Pulmonary Hypertension in the era of COVID pandemic:

The Role of Cardiopulmonary Exercise Test

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Cardiopulmonary exercise test (CPET)

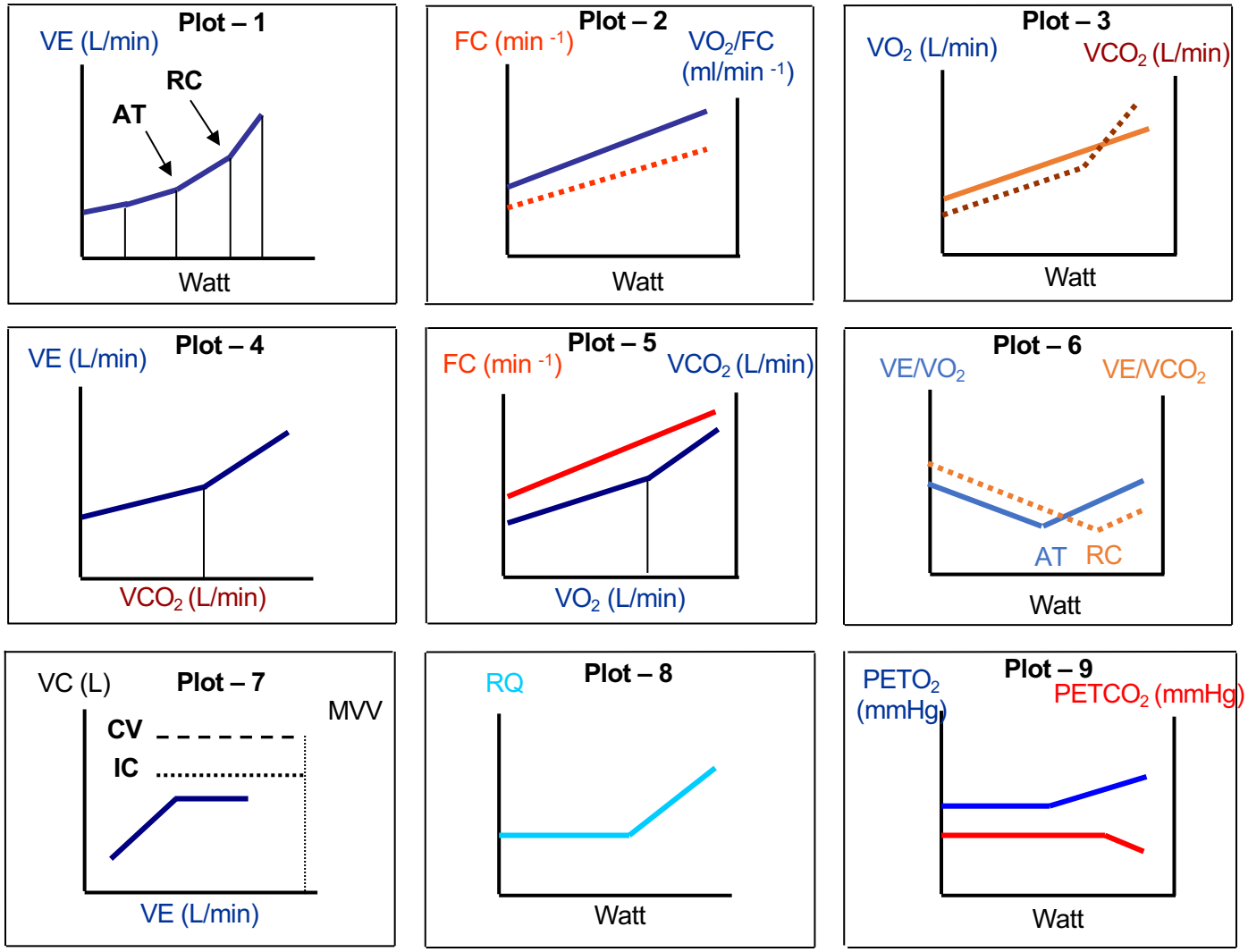
The cardiopulmonary exercise test (CPET) is a noninvasive method to assess functional capacity and exercise limitation, providing information about the cardiovascular, respiratory, metabolic and muscular response to physical effort, thanks to the analysis of ventilation and exhaled gases

- **Cardiopulmonary variables**
  - **Oxygen consumption (VO_2)** → cardiac output
  - **Carbon dioxide consumption (VCO_2)**
  - **Minute ventilation (VE)**
  - **End-tidal pressure of O_2 ($P_{ET}O_2$) and of CO_2 ($P_{ET}CO_2$)**

- **Derived parameters**
  - **Oxygen pulse (VO_2/HR)** → systolic stroke
  - **Ventilatory equivalent for O_2 (VE/VO_2) and CO_2 (VE/VCO_2)** → V/Q
  - **Ventilatory efficiency slope (VE/VCO_2)**
  - **Cardiocirculatory efficiency slope (VO_2/W)**
  - **RER (VCO_2/VO_2)**
  - **Anaerobic threshold (AT)**
  - **VD/VT**

Cardiopulmonary exercise test (CPET)

The Wasserman 9-Panel Plot



Pulmonary Arterial Hypertension (PAH) definition

ESC guidelines 2015

Pulmonary arterial hypertension is a clinical condition characterized by the presence of pre-capillary PH and pulmonary vascular resistance >3 Wood units, in the absence of other causes of pre-capillary PH (PH due to lung diseases, chronic thromboembolic PH, or other rare diseases)

Definition	Characteristics[a]	Clinical group(s)[b]
PH	PAPm ≥25 mmHg	All
Pre-capillary PH	PAPm ≥25 mmHg PAWP ≤15 mmHg	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	PAPm ≥25 mmHg PAWP >15 mmHg	2. PH due to left heart disease 5. PH with unclear and/or multifactorial mechanisms

Pulmonary Hypertension classification

ESC guidelines 2015

1. Pulmonary arterial hypertension

- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2 mutation
  - 1.2.2 Other mutations
- 1.3 Drugs and toxins induced
- 1.4 Associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 Human immunodeficiency virus (HIV) infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

- 1'.1 Idiopathic
- 1'.2 Heritable
  - 1'.2.1 EIF2AK4 mutation
  - 1'.2.2 Other mutations
- 1'.3 Drugs, toxins and radiation induced
- 1'.4 Associated with:
  - 1'.4.1 Connective tissue disease
  - 1'.4.2 HIV infection

1''. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease

- 2.1 Left ventricular systolic dysfunction
- 2.2 Left ventricular diastolic dysfunction
- 2.3 Valvular disease
- 2.4 Congenital / acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
- 2.5 Congenital /acquired pulmonary veins stenosis

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

- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental lung diseases

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

- 4.1 Chronic thromboembolic pulmonary hypertension
- 4.2 Other pulmonary artery obstructions
  - 4.2.1 Angiosarcoma
  - 4.2.2 Other intravascular tumors
  - 4.2.3 Arteritis
  - 4.2.4 Congenital pulmonary arteries stenoses
  - 4.2.5 Parasites (hydatidosis)

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

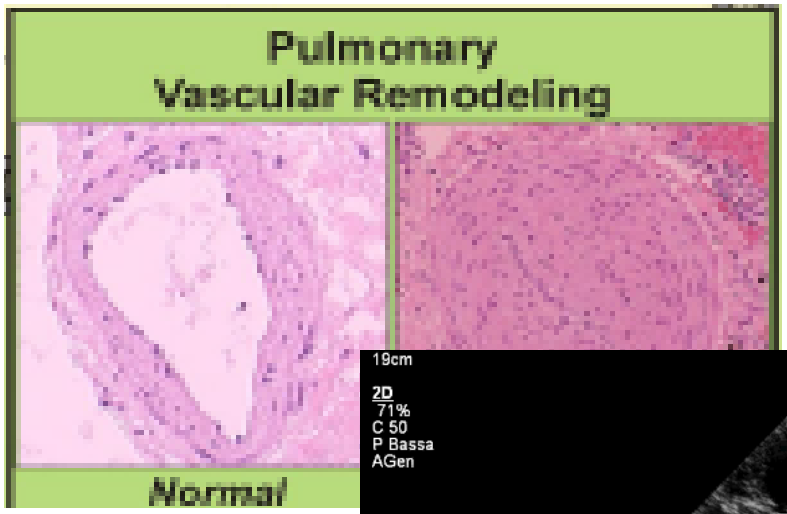
- 5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, neurofibromatosis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

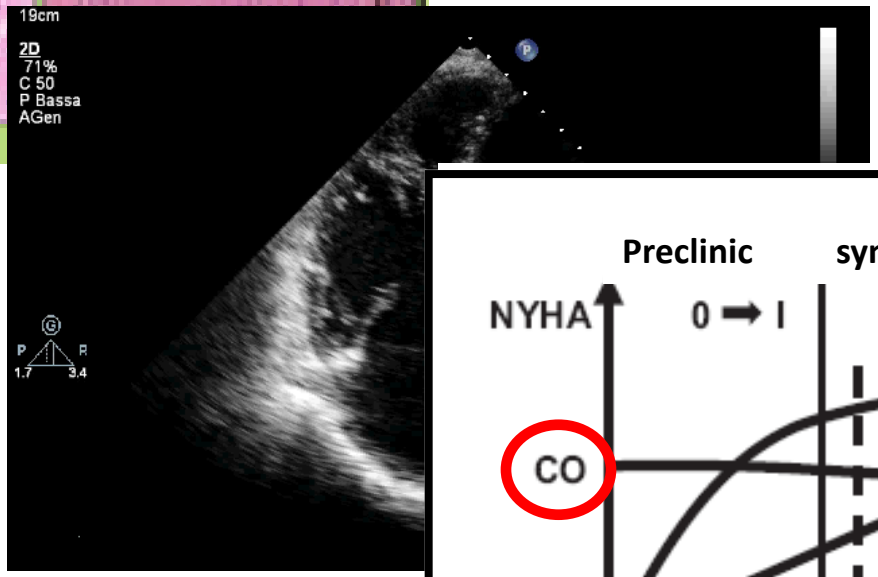
Diagnostic classification of pulmonary hypertension (from Galiè et al, Eur Heart J 2016; 37:67-119)

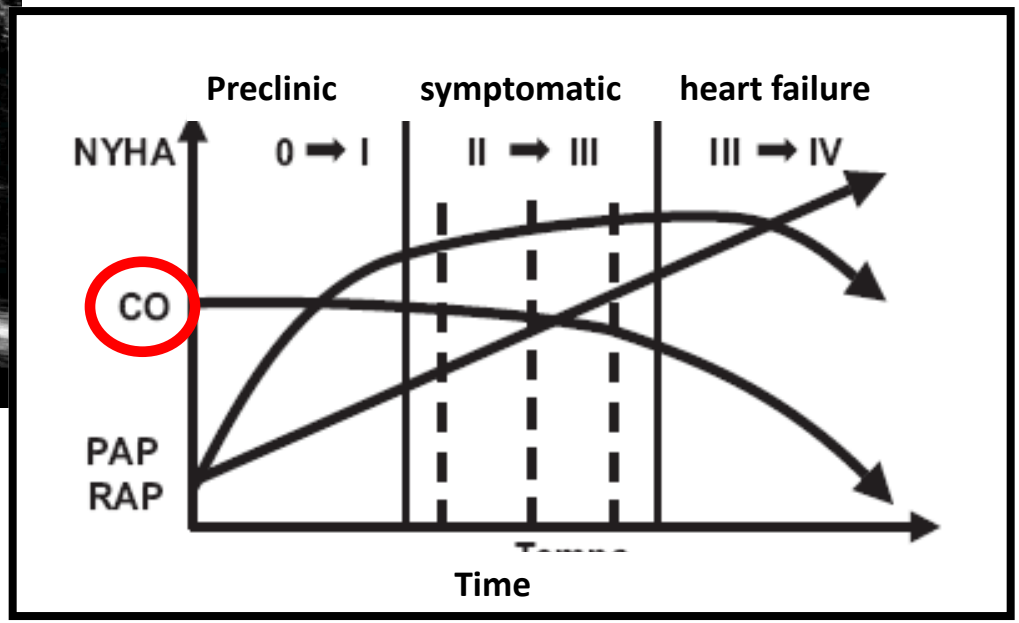
Pulmonary Arterial Hypertension clinical definition

