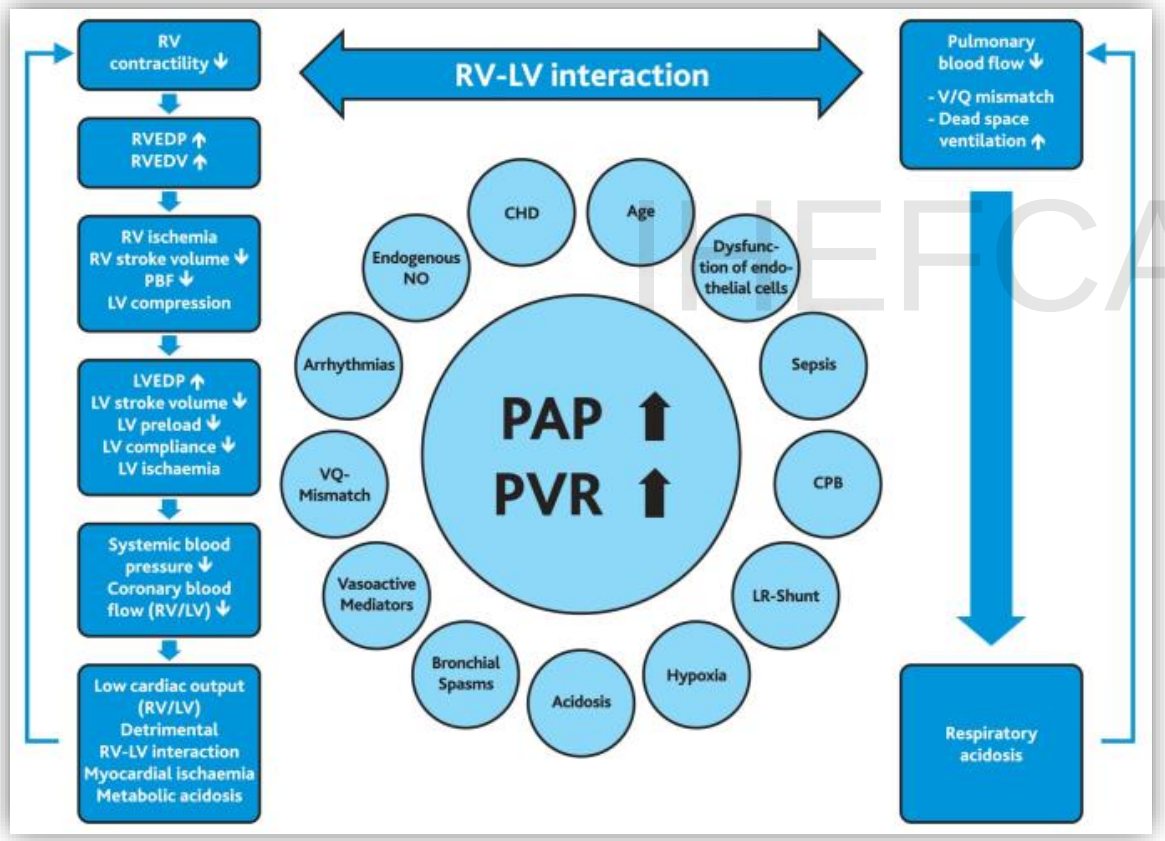
ESC, 2022
Rosenkranz et al. Circ. 2020

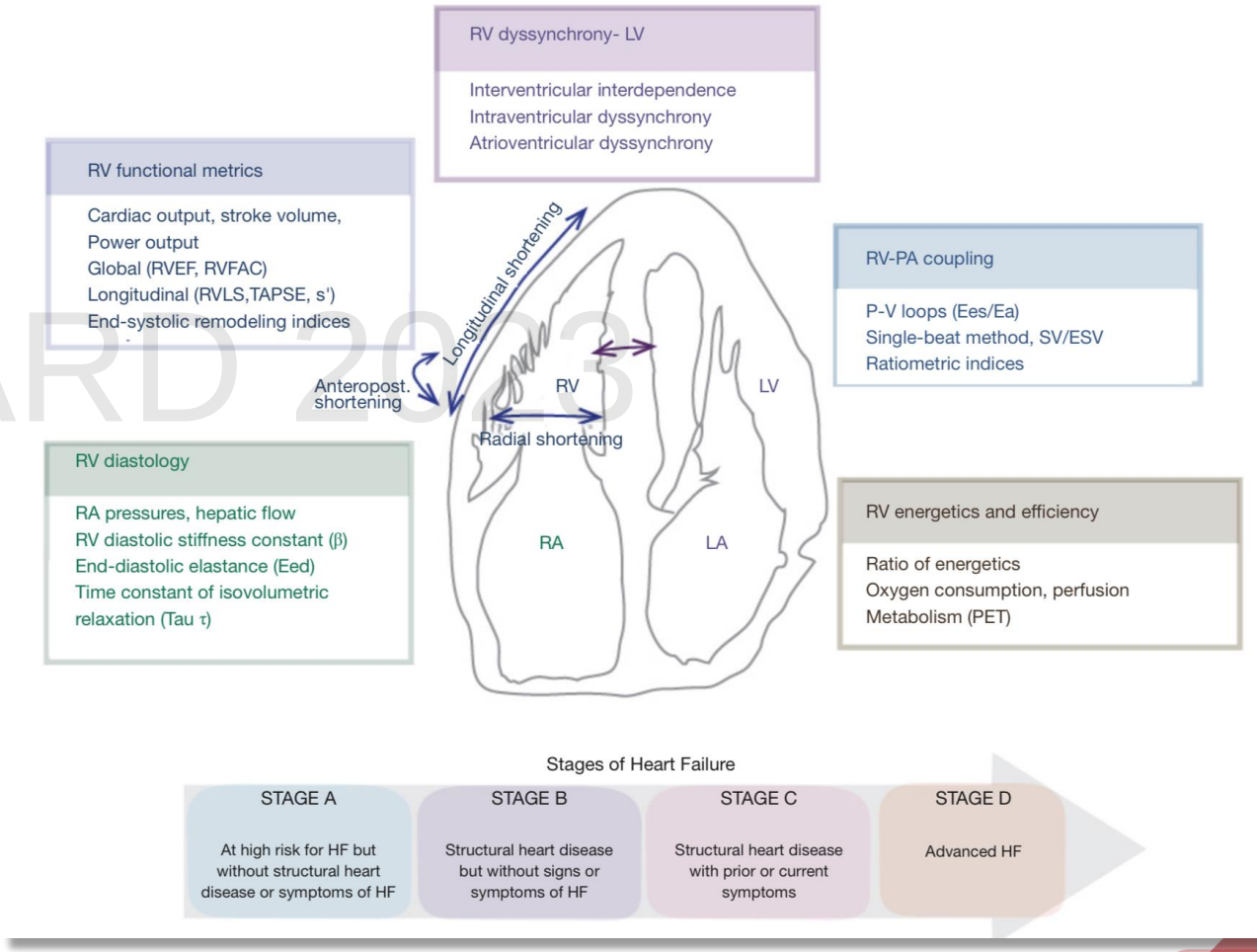
Mechanism and changes associated with RVF



