Con il patrocinio di

Associazione Italiana Pneumologi Ospedalieri

Ospedale San Giuseppe
MultiMedica S.p.A.

PNEUMOLOGIA 2016

Milano, 16 – 18 giugno 2016 · Centro Congressi Palazzo delle Stelline

IPERTENSIONE POLMONARE: DAL CATETERISMO ALLE NUOVE TERAPIE

Test da sforzo e riabilitazione cardio-respiratoria servono?

Dott.ssa Gaia Cattadori
UO Cardiologia Riabilitativa
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2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Table of Contents

Test da sforzo: valutazione di severità in PAH

Table 15 **Recommendations for evaluation of the severity of pulmonary arterial hypertension and clinical response to therapy**

Recommendations	Class[a]	Level[b]	Ref.[c]
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It is recommended to perform regular follow-up assessments every 3–6 months in stable patients (*Table 14*)	I	C	98
Achievement/maintenance of a low-risk profile (*Table 13*) is recommended as an adequate treatment response for patients with PAH	I	C	96–99
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Test da sforzo: severità e prognosi in PAH

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Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
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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
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Test da sforzo: severità e follow up in PAH

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Table 14 Suggested assessment and timing for the follow-up of patients with pulmonary arterial hypertension

	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]

6-minute walk

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6MWT e prognosi in PAH

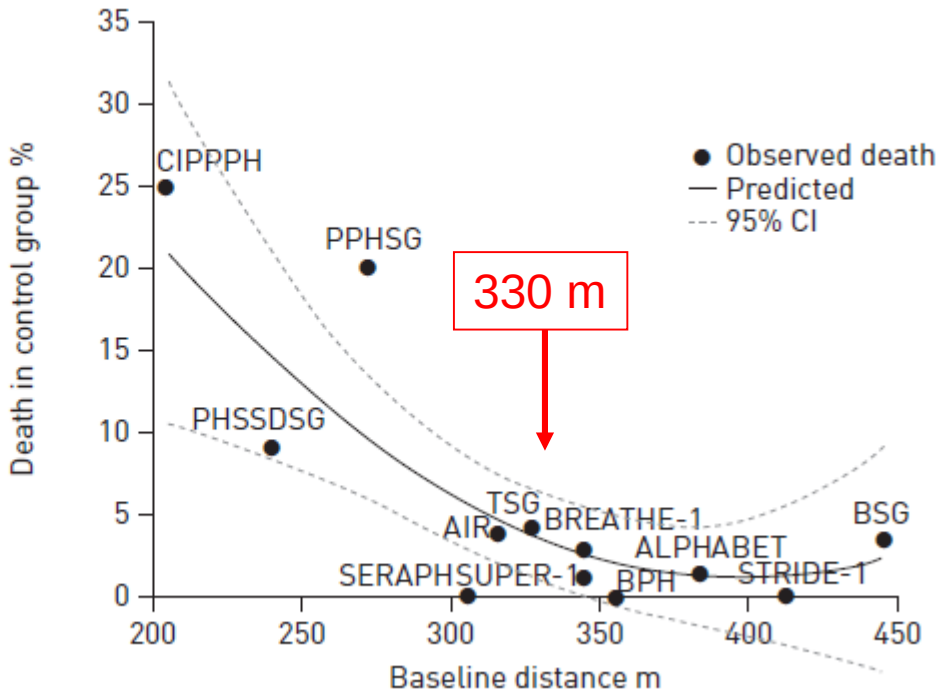

FIGURE 1 Relationship between the mean 6-min walk distance at baseline and the rate of fatal events during follow-up. Reproduced from [24] with permission from the publisher.

Macchia et al. Am Heart J 2007; 153: 1037-1047

6MWT e prognosi in PAH

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CMR = cardiac magnetic resonance; CPET = cardiopulmonary exercise testing; NYHA = New York Heart Association; RAP = right atrial pressure; RVEF = right ventricular ejection fraction; TAPSE = tricuspid annular plane systolic excursion; WHO = World Health Organization; 6MWD = 6-min walking distance.