Dyspnea-fatigue syndrome with eventual systemic congestion, caused by the inability of the RV to maintain flow output

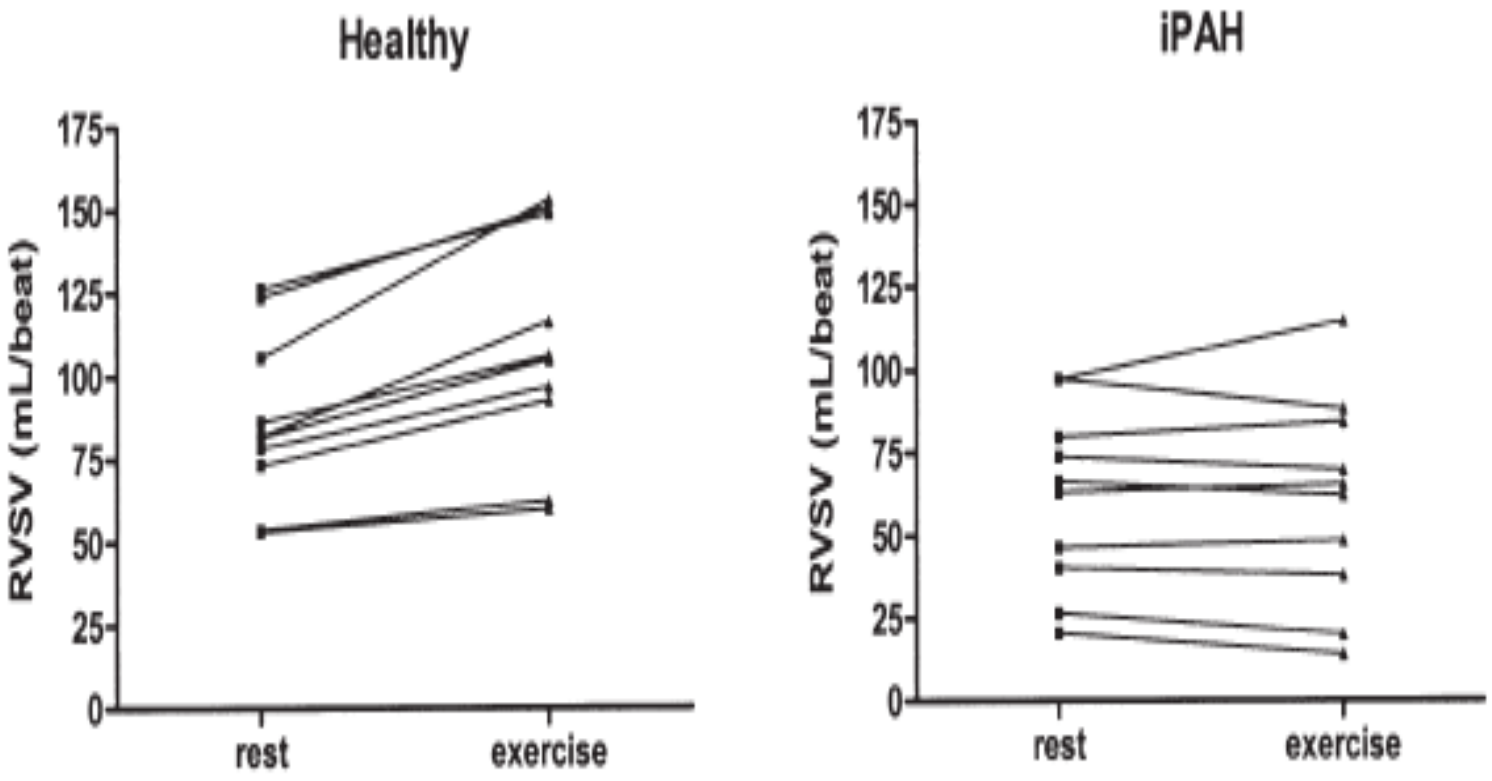
Functional and hemodynamic progression in PAH







Lack of cardiac output increase during exercise

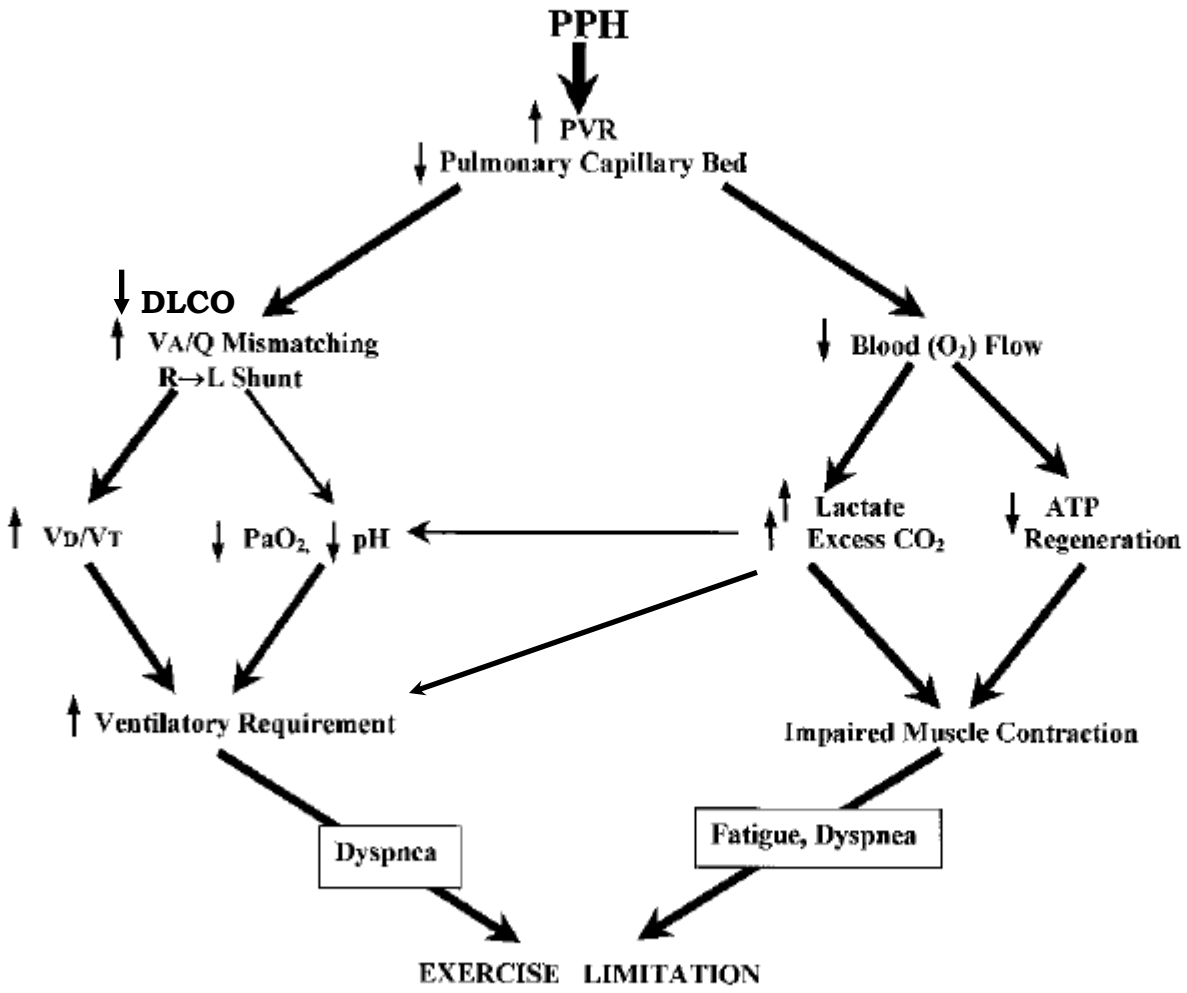


Holverda et al. JACC 2006;8:1724-38

Dyspnoea in PAH

- Failure to increase cardiac output (O_2 transport) appropriately in response to exercise, causing a low work rate lactic acidosis (increased CO_2 production relative to O_2 consumption), thereby increasing acid ventilatory drive
- Failure to perfuse the ventilated lung, thereby increasing the physiologic dead space and ventilatory requirement
- Exercise-induced hypoxemia in most PAH patients, increasing the hypoxic ventilatory drive
- Altered chemosensitivity
- Respiratory and peripheral muscle impairment

Dyspnoea in PAH



Sun XG et al. Circulation 2001;104:429-435

The role of CPET in clinical practice

- The level of exercise intolerance and identification of the mechanisms limiting exercise tolerance
- Evaluation of disease progression and response to interventions
- Functional and prognostic evaluation

PAH clinical assessment and FU definition

ESC guidelines 2015

	At baseline	Every 3–6 months[a]	Every 6–12 months[a]	3–6 months after changes in therapy[a]	In case of clinical worsening
Medical assessment and determination of functional class	+	+	+	+	+
ECG	+	+	+	+	+
6MWT/Borg dyspnoea score	+	+	+	+	+
CPET	+		+		+[e]
Echo	+		+	+	+
Basic lab[b]	+	+	+	+	+
Extended lab[c]	+		+		+
Blood gas analysis[d]	+		+	+	+
Right heart catheterization	+		+[f]	+[e]	+[e]

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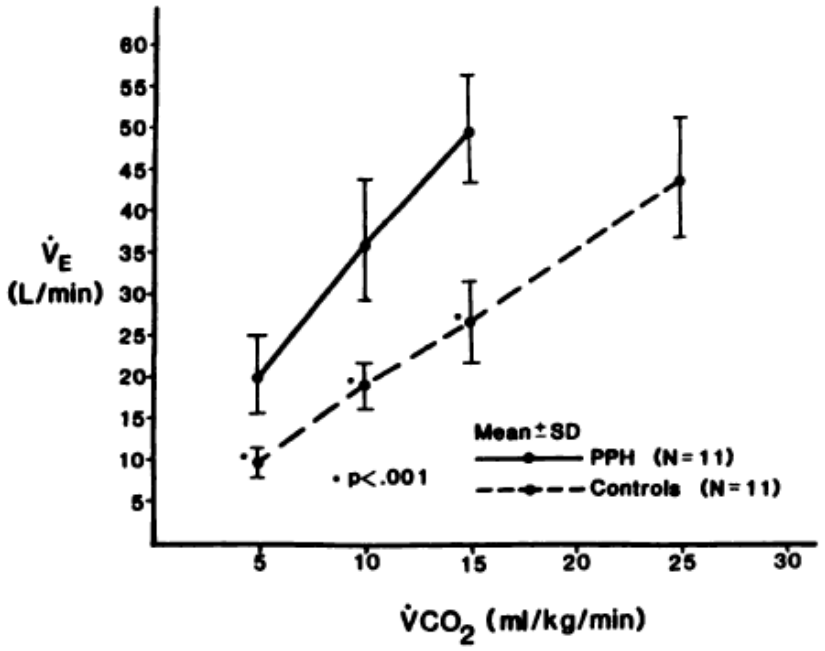
PAH - Ventilatory abnormalities

- Elevated ventilatory response to exercise due to high VA/Q ratio
- High VE/VCO_2 slope