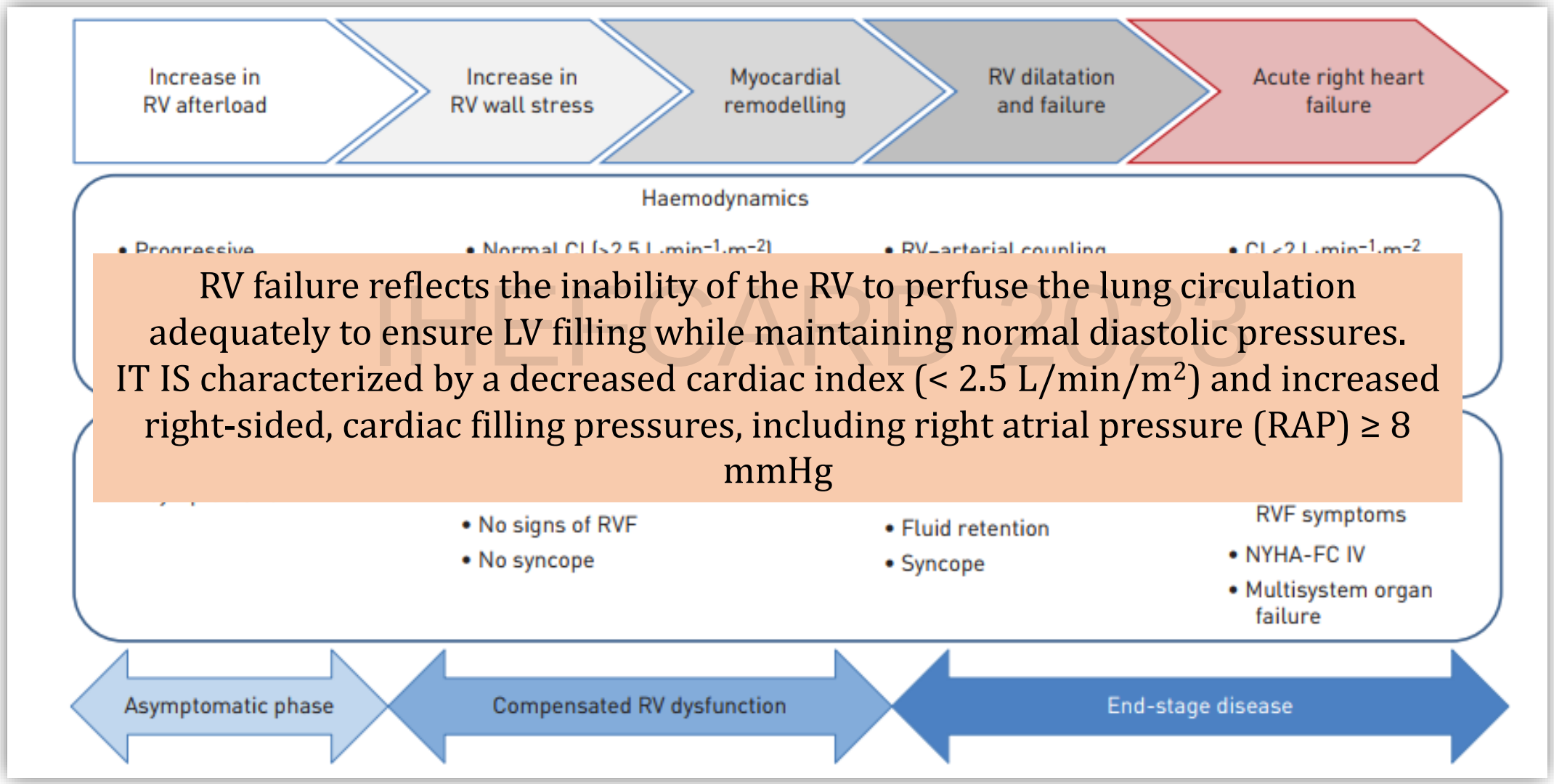


Physiological changes during RV dysfunction

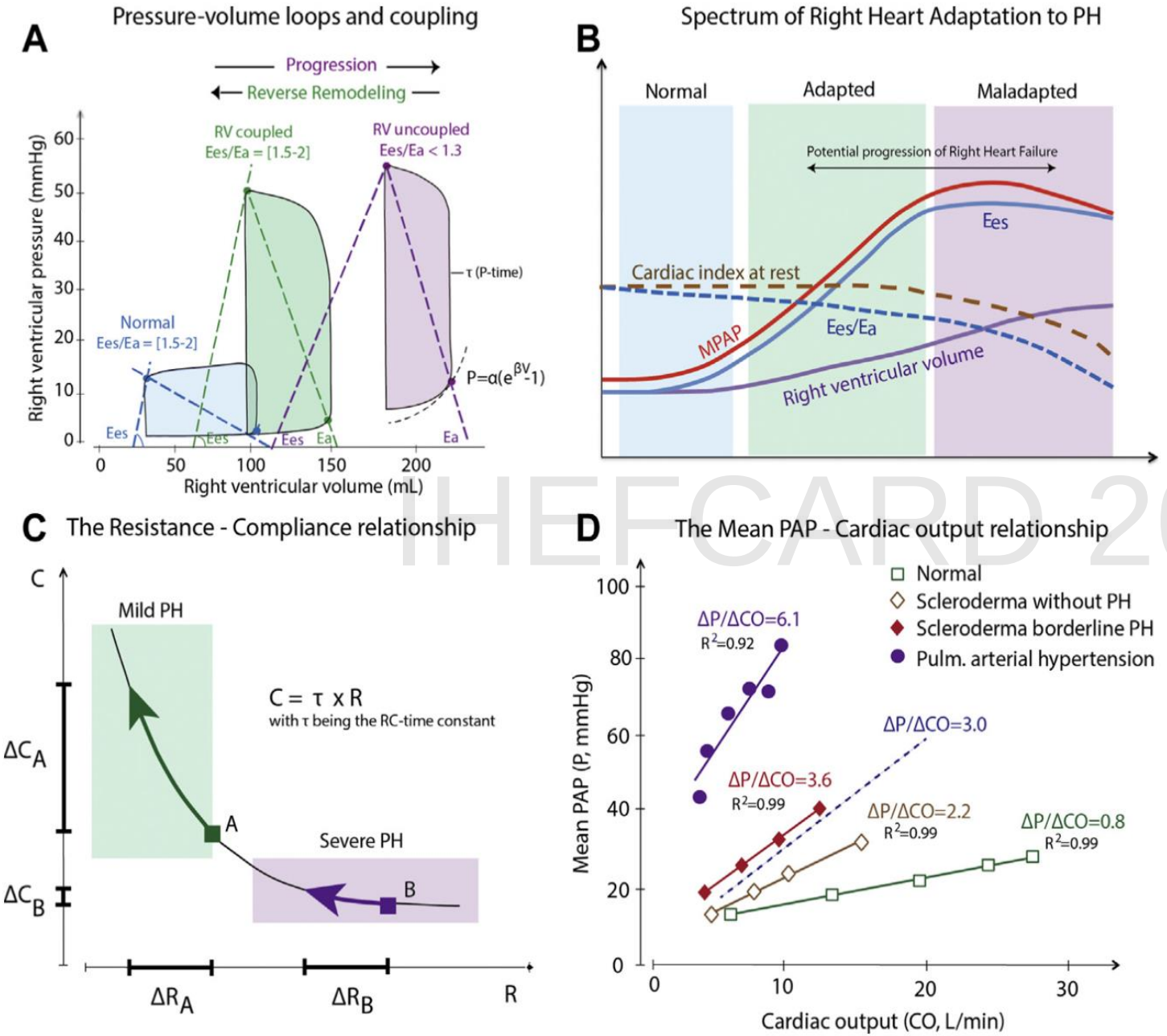




Gradual evolution towards end-stage Pulmonary Hypertension



RV failure reflects the inability of the RV to perfuse the lung circulation adequately to ensure LV filling while maintaining normal diastolic pressures. IT IS characterized by a decreased cardiac index (< 2.5 L/min/m^2) and increased right-sided, cardiac filling pressures, including right atrial pressure (RAP) ≥ 8 mmHg

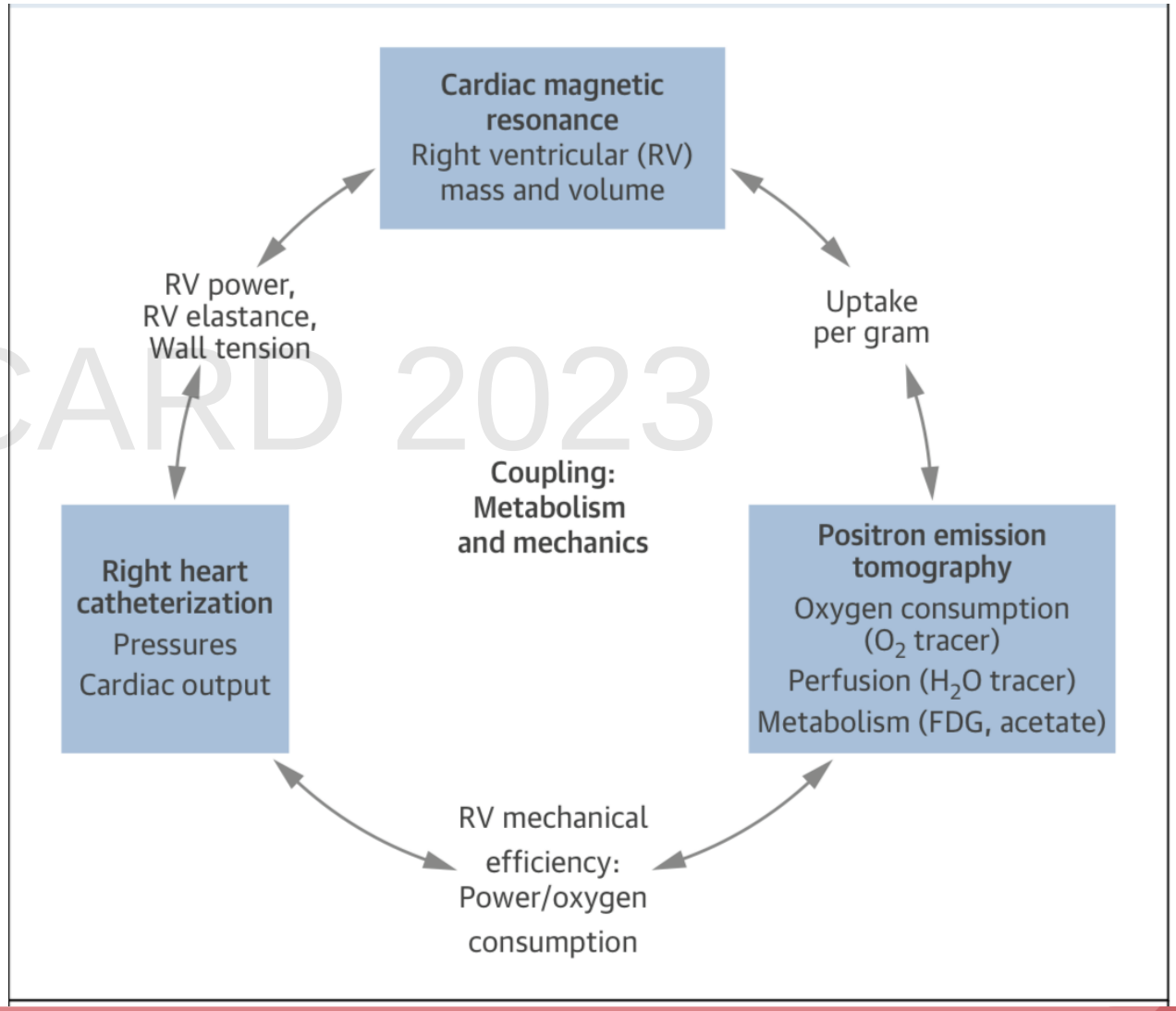


- Uncoupling will only occur in end-stage disease
- Volumetric measures, including measures of SV, RV end-diastolic volume, and RV end-systolic volume (RVESV), are parameters to be monitored during follow-up of patients with PH.