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McLaughlin al. JACC 2015; 65: 1976-97

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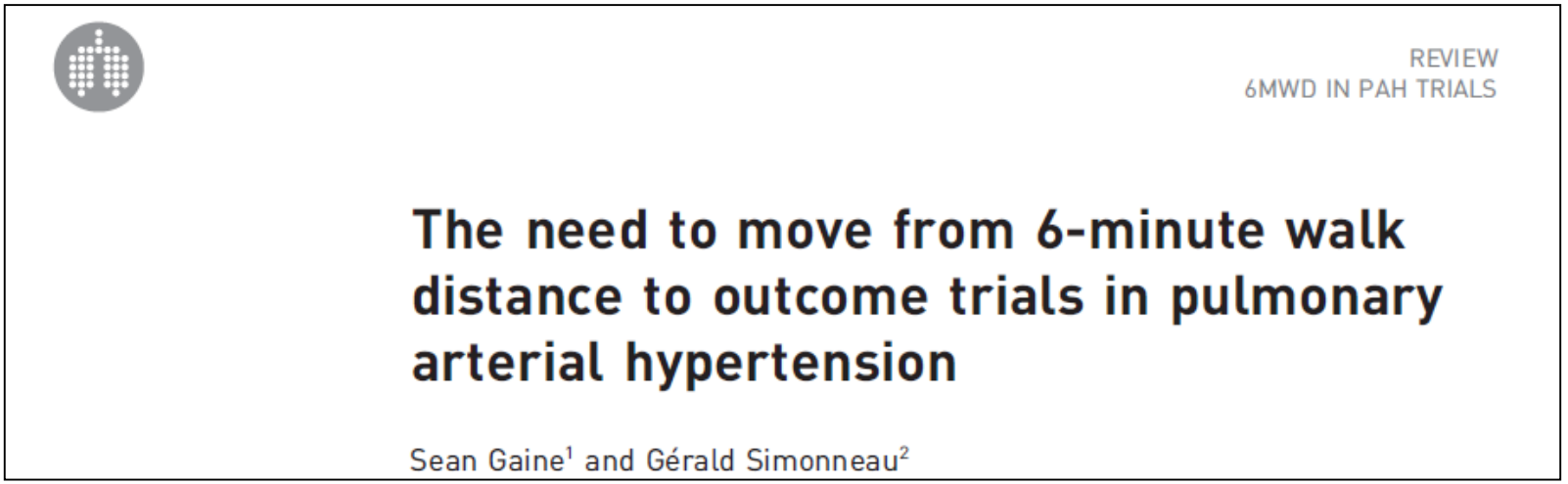

REVIEW
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Sean Gaine[1] and Gérald Simonneau[2]

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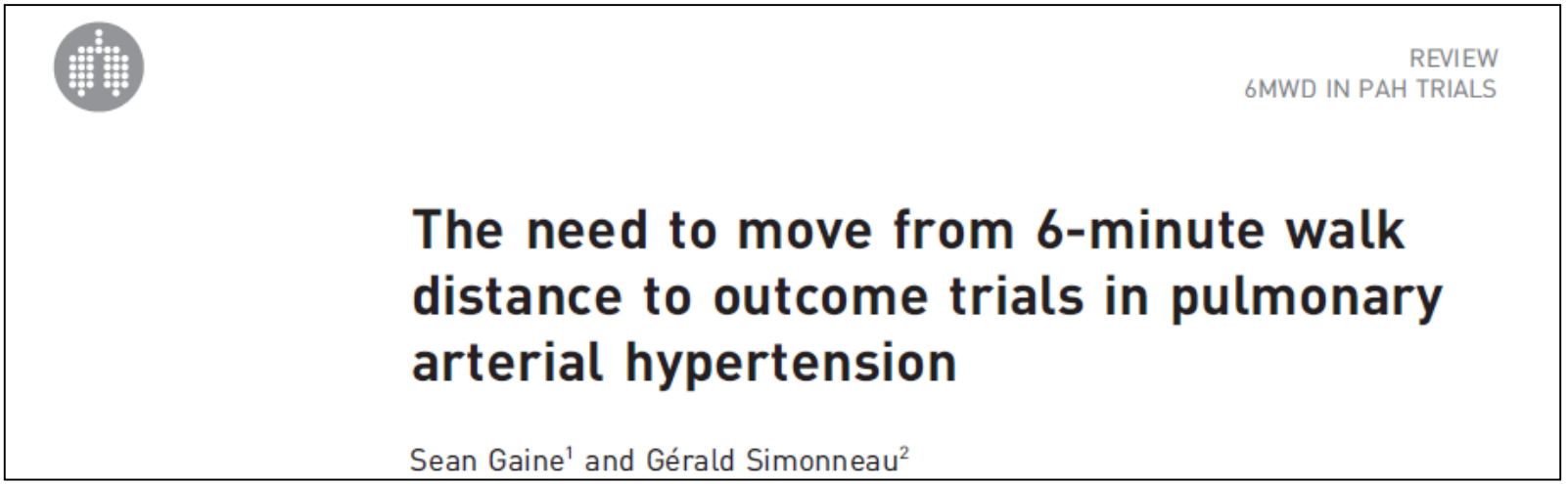
Eur Resp Rev 2013; 22: 487-494.