PAH - Ventilatory abnormalities



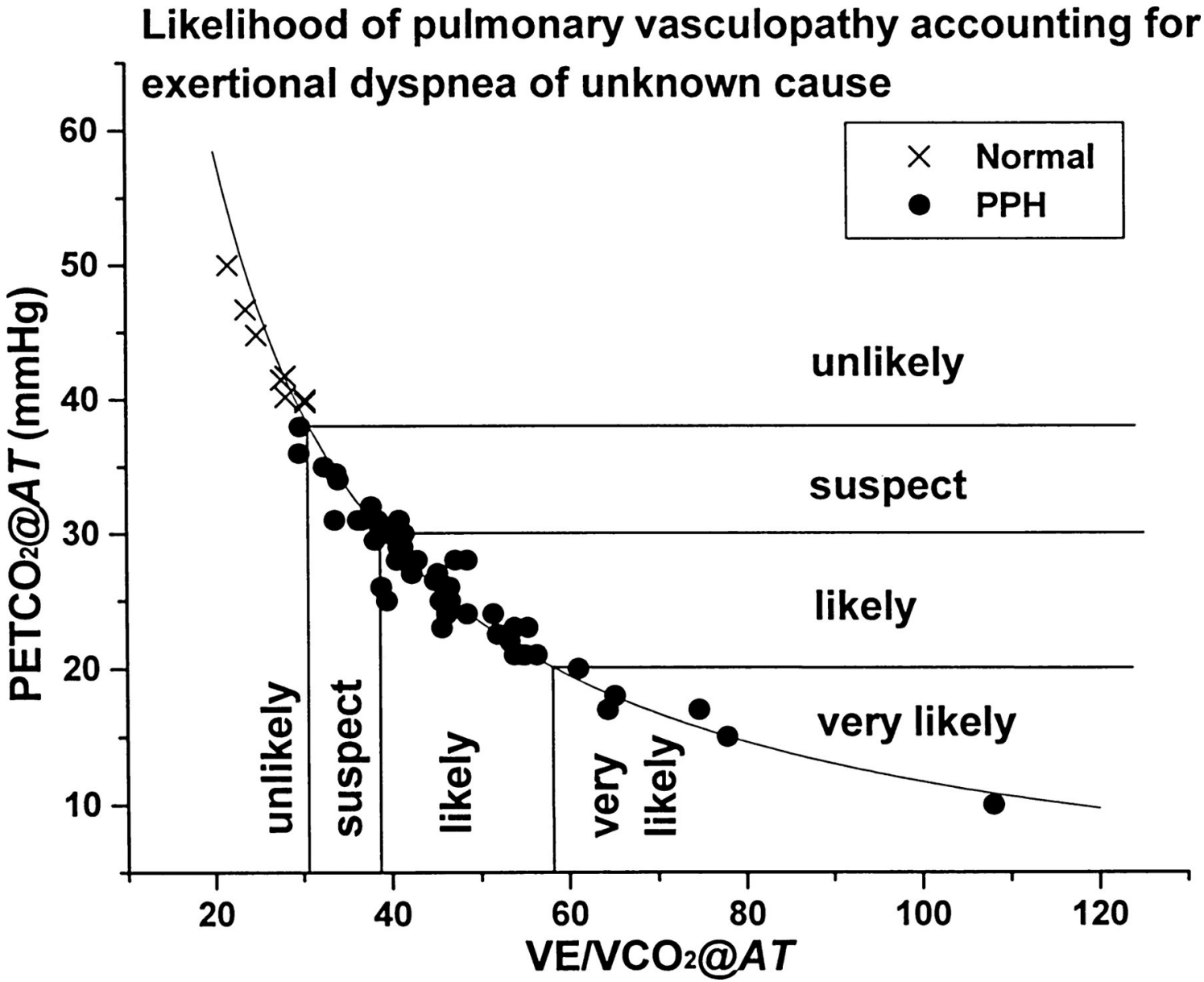
D'Alonzo GE et al. Chest 1987;92;57-62

PAH - Ventilatory abnormalities

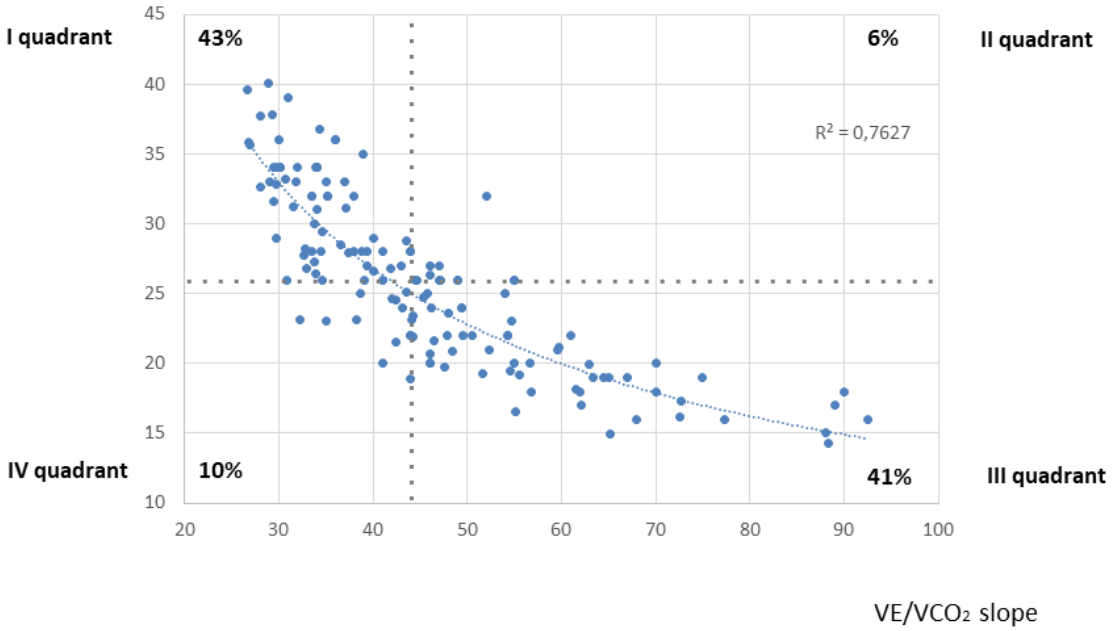
- Elevated ventilatory response to exercise due to high VA/Q ratio
- High VE/VCO_2 slope
- High VE/VCO_2 at AT
- Higher VE/VO_2 at any given work rate
- VE/MVV usually normal
- VD/VT increasing to > 30% during exercise

PAH - Gas exchange abnormalities

- Higher $P(A\text{-}a)O_2$
- Reduced $P_{ET}CO_2$
- Increased $P(a\text{-}ET)CO_2$
- Drop in oximeter saturation > 3% without $PaCO_2$ rise