Vonk Noordegraaf et al., JACC. 2017.

How to determine the RV failure in Pulmonary Hypertension?

- Complete evaluation for the evaluation of RV failure requires:
  - echocardiographic or magnetic resonance imaging
  - right heart catheterisation measurements

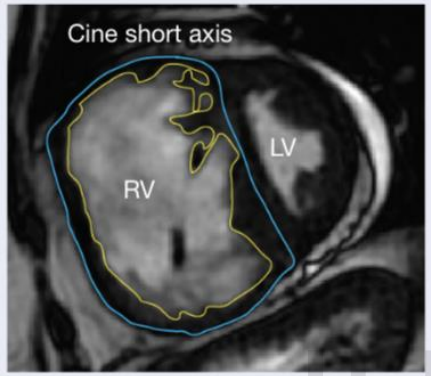


Vonk Noordegraaf et al., JACC. 2017.

RV global functional metrics

RV ejection fraction (RVEF)

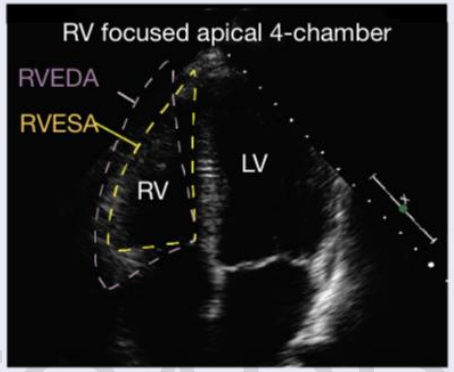
RVEF (%)= (RVEDV-RVESV)/RVEDV



Methods: CMR (Gold standard) or 3D Echo

RV fractional area change (RVFAC)

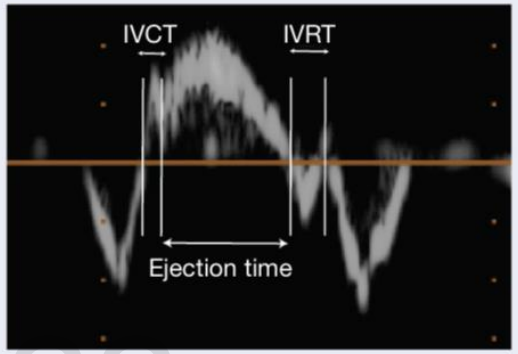
RVFAC (%)= (RVEDA-RVESA)/RVEDA



Methods: 2D Echo

RV myocardial performance index

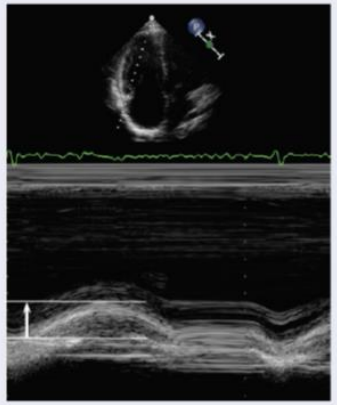
RV MPI = (IVRT + IVCT)/Ejection time



Methods: Tssue Doppler Imaging or Doppler

RV longitudinal metrics

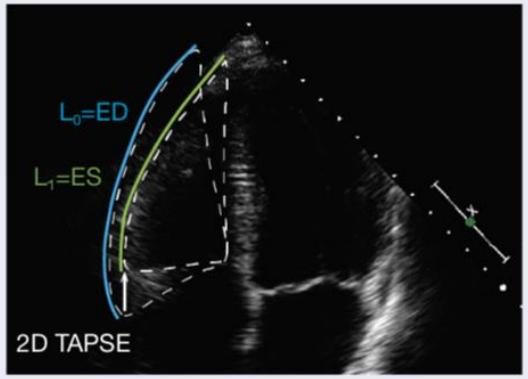
TAPSE



Methods: M-mode guided by 2D

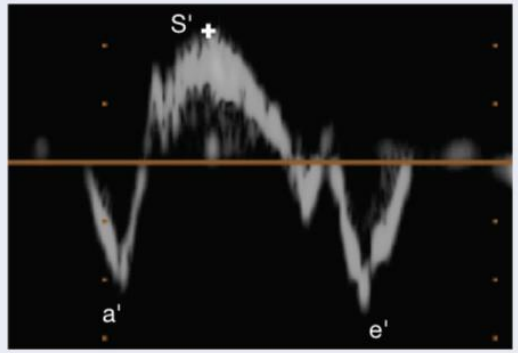
RV free-wall longitudinal strain (RVLS)