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- «ceiling effect»

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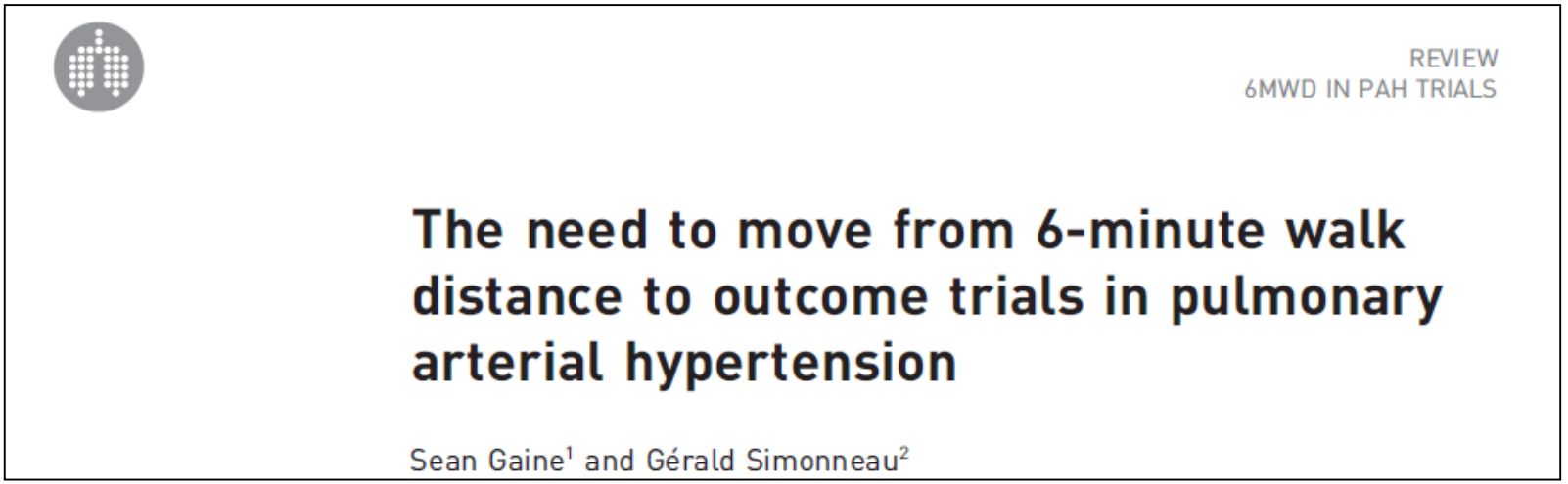

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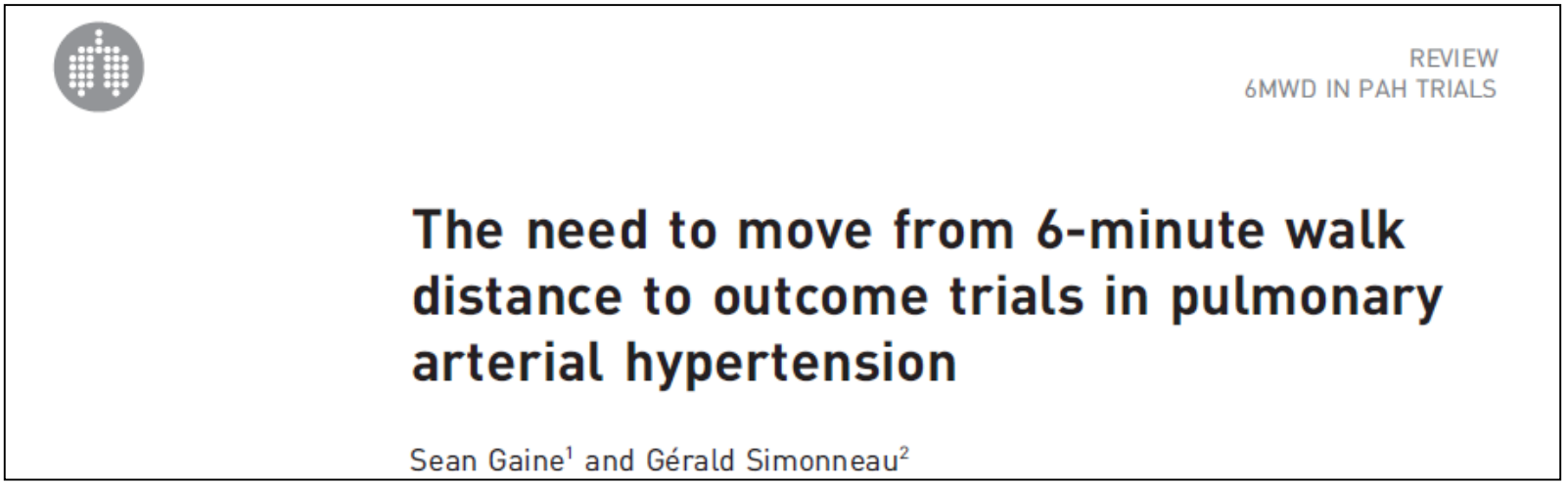