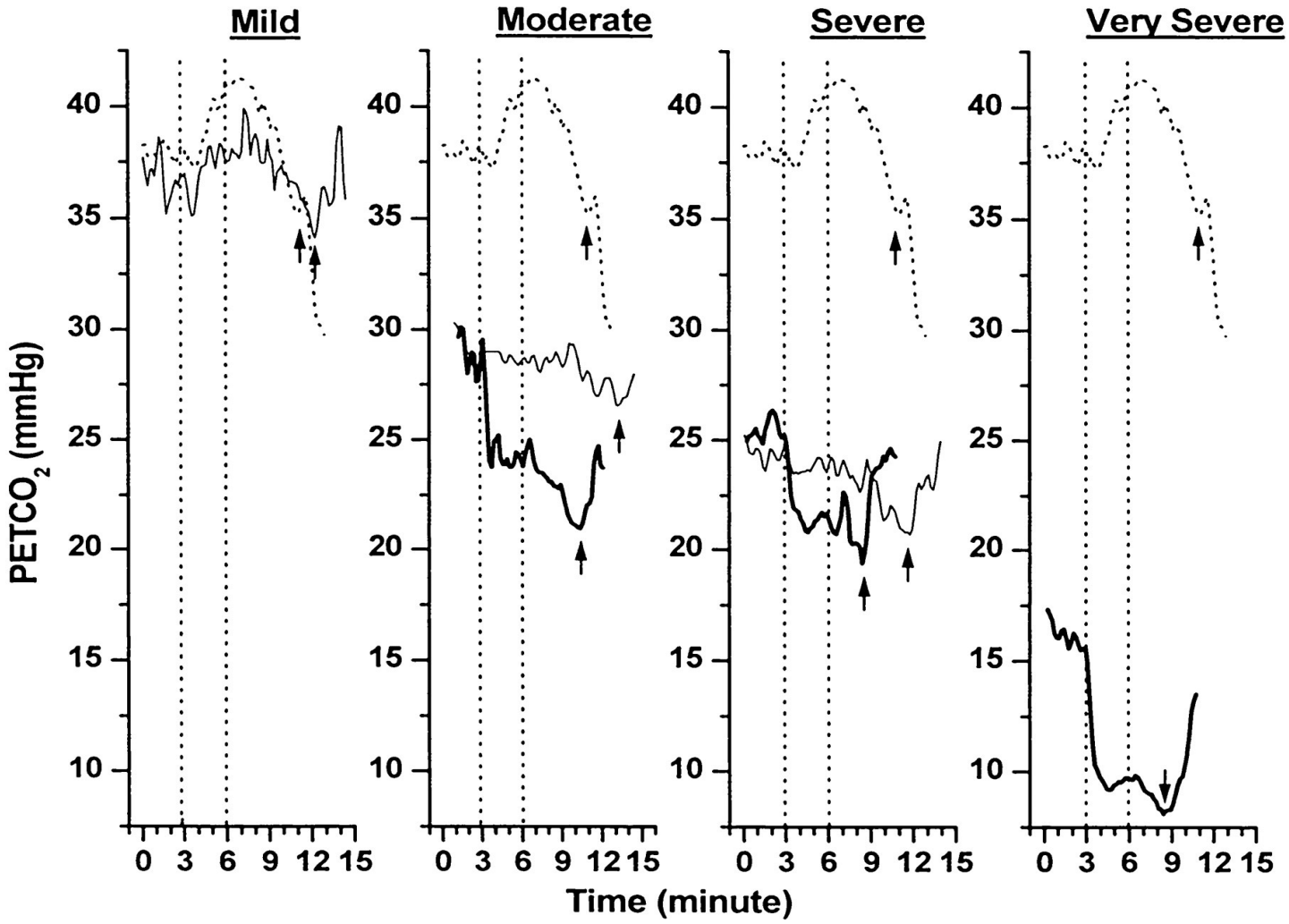


Yasunobu Y et al. Chest 2005;127:1637-1646



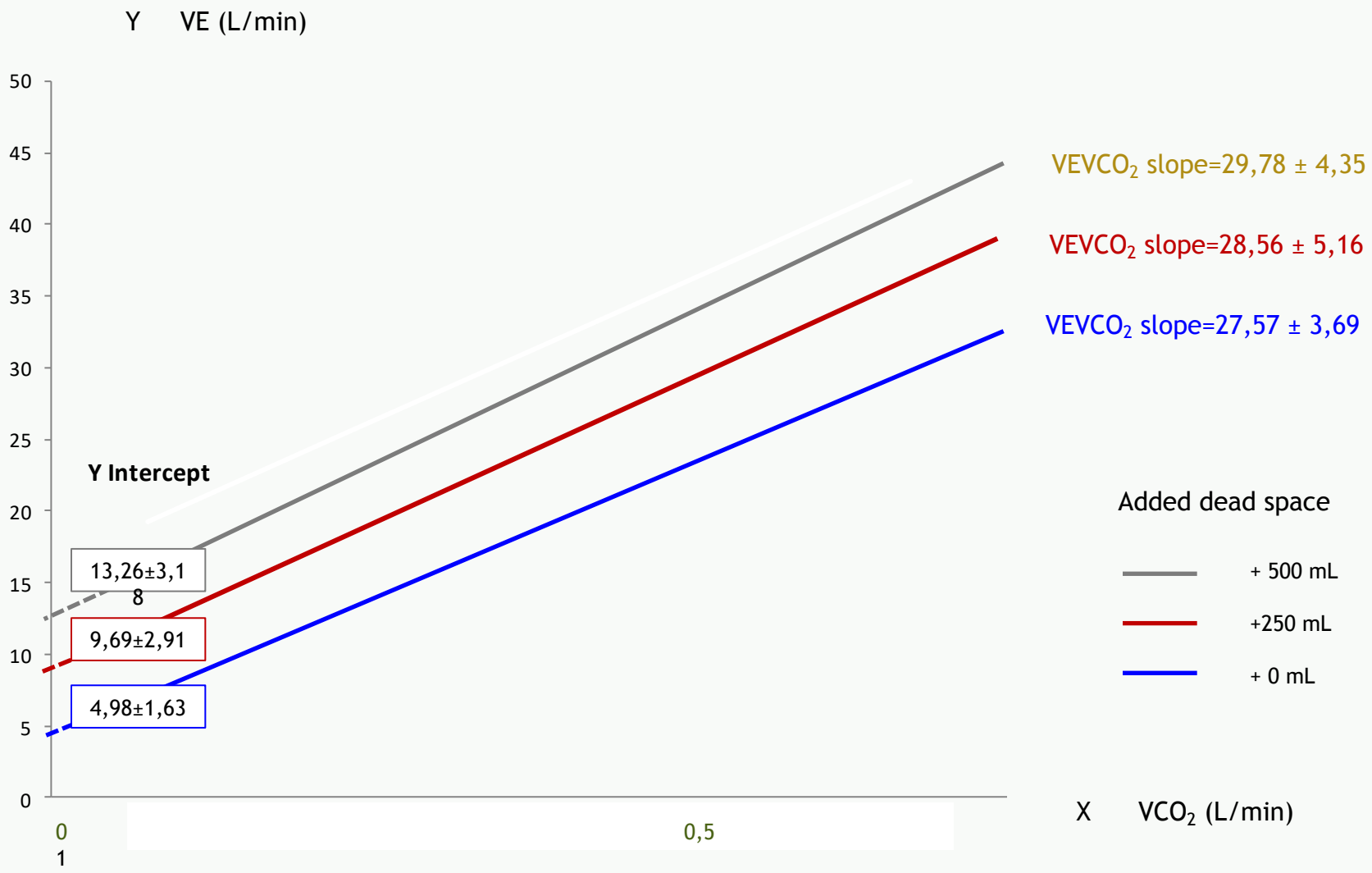
Quadrant	N pts (%)	mPAP (mmHg)	RAP (mmHg)	CI (L/min/m²)	PVR (WU)
I Peak $P_{ET}CO_2$ > median - VE/VCO_2 slope < median	63 (48%)	41 ± 15*	7 ± 3	2.7 ± 0.7	7.9 ± 5.2*
II Peak $P_{ET}CO_2$ and VE/VCO_2 slope > median	14 (10%)	47 ± 18	8 ± 5	2.5 ± 0.4	8.4 ± 5.8
III Peak $P_{ET}CO_2$ < median - VE/VCO_2 slope > median	58 (41%)	49 ± 14*	8 ± 4	2.4 ± 0.7	10.7± 5.7*
IV Peak $P_{ET}CO_2$ and VE/VCO_2 slope < median	9 (6%)	47 ± 16	7 ± 5	2.4 ± 0.7	8.7 ± 4.0

Pezzuto et al, Pulmonary Circulation 2022

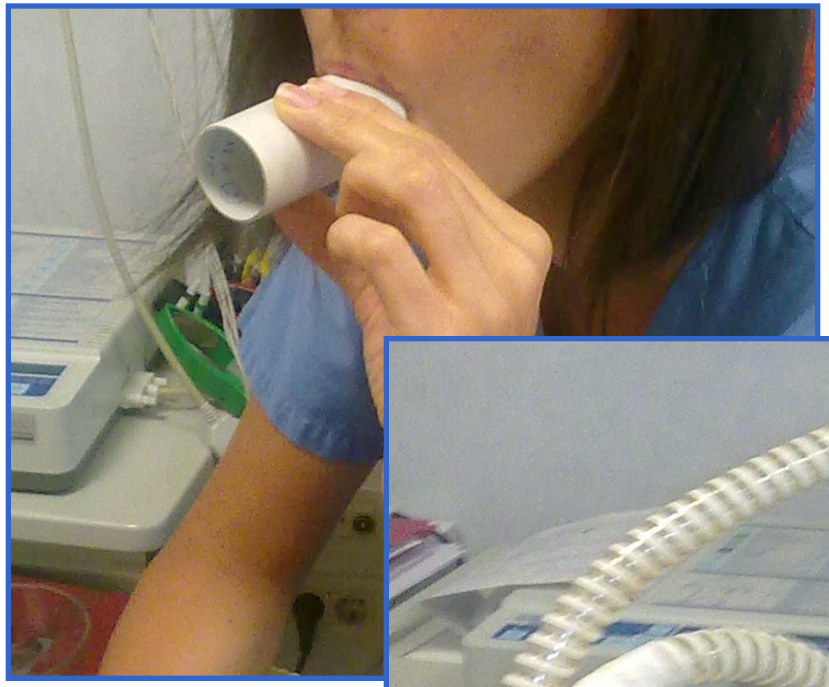


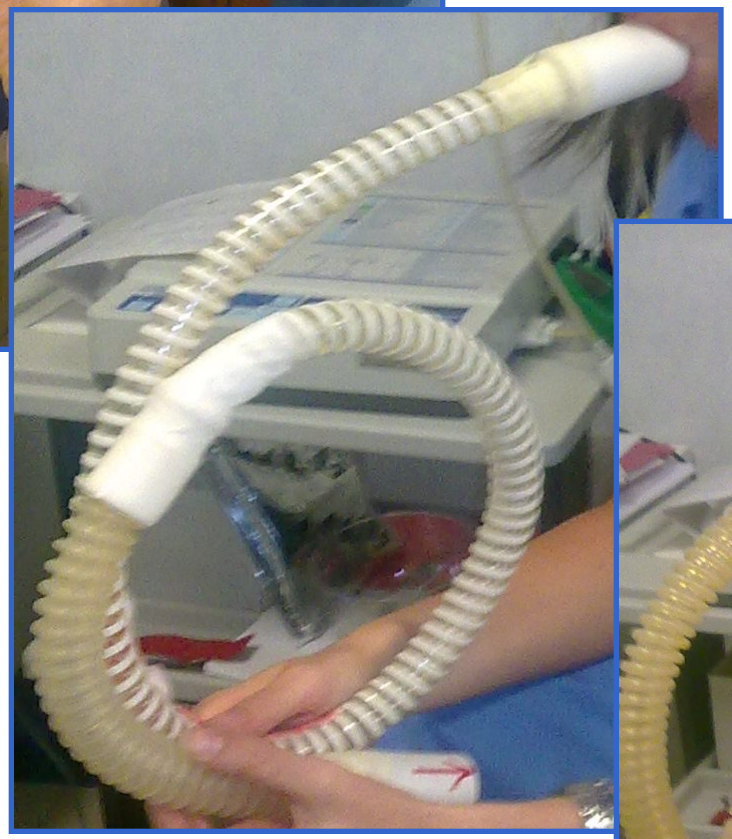
The dotted line at 3 min shows the start of unloaded pedaling, and the dotted line at 6 min shows the start of increasing work rate exercise.

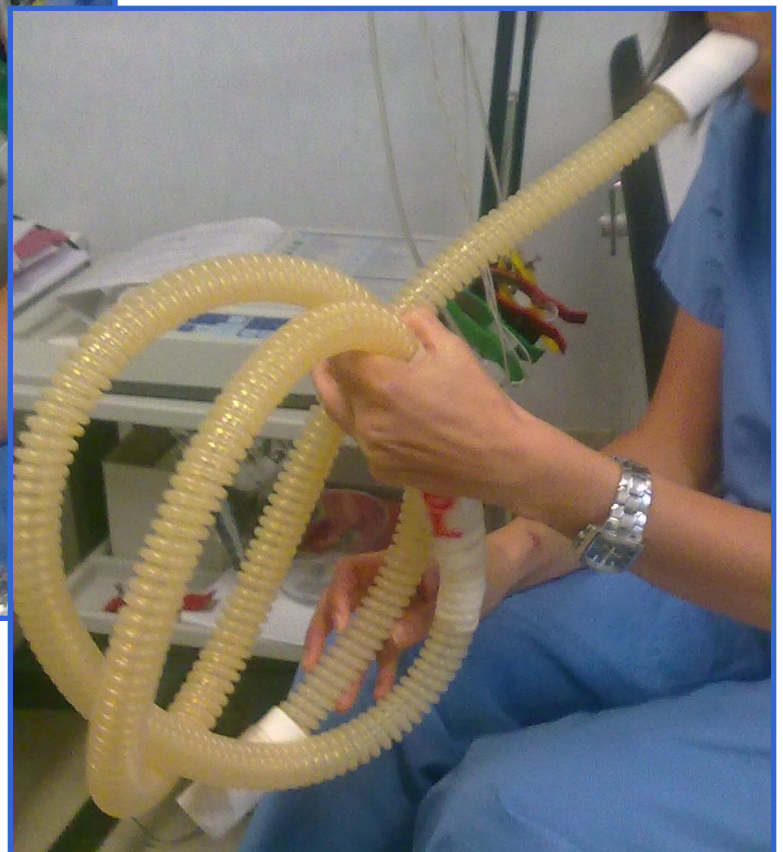
Yasunobu Y et al. Chest 2005;127:1637-1646