RVLS (%)= $(L_1-L_0)/L_0$



Methods: Speckle tracking or manual

TDI-based S' maximal velocity

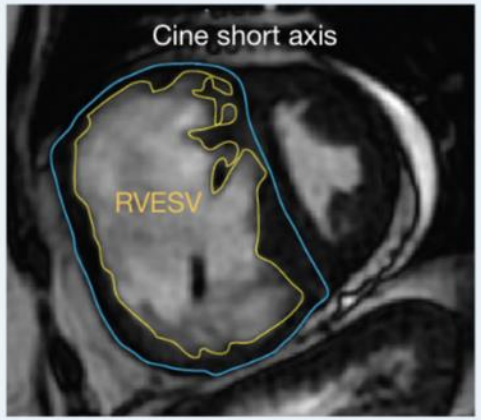


Methods: Tissue Doppler Imaging

Right heart remodeling

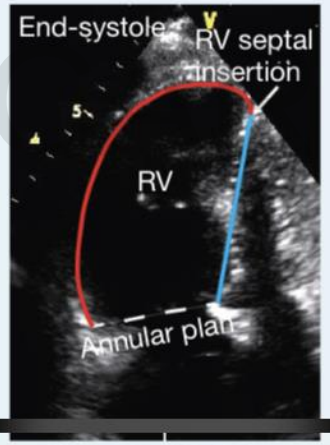
RV end-systolic volume index

RVESV index = RVESV/body surface area



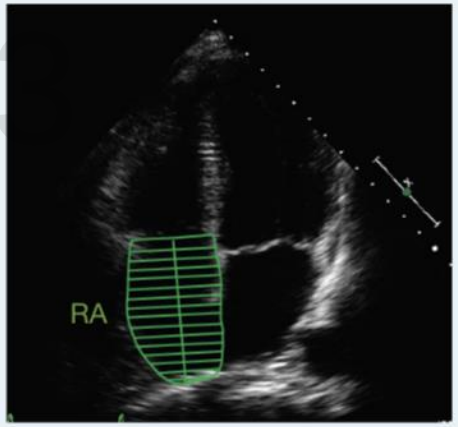
RV end-systolic remodeling index

RVESR index = lateral length/septal length



RA volume index

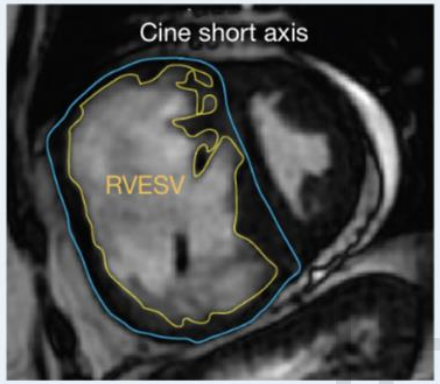
RAV index = RAV/body surface area



Right heart remodeling

RV end-systolic volume index

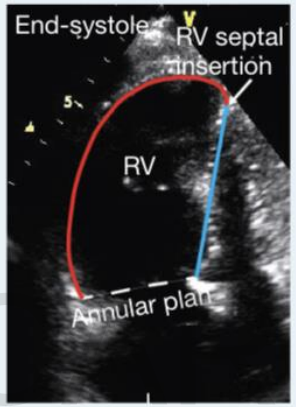
RVESV index = RVESV/body surface area



Methods: CMR (Gold standard) or 3D Echo

RV end-systolic remodeling index

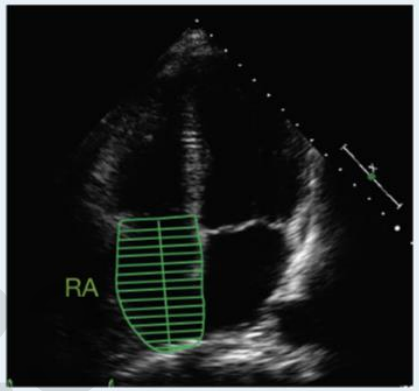
RVESR index = lateral length/septal length



Methods: 2D Echo

RA volume index

RAV index = RAV/body surface area

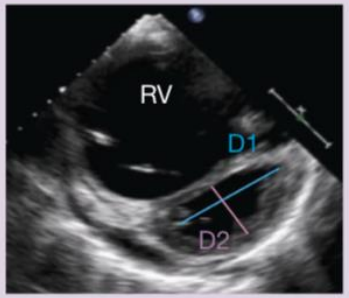


Methods: 2D Echo or CMR

RV dyssynchrony
RV-LV dependence

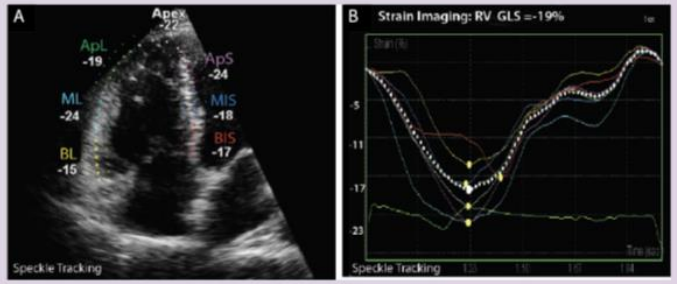
LV end-systolic eccentricity index

EIs= D1/D2



Methods: 2D Echo or CMR

Strain-based RV dyssynchrony



Methods: 2D or 3D Echo speckle-tracking or CMR

Management of RV failure in Pulmonary Hypertension

- Treatment of RV failure in PAH relies on:
  - Fluid management to optimise ventricular diastolic interactions
  - Decreasing afterload with drugs targeting pulmonary circulation
  - Inotropic interventions to reverse cardiogenic shock.
  - To date, there has been no report of the efficacy of drug treatments that specifically target the right ventricle.