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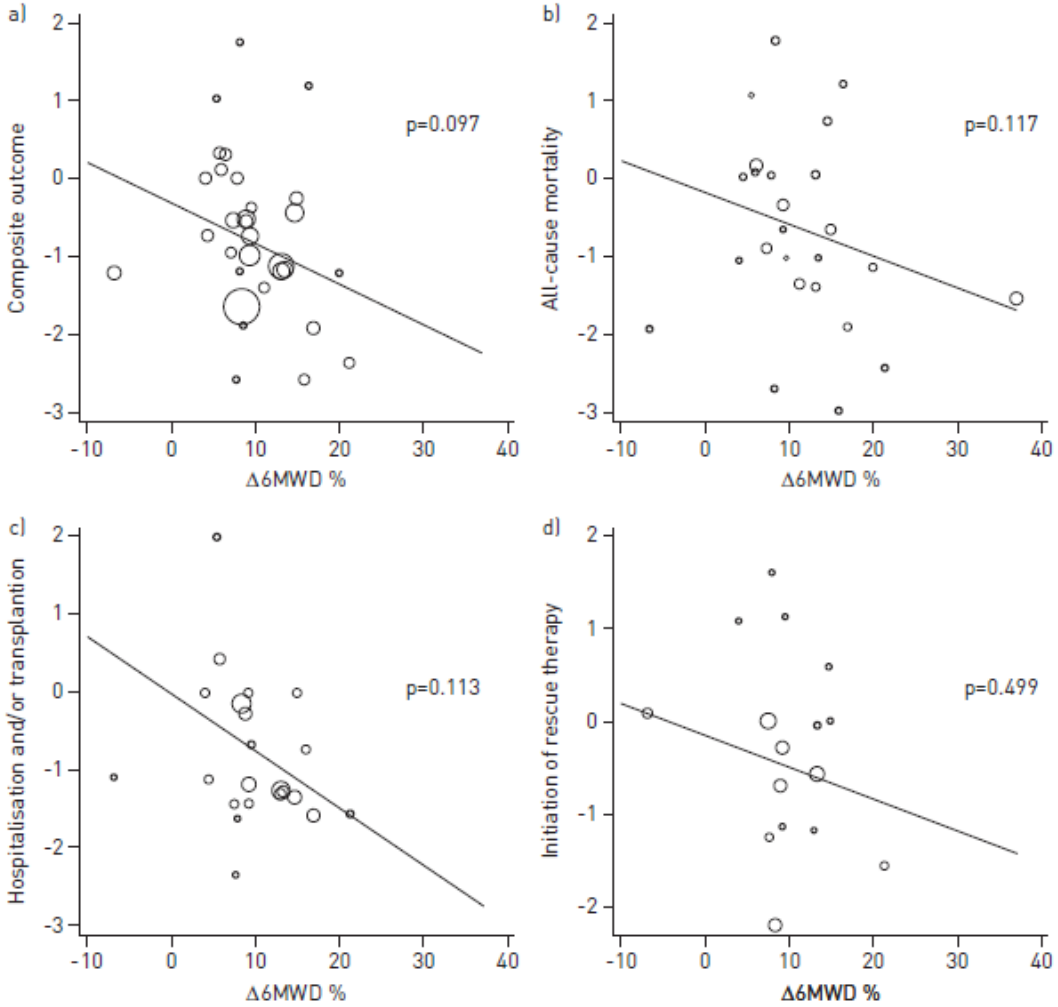
6MWT e prognosi in PAH



Dati post- e Δ non validati e predittori di eventi->**dubbi sulla validità di end-point surrogato**