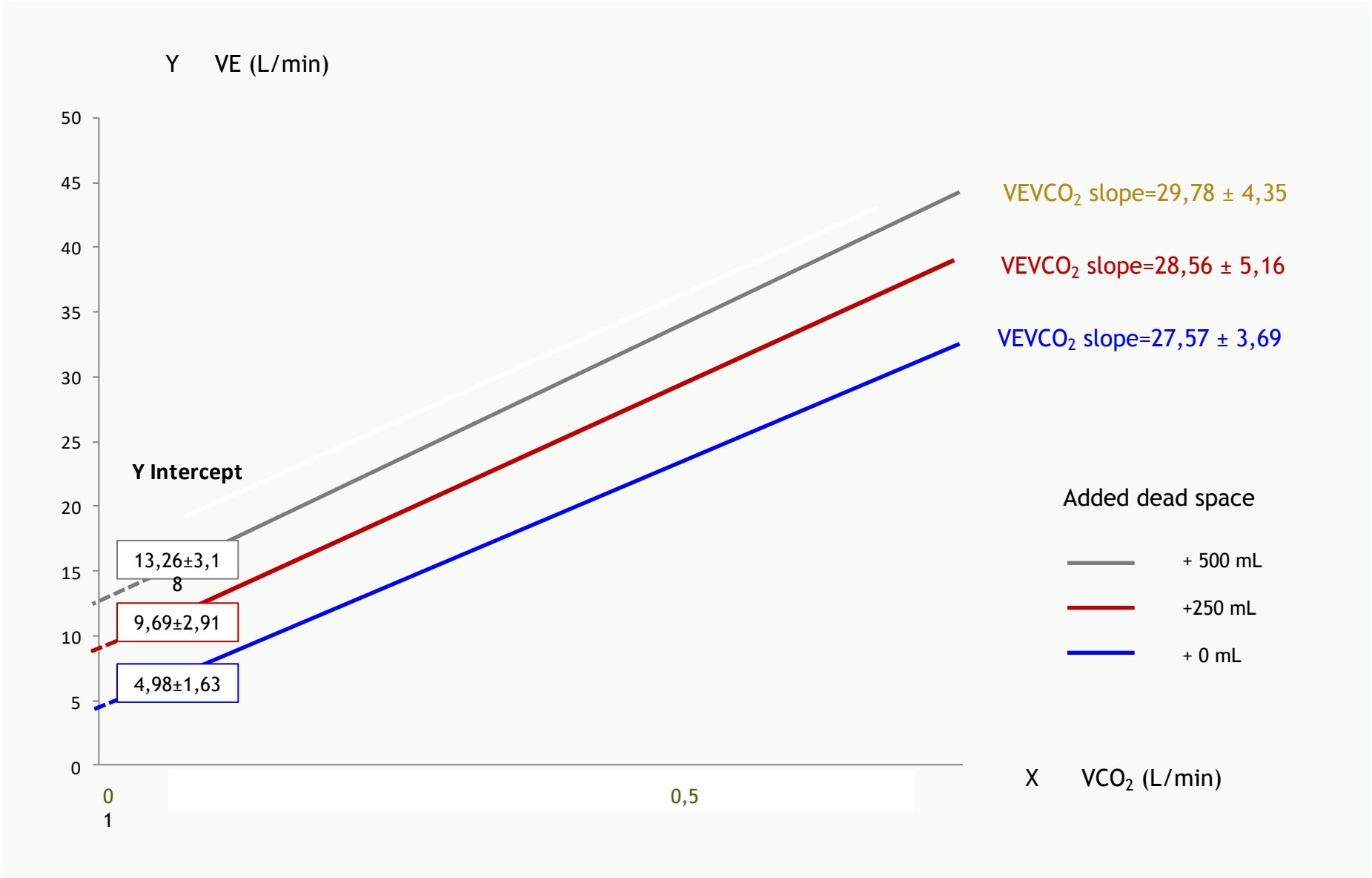


Gargiulo P et al. PLoS One 2014

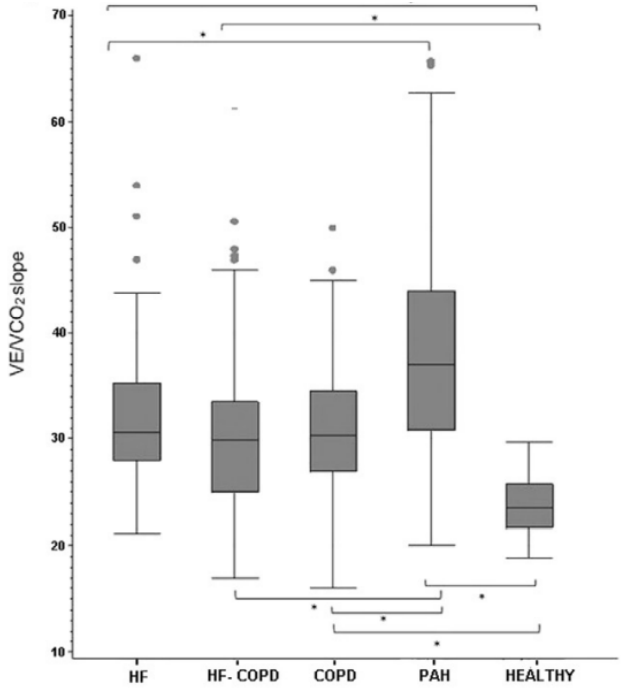


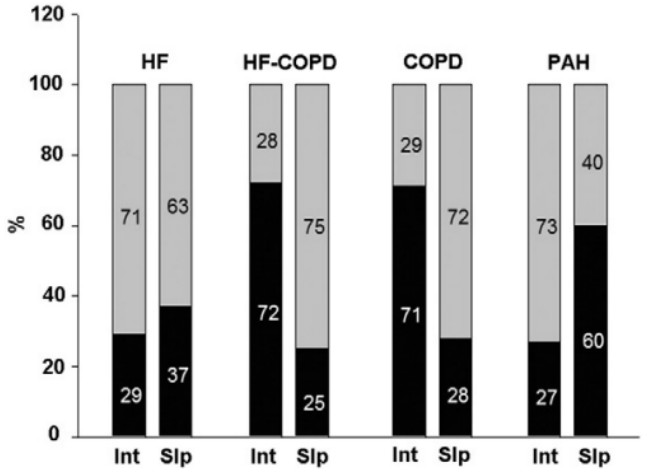


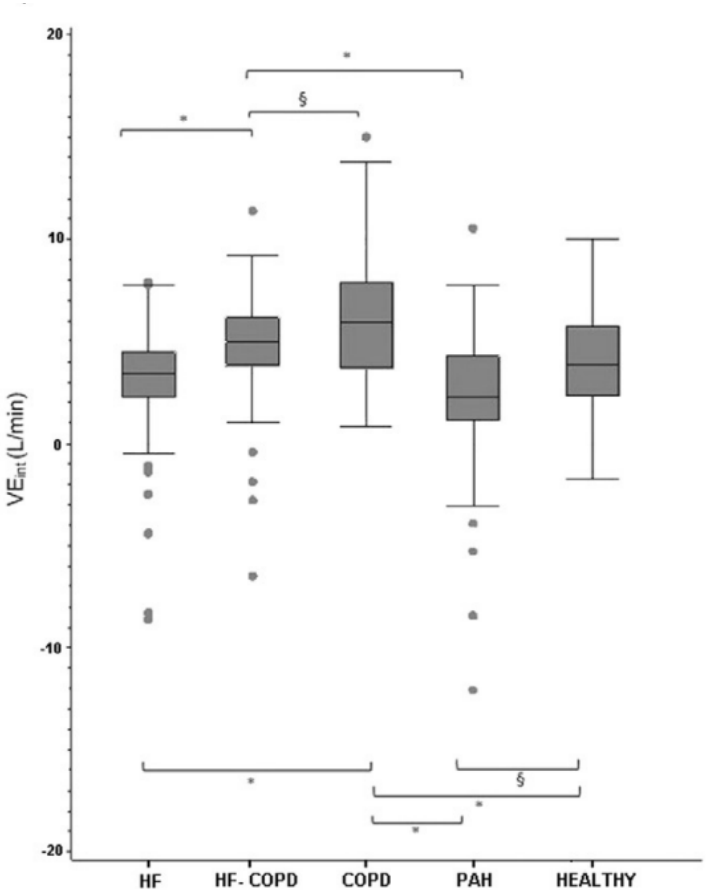




Gargiulo P et al. PLoS One 2014





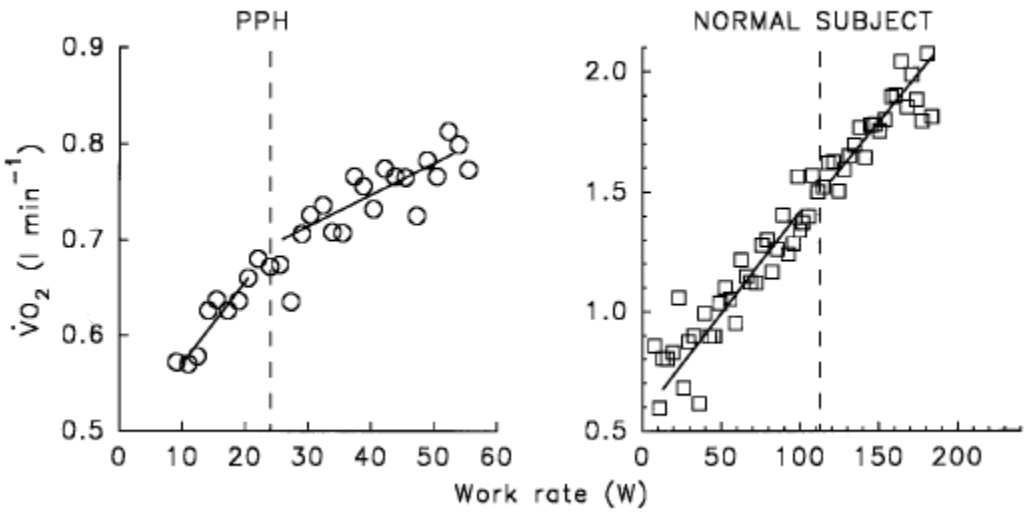


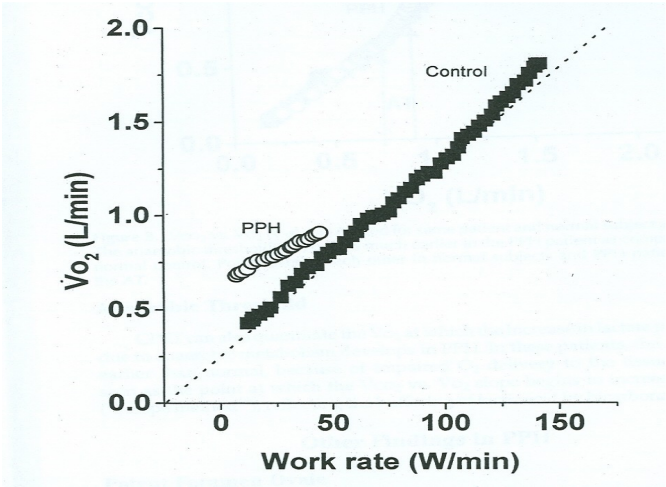
Apostolo A et al. Int J Cardiolo 2015;189:134-40

PAH - Cardiovascular abnormalities

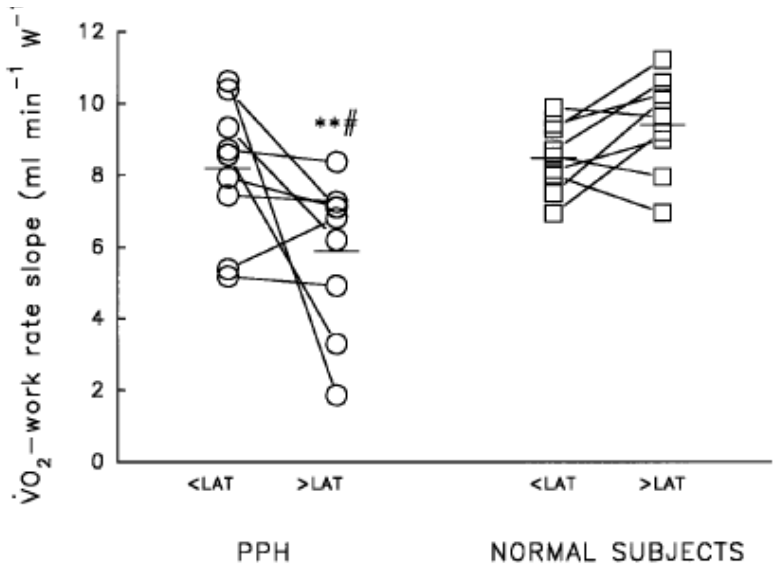
- Low peak VO_2
- Low peak O_2 pulse
- Higher HR
- Low VO_2/Work slope
- Low AT

PAH - Cardiovascular abnormalities





Oudiz and Sun. Abnormalities in Exercise Gas Exchange in Primary Pulmonary Hypertension. K. Wasserman: Cardiopulmonary ExerciseTesting and Cardiovascular Health.



Riley MS et al. Eur Journal of Appl Physiol 2000;83:63-70

The role of CPET in clinical practice

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Response to therapy

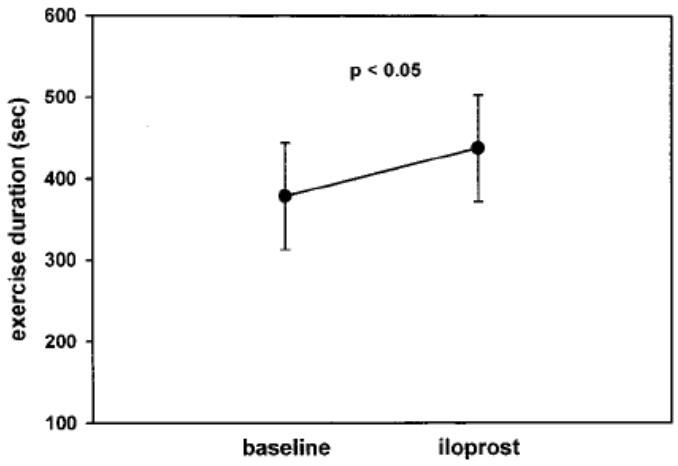


Figure 1. Effects of iloprost inhalation on exercise duration.