Treating the cause

RV Preload optimisation

RV afterload reduction

Mechanical support

RV contractile support

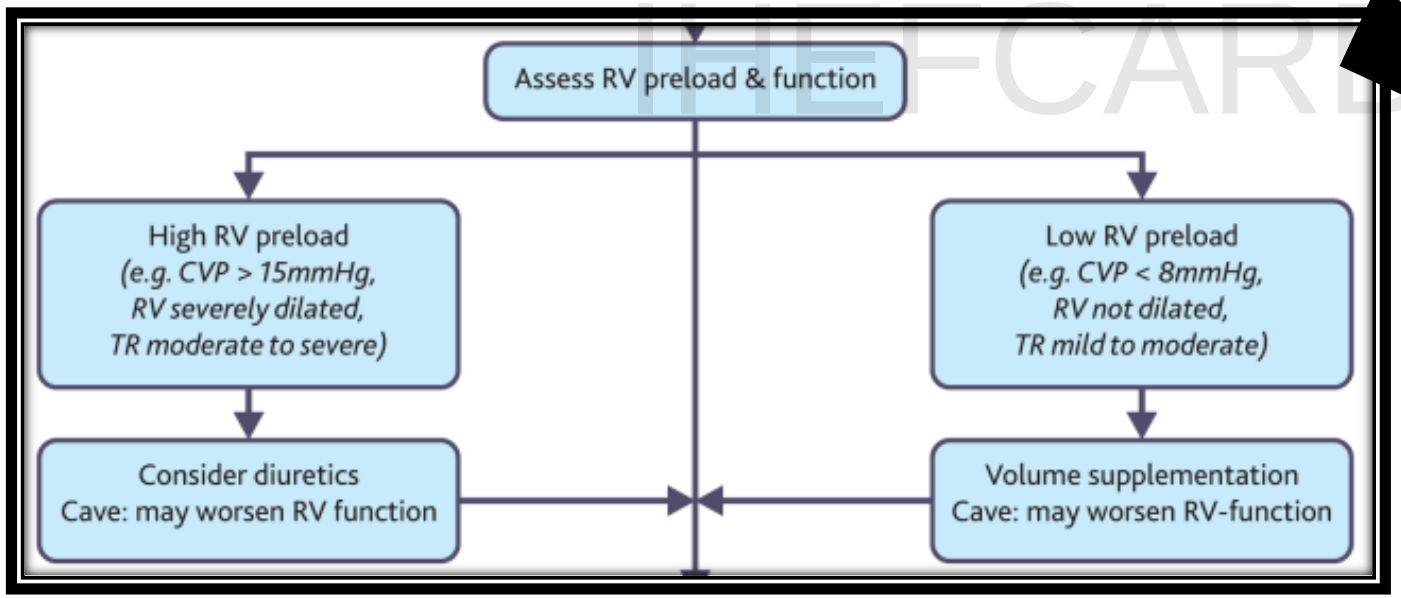
Volume optimization

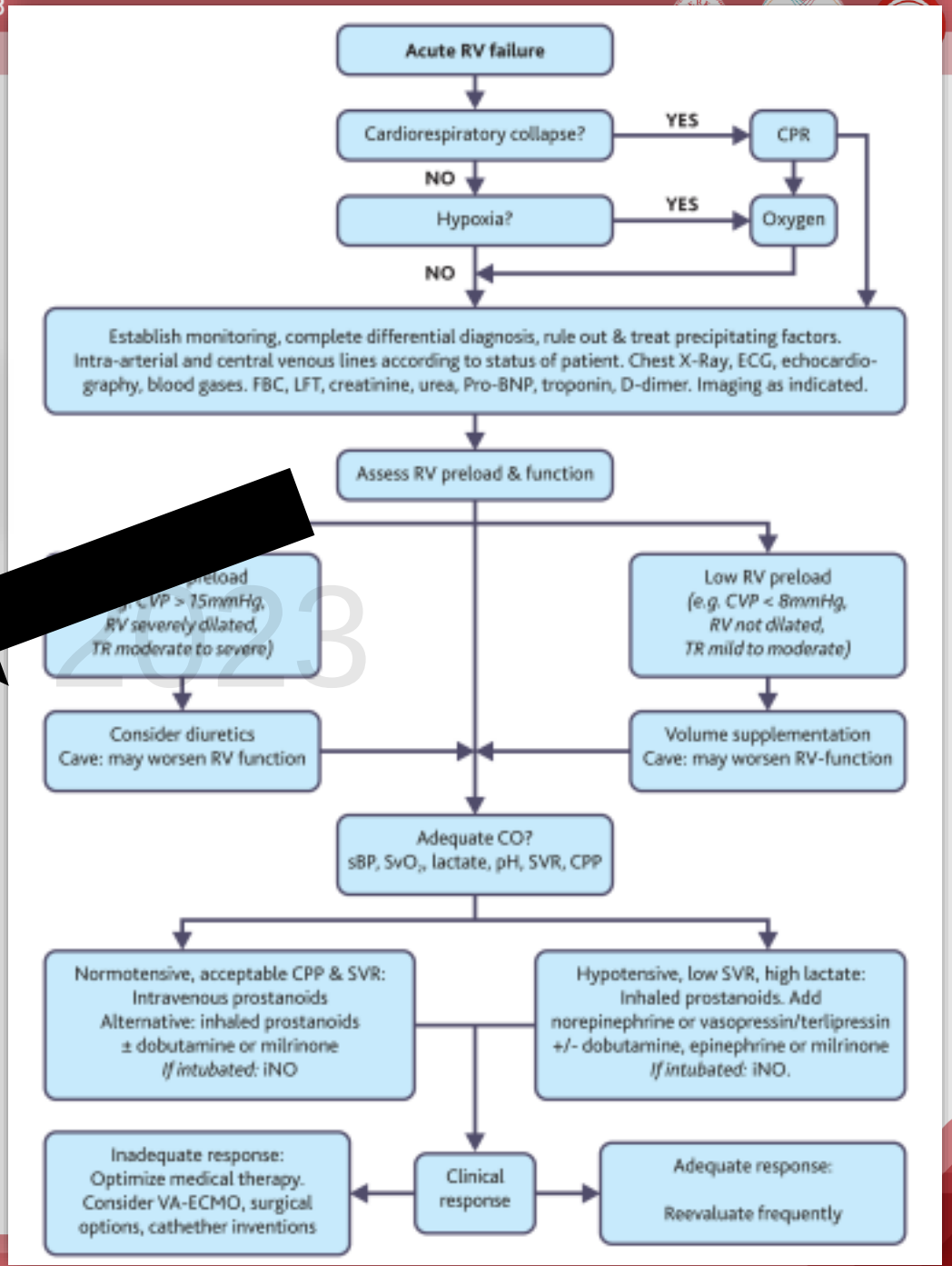
- The goal is to **optimize preload of the RV** to maximize perfusion while taking care to not overload it and decrease output
- Both **hypovolemia and hypervolemia** may result in reduced CO
- Because of tricuspid regurgitation and chronically elevated right-sided pressures, central venous pressure (CVP) is not an accurate indicator of LV preload in patients with pulmonary hypertension
- However, **following trends in CVP** is useful, and therefore early placement of a central venous line should be considered

Wilcox SR, Kabrhel C, Channick RN, 2015. Pulmonary Hypertension and Right Ventricular Failure in Emergency Medicine, *American College of Emergency Physicians*

Volume optimization

Optimize fluid status:
- IV diuretics if volume overload
- RRT if situation insufficiently managed with diuretics
- Cautious fluid filling if low CVP; avoid overfilling