Gaine et al. Eur Resp Rev 2013; 22: 487-494

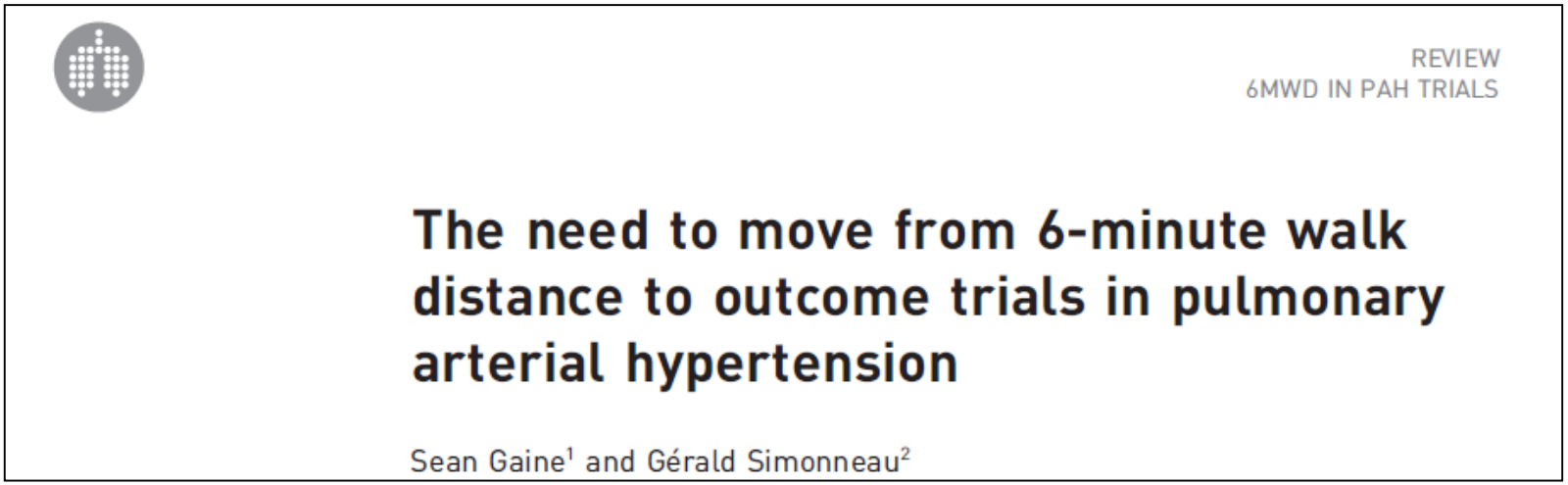
Use of exercise testing in the evaluation of interventional efficacy: an official ERS statement

Luis Puente-Maestu[1,2,3], Paolo Palange[4], Richard Casaburi[5], Pierantonio Laveneziana[6,7], François Maltais[8], J. Alberto Neder[9,10], Denis E. O'Donnell[11], Paolo Onorati[4,12], Janos Porszasz[5], Roberto Rabinovich[13], Harry B. Rossiter[5,14], Sally Singh[15], Thierry Troosters[16,17] and Susan Ward[18]

TABLE 2 Measurement properties of the tests reviewed

	Main variables	Practice test needed	Standardisation	MCID	Reproducibility
IET	V'_{O_2peak}, WR_{peak} and V'_E-V'_{CO_2} indices	No	Adjusting WR increments to the patient capacity Criteria for "good effort"	No Suggested targets in PAH: V'_{O_2} >10 L·min^{-1}·kg^{-1} V'_E-V'_{CO_2} slope <45	V'_{O_2peak} 5–10% WR_{peak} 5–10% V'_E-V'_{CO_2} indices ±2.3 both within and between individuals
CWRET	t_{LIM}, isotime IC and isotime dyspnoea	No	Intensity of baseline tests to attain t_{LIM} between 180 and 480 s recommended to reduce variability Pedalling rate Criteria to terminate the test	105 s or 33% Bronchodilator trials suggest that clinical outcomes improve with increases >60 s	t_{LIM}: 5–10% within individuals 23.7% between individuals
ISWT	Time/distance, dysponea and S_{pO_2}	Yes	Audio signal	47 m	NA
ESWT	Time/distance, dyspnoea and S_{pO_2}	Yes	Audio signal Optimum intensity/duration of baseline test yet to be defined	Time 56–71 s Distance 72–81 m	Time −7±72 s Distance −7±113 m both within individuals
6MWT	Distance/S_{pO_2} and dyspnoea	Yes	Track length Encouragement	25–33 m In PAH, MCID relates to symptom amelioration, but not to survival	Distance 5–8% when performed twice within individuals