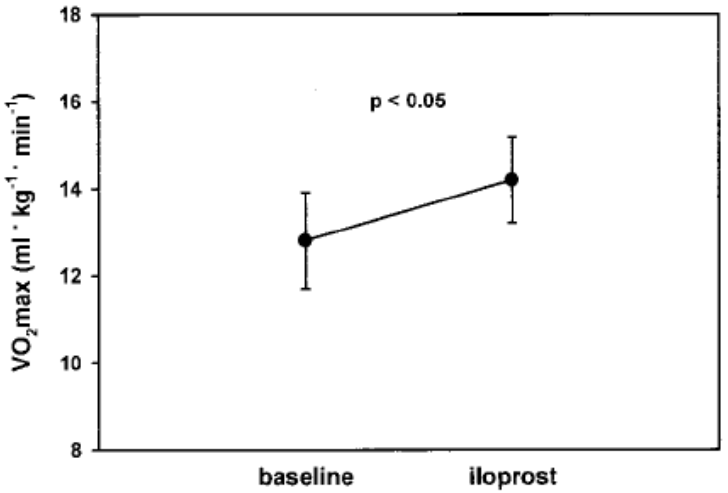


Figure 2. Effects of iloprost inhalation on $\dot{V}o_{2\ max}$.

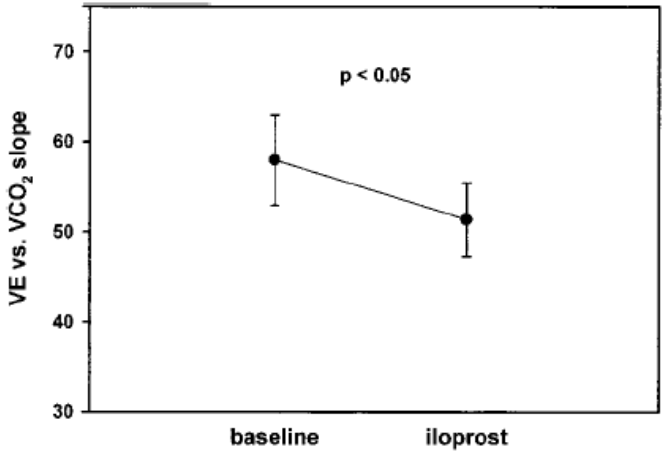
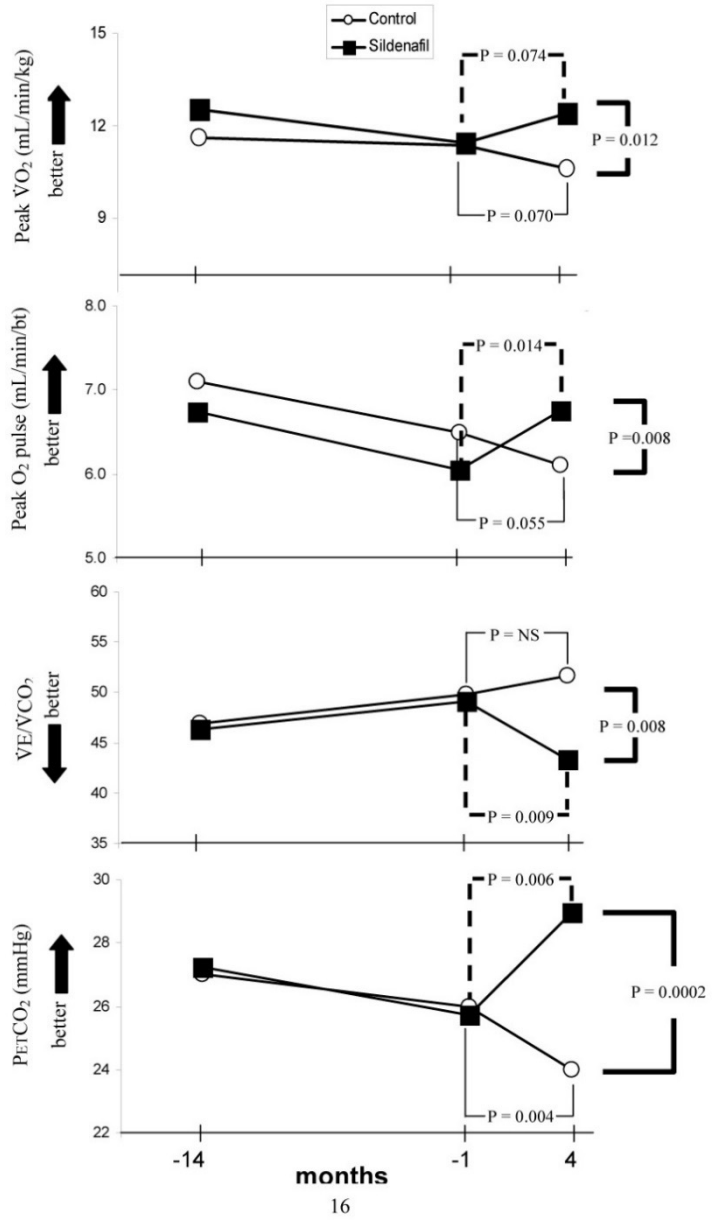


Figure 3. Effects of iloprost inhalation on $\dot{V}_E$-vs-$\dot{V}co_2$ slope.

Effects of Iloprost inhalation on exercise capacity and ventilatory efficiency in patients with primary pulmonary hypertension

Wensel R et al. Circulation 2000;101:2388-2392

Response to therapy



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Demographics	sildenafil	controls	P value
Age (yrs)	41.4 ± 3.4	45.4 ± 2.4	0.4
Sex (F/M)	13/1	13/1	0.5
Height (cm)	163 ± 2.6	165 ± 2.4	0.9
Weight (kg)	73 ± 5	72 ± 11	0.7
Race			0.5
White (%)	7 (50)	5 (37)	
Hispanic (%)	4 (29)	3 (21)	
Asian (%)	2 (14)	6 (42)	
Black (%)	1 (7)		
NYHA/WHO Class			0.5
II	1	4	
III	11	9	
IV	2	1	
Cause of pulmonary hypertension			0.5
Idiopathic (n)	11	11	
Associated with CTD (n)	2	2	
Corrected CHD (n)	1	1	
Resting haemodynamics			
mRAP, mmHg	9.1 ± 1.0	8.1 ± 0.9	0.4
mPAP, mmHg	50 ± 3.3	54 ± 4.3	0.4
mPWP, mmHg	10 ± 1.3	11 ± 1.1	0.9
CO, L • min^{-1}	3.9 ± 0.4	4.0 ± 0.4	1.0
Cardiac Index, L • min^{-1}• m^2	2.2 ± 0.2	2.2 ± 0.2	1.0
PVR dyne•s•cm^{-5}	901 ± 127	1048 ± 175	0.4
mBP, mmHg	91 ± 3	92 ± 4	0.7
Background PAH therapy			0.5
prostacyclin analogue (n)	6	7	
endothelin antagonist (n)	7	6	
none (n)	1	1	

Effect of sildenafil on ventilatory efficiency and exercise tolerance in pulmonary hypertension

Oudiz RJ et al. Eur J Heart Fail 2007;9:917-21

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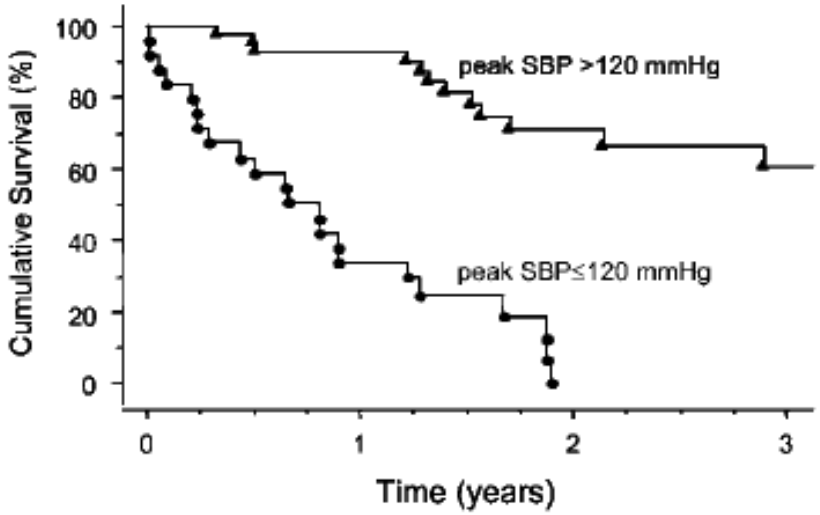
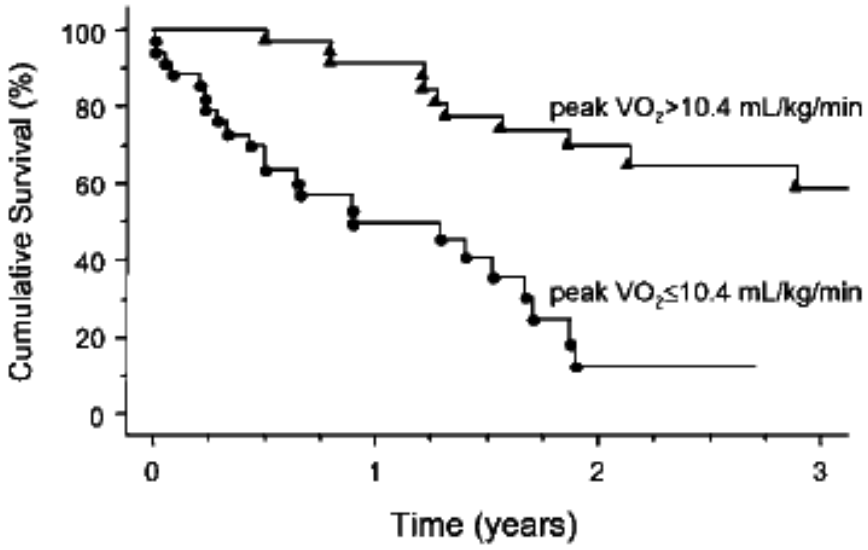
CPET in PAH - Prognostic evaluation