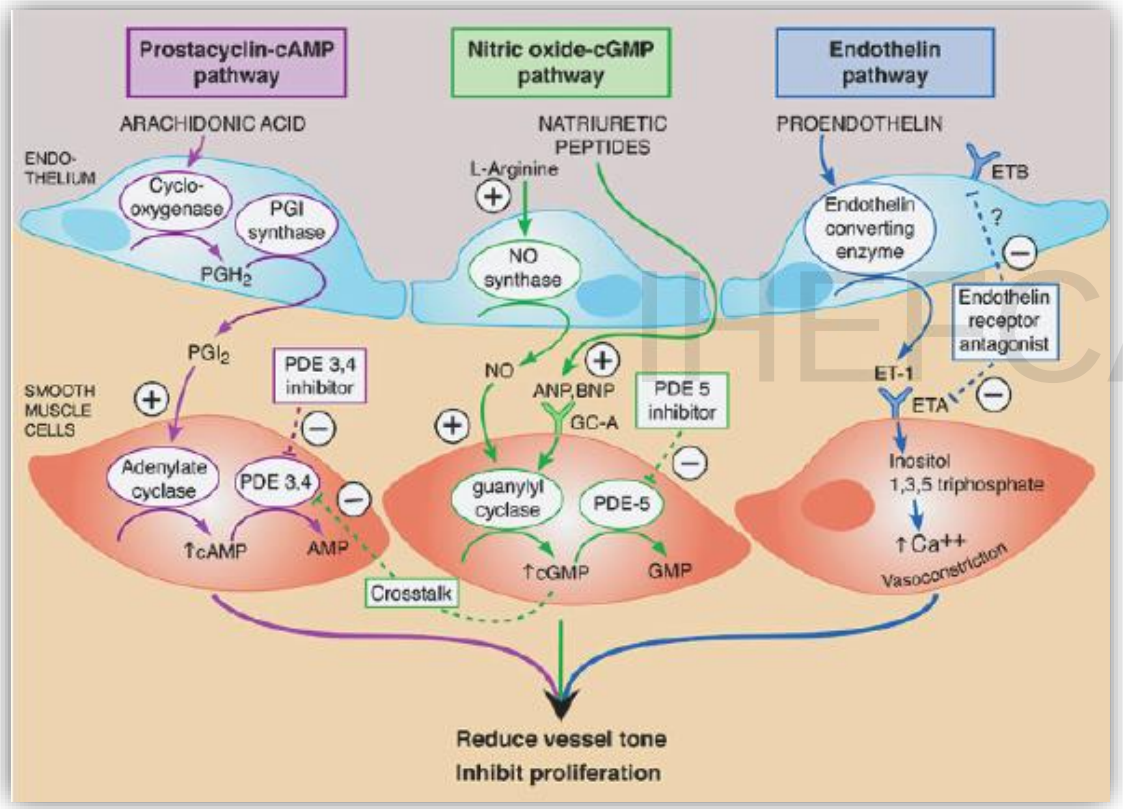


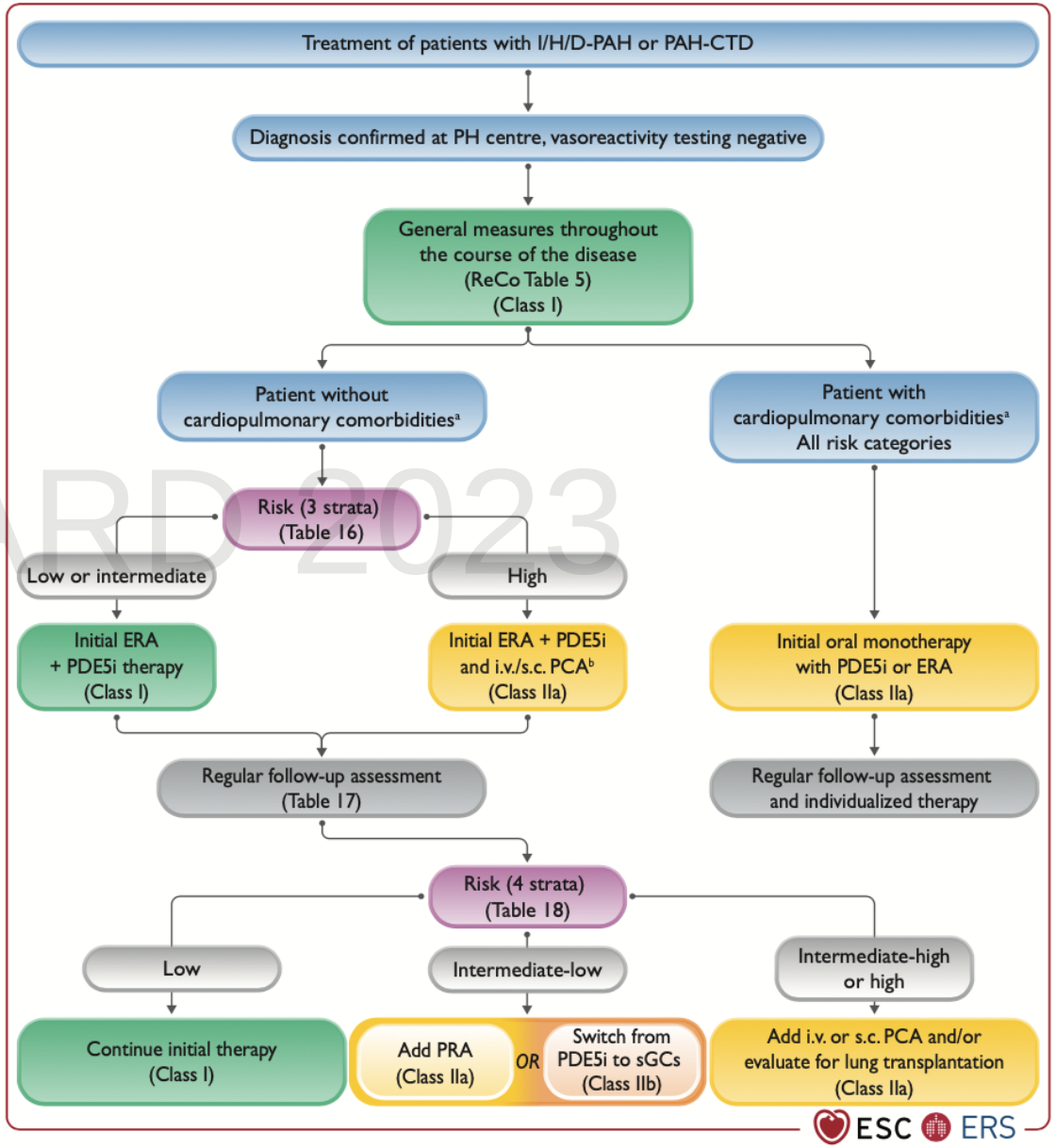


[1] Wilcox SR, Kabrhel C, Channick RN, 2015. Pulmonary Hypertension and Right Ventricular Failure in Emergency Medicine, *American College of Emergency Physicians*