Puente-Maestu et al. Eur Resp J 2016; 47: 429-460



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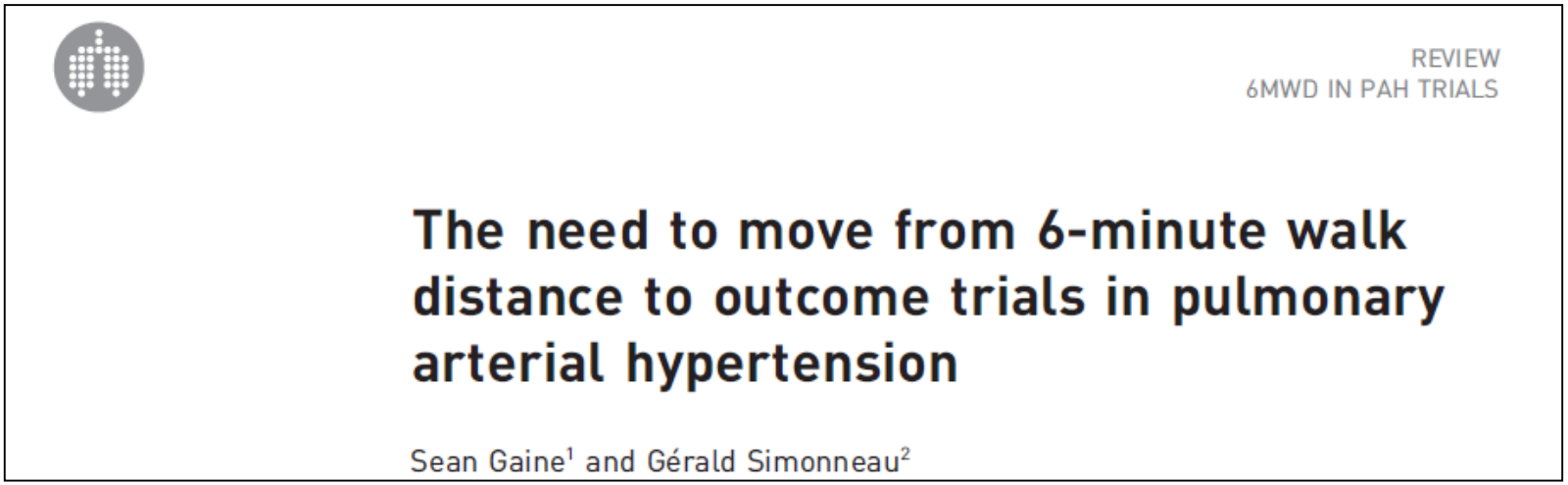

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- Nessuna informazione su fisiopatologia

Eur Resp Rev 2013; 22: 487-494.