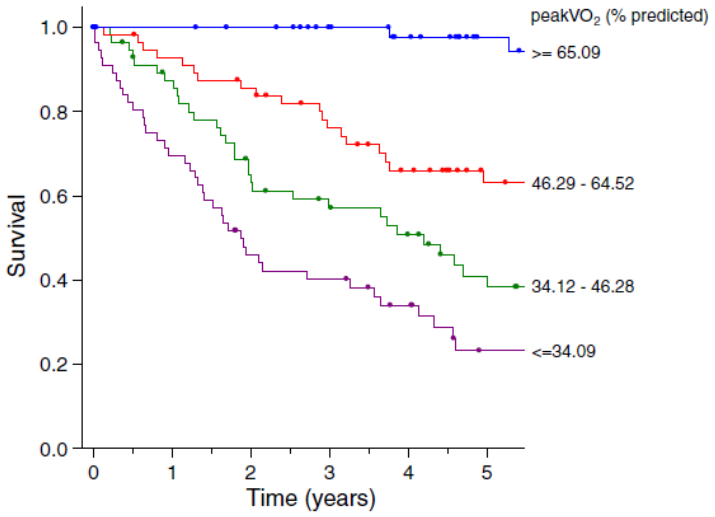


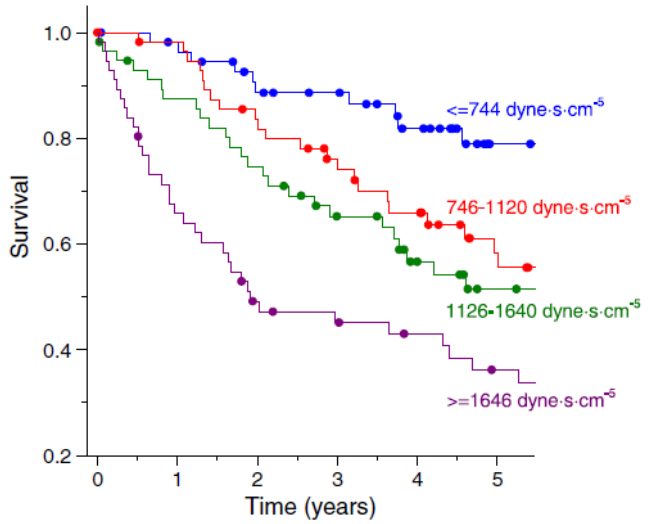


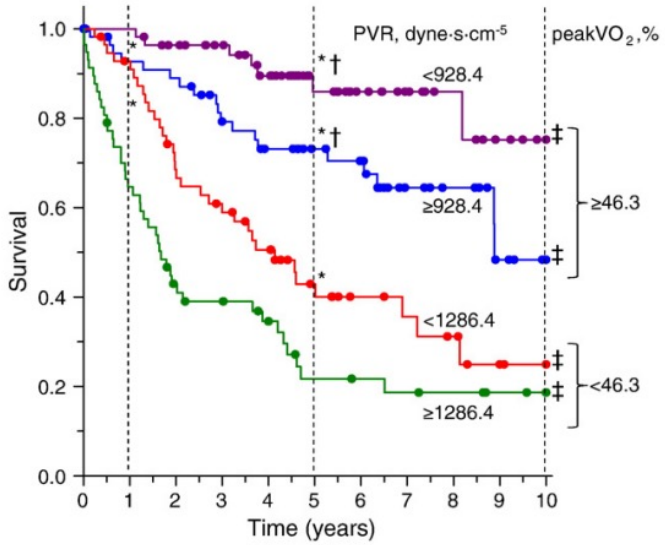
Peak VO_2 and peak SBP are independent and strong predictors of survival in PPH patients. Hemodynamic parameters, although also accurate predictors, provide no independent prognostic information.

Wensel R at al. Circulation 2002;106:319-324

CPET in PAH - Prognostic evaluation

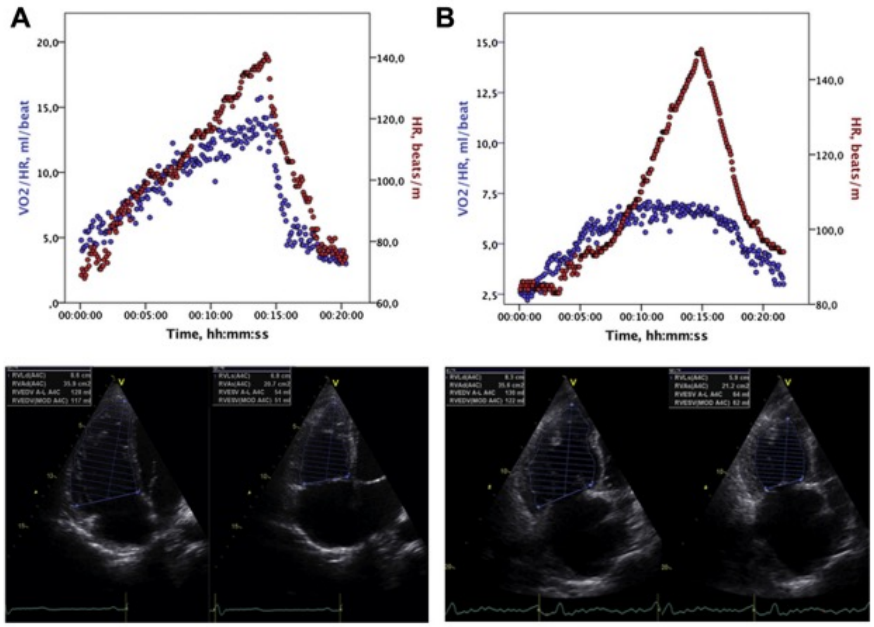


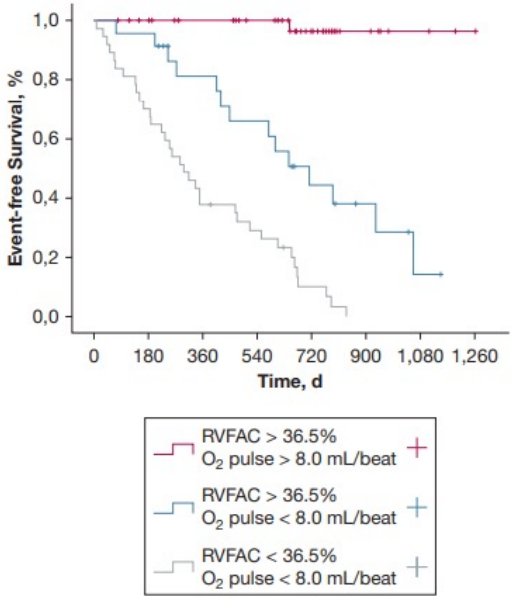




Wensel R et al. Int J Cardiol 2013 167:1193-8

CPET in PAH - Prognostic evaluation

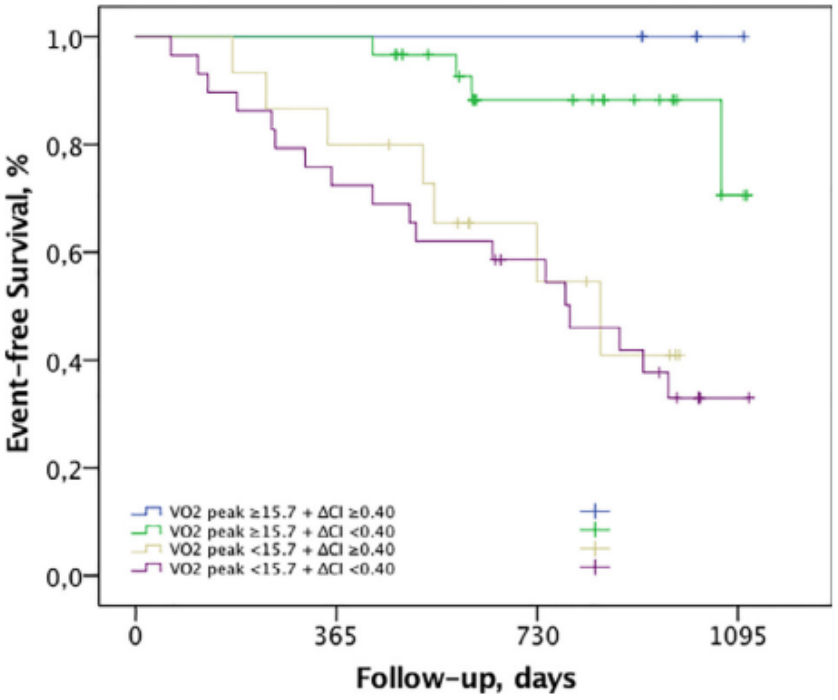




	Unit	HR	(95% CI)	*P*	c-statistic (95% CI)
Model 1					0.66 (0.55-0.76)
WHO class	1	15.8	(2.15-116)	.007	
CI	0.5	0.49	(0.33-0.70)	.0001	
Model 2					0.81 (0.72-0.88)
RVFAC	1	0.91	(0.86-95.0)	.0001	
O_2 pulse	1	0.62	(0.48-0.79)	.0001	

Badagliacca R et al. Chest 2016;150:1313-1322

CPET in PAH - Prognostic evaluation



	Unit	Hazard ratio	95% confidence interval	*p*	c-statistic (95% CI)
Model 1					0.68 (0.56 to 0.81)
ΔCI (liters/min/m^2)	1	0.2	0.02 to 0.5	0.01	
ΔWHO class	1	4.4	2.1 to 9.2	0.0001	
RAP (mm Hg)	1	1.2	1.03 to 1.5	0.024	
Model 2					0.79 (0.68 to 0.88)
ΔCI (liters/min/m^2)	1	0.1	0.01 to 0.16	0.0001	
VO_2 peak (ml/kg/min)	1	0.8	0.6 to 0.9	0.0001	
VO_2 peak % predicted (alt)	1	0.9	0.83 to 0.92	0.001	

Badagliacca R et al. 2019;38:306-314

The role of CPET in PAH

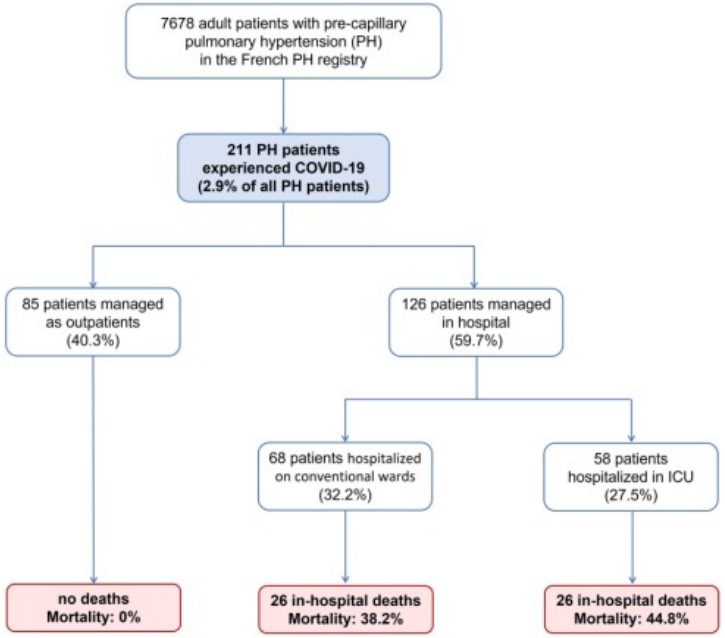
ESC Guidelines

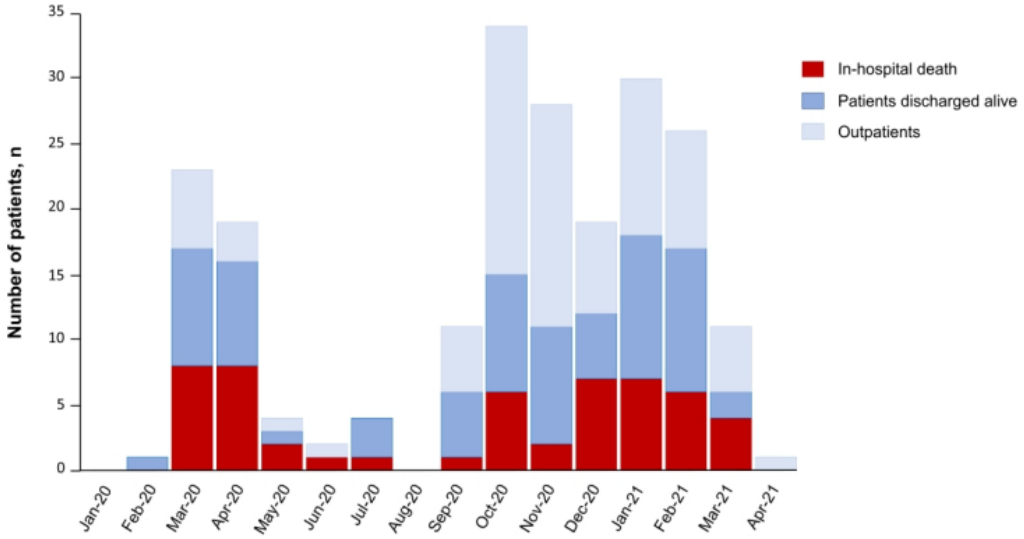
Table 13 Risk assessment in pulmonary arterial hypertension

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%

PAH in Covid pandemic

The PH French Registry





COVID-19 in patients with precapillary PH was associated with a high in-hospital mortality

Montani D et al. AM J Respir Crit Care Med 2022

PH as a consequence of Covid

The effects of SARS-CoV-2 on pulmonary vasculature

- The lungs seem to be the primary target of infection, with major involvement of the pulmonary vasculature.

- Vascular changes affect the entire pulmonary vascular tree, from large-calibre vessels to capillaries, and all components of the vascular wall from the lumen to the perivascular regions can be affected.