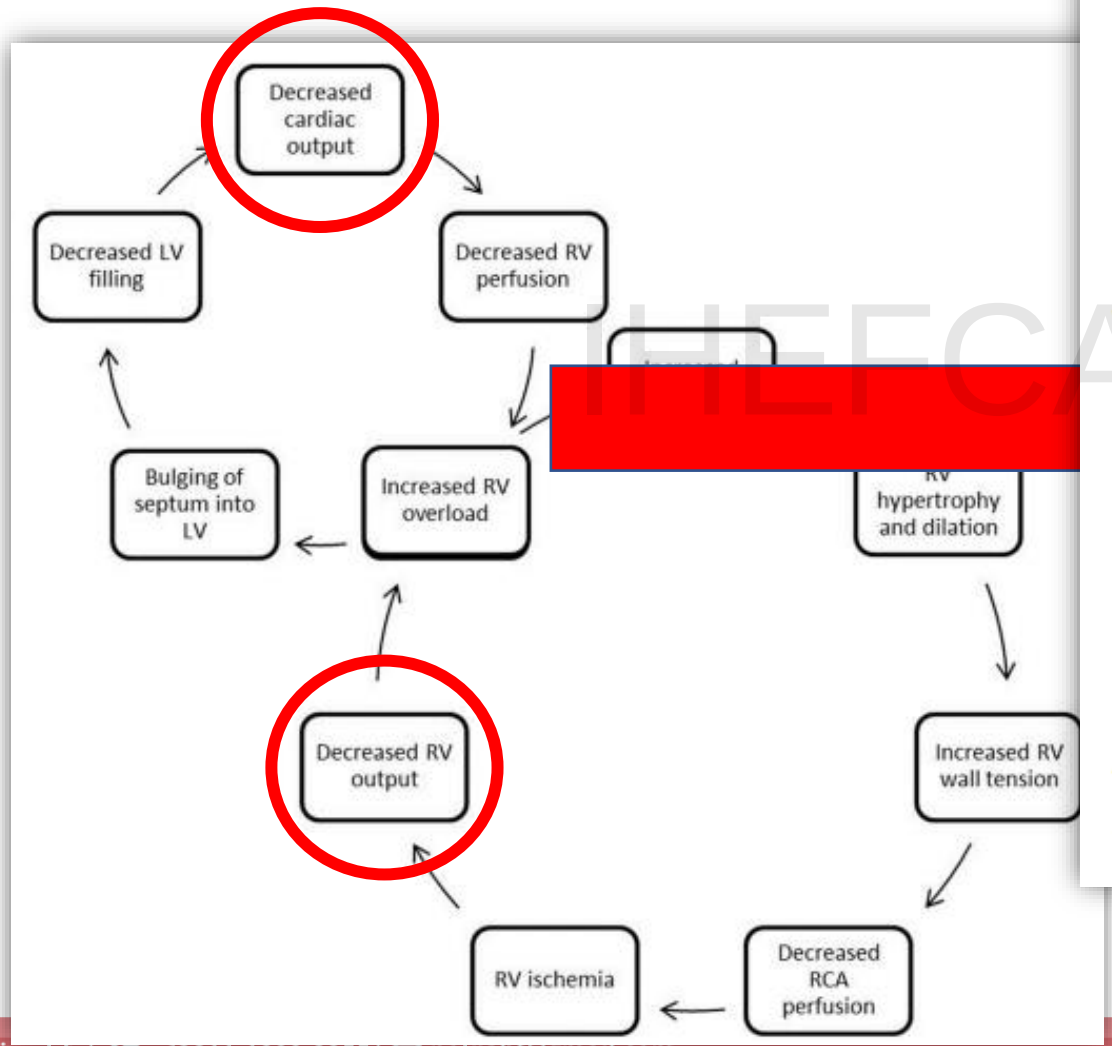
[2] Kaestner M, et al. Heart 2016;102:ii57–ii66. doi:10.1136/heartjnl-2015-307774

Reducing RV Afterload





Maintaining CO and Systemic BP



Agent	Receptor Binding α_1	β_1	β_2	D	V1	Notes
Norepinephrine	++	+				Improves PA/RV coupling in animals (73–75)
Phenylephrine	++					Increases PVR (71, 74, 77); may induce reflex bradycardia
Epinephrine	++	++	+			(79)
Vasopressin					+	Dose dependent pulmonary vasodilatation (0.01–0.03 U/min) and vasoconstriction (24, 82, 83)
Dopamine						Risk of arrhythmias
Low (<5 μg/kg/min)		+		++		
Medium (>10 μg/kg/min)	+	++		++		
High (>10 μg/kg/min)	++	++		++		
Dobutamine		++	+			β_2-mediated drop in SVR (31); risk of arrhythmias
Milrinone						Phosphodiesterase-3 inhibitor; inotropy and pulmonary vasodilatation; drop in LVEDP and SVR (72, 84, 89); risk of arrhythmias

Definition of abbreviations: D = dopaminergic receptor; LVEDP = left ventricular end-diastolic pressure; PA = pulmonary artery; PVR = pulmonary vascular resistance; RV = right ventricle; SVR = systemic vascular resistance; V1 = vasopressin receptor 1. + = low to moderate affinity, ++ = moderate to high affinity.

Hoeper and Granton. Intensive Care Unit Management of Patients with Severe Pulmonary Hypertension and Right Heart Failure. *Am J Respir Crit Care Med Vol 184. pp 1114–1124, 2011*

Mechanical Support of the Failing Right Heart

Consideration for RH support = RHF phenotype (predominant vs. bi-ventricular) + Expected duration of Support + PVR + Respiratory failure + Surgical considerations

Extracorporeal or Paracorporeal

Impella RP©
Microaxial pump

TandemHeart™
Centrifugal pump

Protek Duo®
Centrifugal pump

CentriMag©
Centrifugal pump

Excor Pediatric©
Pulsative flow pump

VA- ECMO
Continuous flow

Novalung©
Pumpless oxygenator

Implantable

HVAD™

SynCardia©

Short-term

Biventricular failure
(e.g. HFrEF, pre- or post-transplant, post-LVAD)

Short-term
Bridge to recovery
Bridge to transplant

VA-ECMO#
Additional RV support to LV support:
- ImpellaRP©
- TandemHeart™ pVAD
- RA-PA ECMO
- RA-PA pumps (CentriMag©, ProtekDuo®)
- Excor Pediatric©

Paracorporeal dual pump (e.g. Thoratec PVAD)

Durable
Bridge to transplant
Destination therapy

BiVAD (RVAD + LVAD)*
Total artificial heart (e.g. SynCardia©)

Predominant RHF with low/mild PVR
(e.g. Acute RV myocardial infarction)

ImpellaRP©
TandemHeart™ pVAD
VA-ECMO
Oxy-RVAD
(e.g. HVAD * or ProtekDuo® plus TandemLung®)

Predominant RHF with high PVR
(e.g. Pulmonary arterial hypertension)

ECMO (VA, VAV, VA+atrioseptostomy, VV+atrioseptostomy)

Pumpless PA-LA oxygenator
(e.g. Novalung©)

#Favored in case of respiratory failure
*Off-label for RHF

Durable

Summary

- Decreased RV function predicts worsening of Pulmonary Hypertension and lead to high mortality rate
- Careful follow up of PH patients using multimodality approach is needed to understand the stage of RV function
- To date, the has been no medications showed efficacy towards improvement of RV function in PH patients
- Lung transplantation in the only best approach for end stage RV failure in PH patients.

COHARD-PH REGISTRY

thank you






















Thank you