Test da sforzo cardiopolmonare

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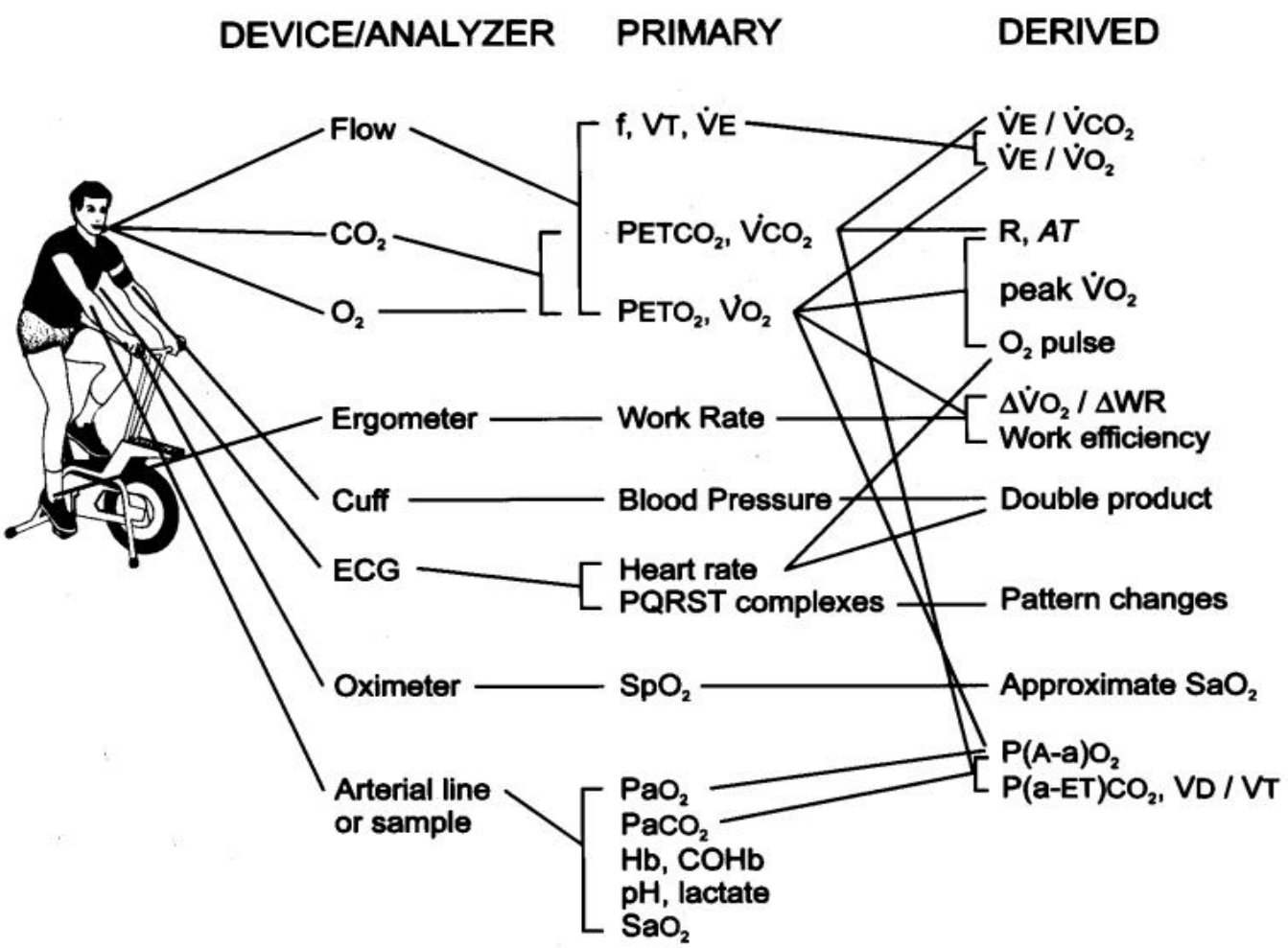

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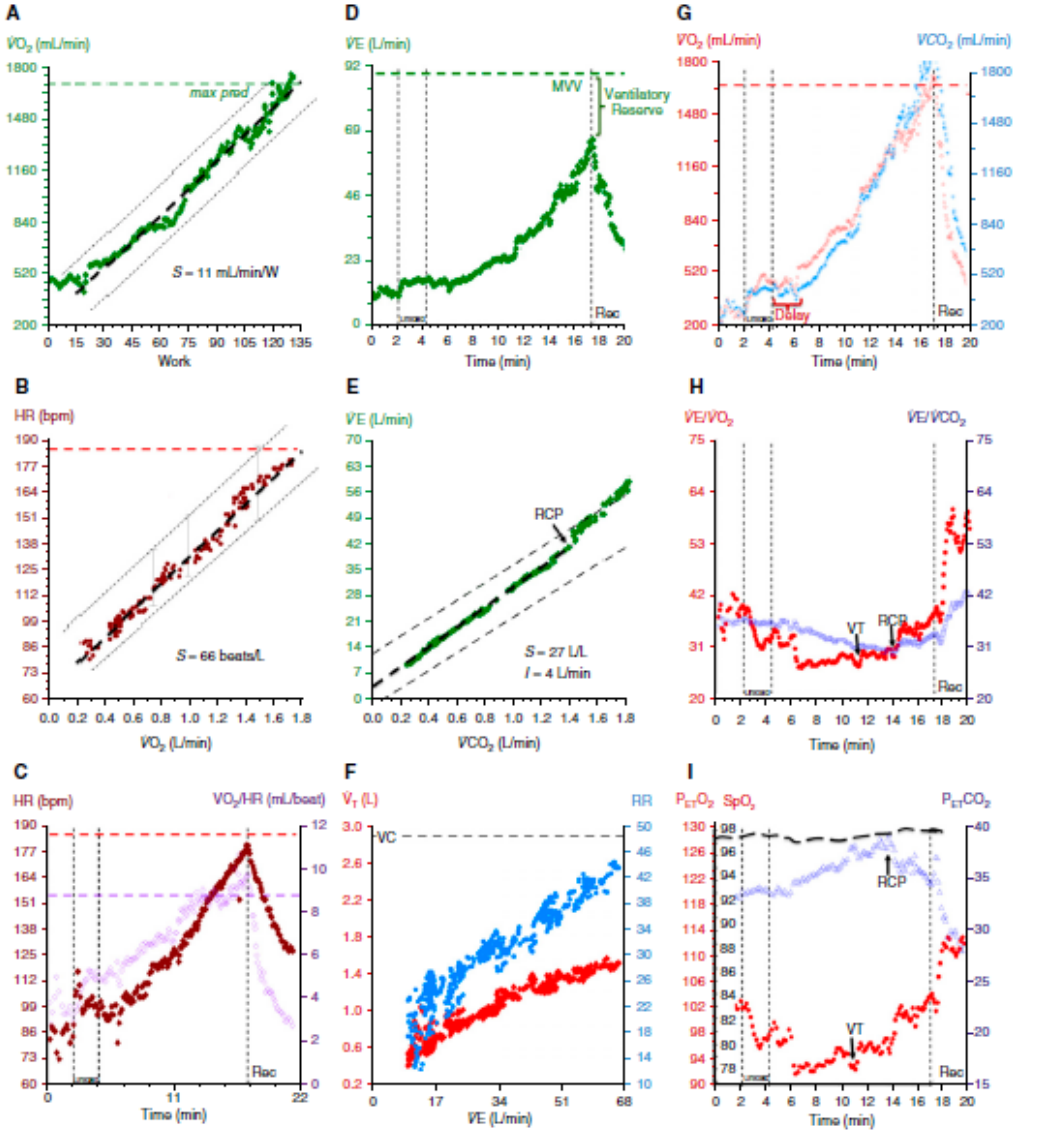