- Several pathways (hypoxia, inflammation and complement activation) have been proposed as possible drivers of pulmonary vascular injury mediated by SARS-CoV-2 infection.

PH as a consequence of Covid

The effects of SARS-CoV-2 on pulmonary vasculature

- The pathobiology of the pulmonary vasculature in patients with COVID-19 shares many features with that of the pulmonary vasculature in patients with pulmonary hypertension (medial hypertrophy and smooth muscle cell proliferation, intravascular clotting, genetic factors).

PH as a consequence of Covid

The effects of SARS-CoV-2 on pulmonary vasculature

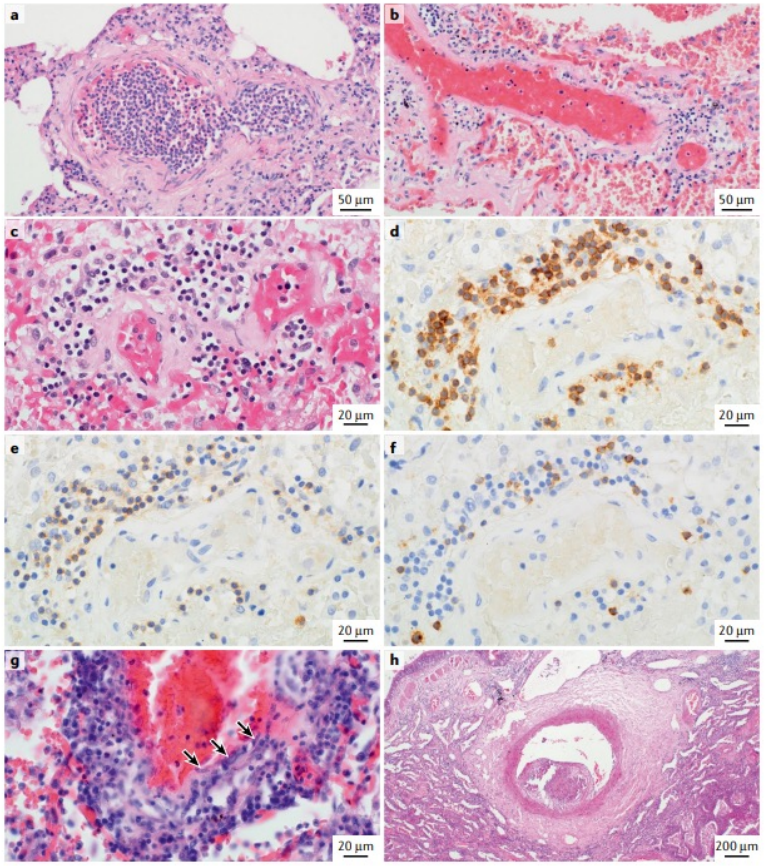
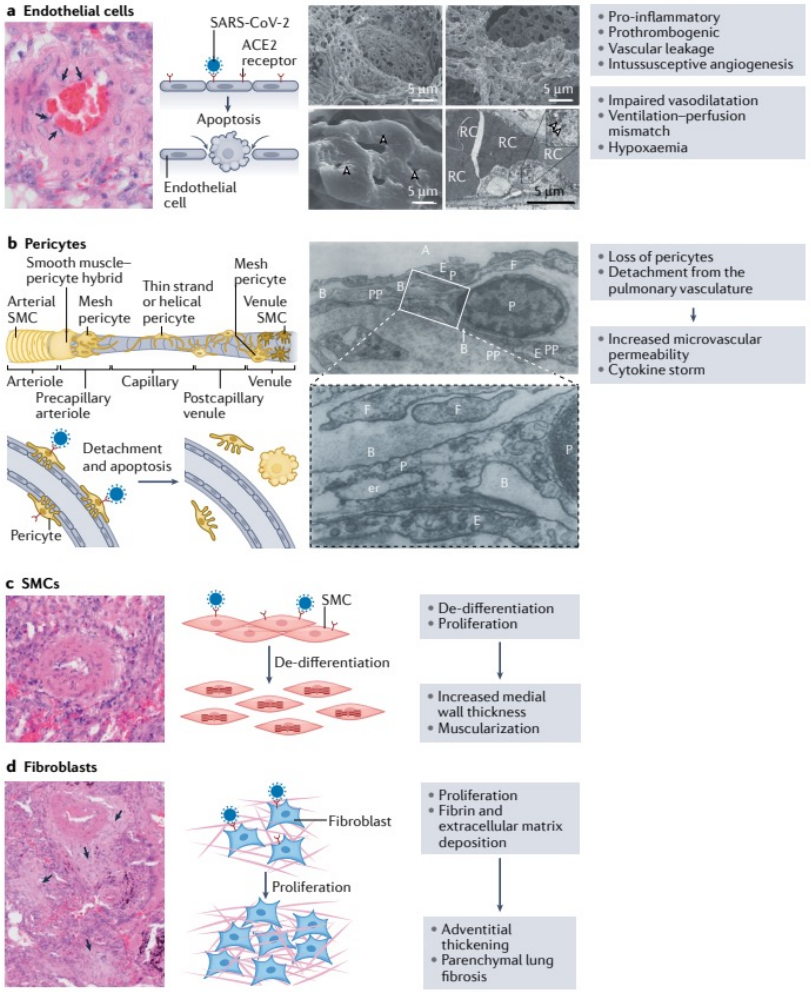


Fig. 4 | **Microvasculature changes in lungs from patients with severe COVID-19.** Haematoxylin and eosin (H&E) staining and immunostaining images showing microvasculature changes in patients with severe coronavirus disease 2019 (COVID-19). **a** | Arteriole filled with neutrophils that are in part adherent to the endothelium. **b**,**c** | Pulmonary microvessels (either arterioles or venules) displaying perivascular lymphocytic infiltrate. **d** | Immunostaining with anti-CD3 showing the vessel displayed in part **c**. **e** | Anti-CD4 staining on a serial section of the same vessel. **f** | Anti-CD8 staining on another serial section of the same vessel. **g** | Lymphocytic endothelialitis or venulitis with transmural infiltrate involving the intima; note the immediate vicinity of lymphocytes (dark blue, round nuclei) and endothelial cells (arrows). This inflammatory pattern is not frequently encountered and seems also to involve post-capillary vessels, as shown. **h** | Elastic-type artery (>500 µm in diameter) containing a wall-adherent, organized thrombotic lesion with endothelium-lined, cushion-like intimal fibrosis protruding into the vascular lumen.



Halawa S et al. Nature Reviews 2022;19:314-331

PH as a consequence of Covid

The effects of SARS-CoV-2 on pulmonary vasculature

- The pathobiology of the pulmonary vasculature in patients with COVID-19 shares many features with that of the pulmonary vasculature in patients with pulmonary hypertension (medial hypertrophy and smooth muscle cell proliferation, intravascular clotting, genetic factors).

- The prevalence of PH during the acute phase of COVID-19 is fairly high.
  - In 200 consecutive Covid-19 patients admitted to non-intensive care units in Milan, Italy, the prevalence of PH (sPAP >35 mmHg and RV dysfunction was 12.0% and 14.5%, respectively (Pagnesi M et al, Heart 2020).
  - In a Swedish study in 2021 26 out of 67 patients (39%) with severe Covid-19 had acute PH (Nordefeldt J et al, Acta Anaesthesiol Scand 2021).

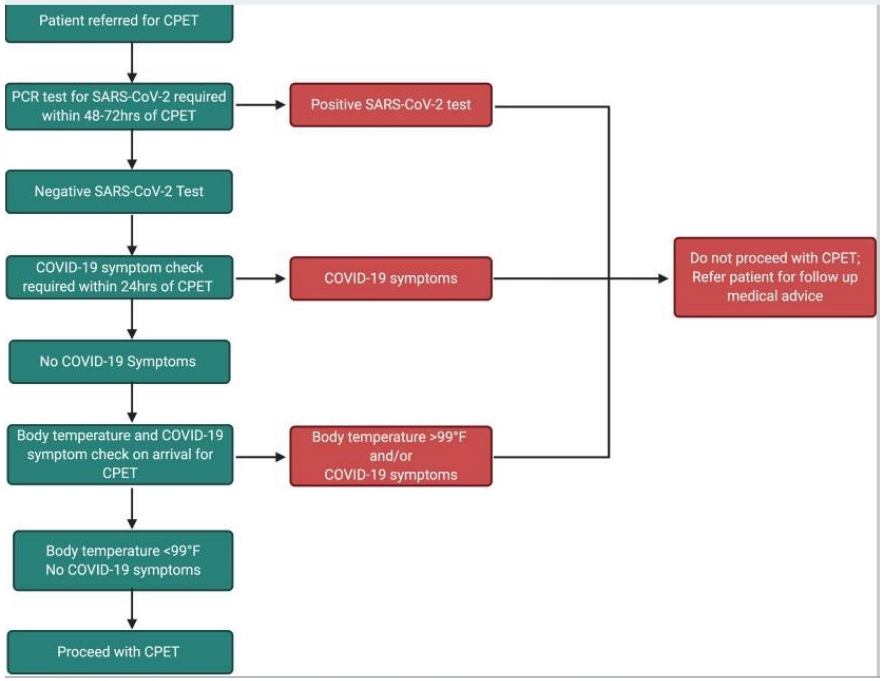
- Possible sequelae:
  Lung fibrosis → Group 3 PH
  PE, intravascular clotting, thrombotic michroangiopathy → Group 4 PH

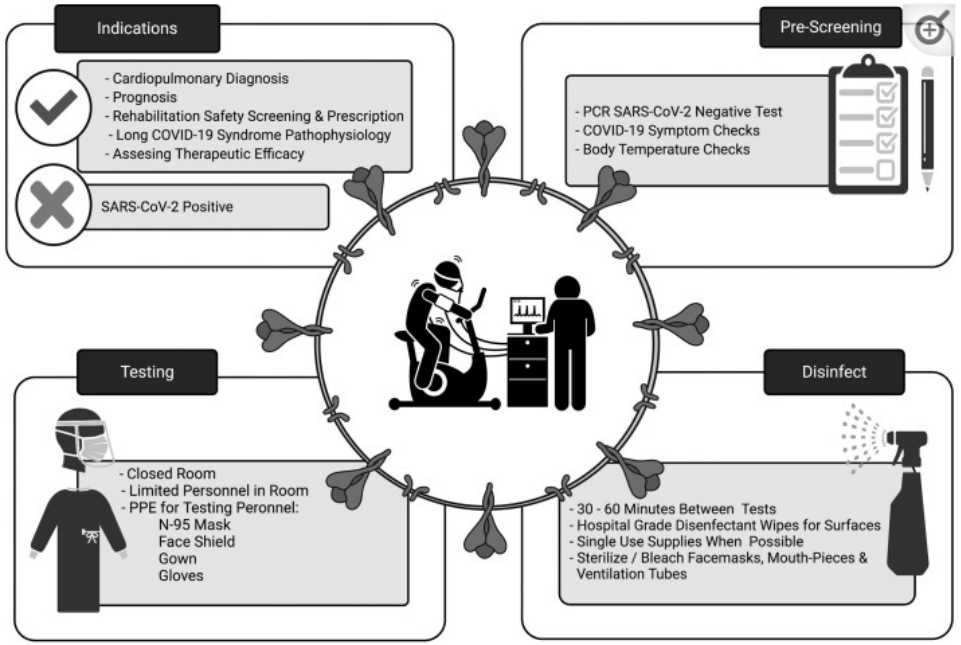
Halawa S et al. Nature Reviews 2022;19:314-331

The role of CPET in Covid pandemic

- Clinical assessments of convalescent COVID-19 patients
- Research aimed at understanding the long-term health effects of SARS-CoV-2 infection

The role of CPET in Covid pandemic





Mihalick VL et al. Prog Cardiovasc Dis 2021;67:35-39

Thank you for your attention!