Test da sforzo cardiopolmonare in PAH

CASE CONFERENCES

The Clinical Physiologist
Section Editor: John W. Kreit, M.D.

Exercise Intolerance in Pulmonary Arterial Hypertension

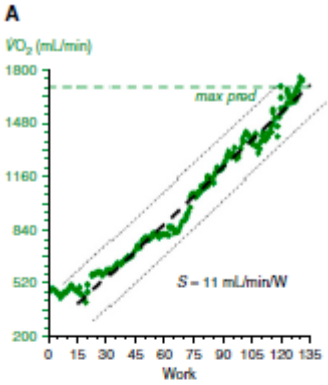
The Role of Cardiopulmonary Exercise Testing

J. Alberto Neder[1,3], Roberta P. Ramos[1,2], Jaquelina S. Ota-Arakaki[2], Daniel M. Hirai[1,3], Christine L. D'Arsigny[4], and Denis O'Donnell[4]

[1]Pulmonary Function and Clinical Exercise Physiology Unit, Respiratory Division, and [2]Pulmonary Vascular Group, Respiratory Division, Department of Medicine, School of Medicine, Federal University of São Paulo, São Paulo, Brazil; and [3]Laboratory of Clinical Exercise Physiology, and [4]Respiratory Investigation Unit, Department of Medicine, Division of Respiratory and Critical Care Medicine, Queen's University, Kingston, Ontario, Canada

Test da sforzo cardiopolmonare: peakVO_2

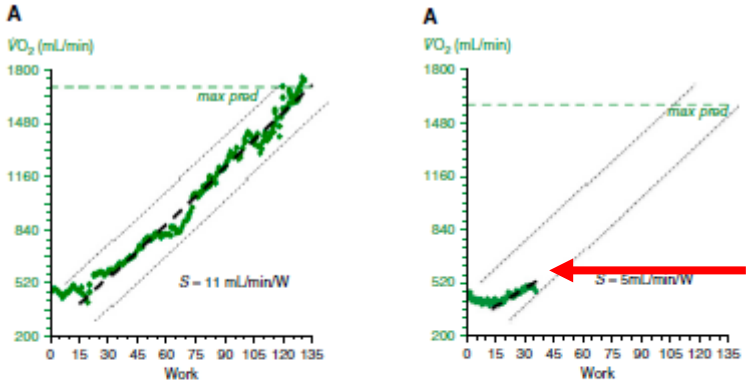
NORMALE



Neder et al. AnnalsATS Vol 12 n.4 April 2015

Test da sforzo cardiopolmonare: peakVO_2

PAH



peakVO_2

Neder et al. AnnalsATS Vol 12 n.4 April 2015

CPET e prognosi in PAH

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TABLE 3 High Risk Factors

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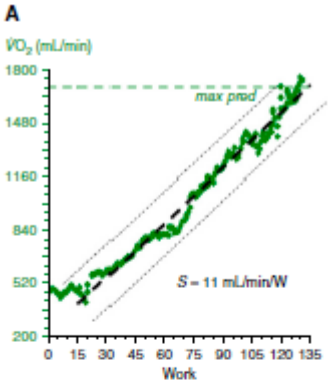
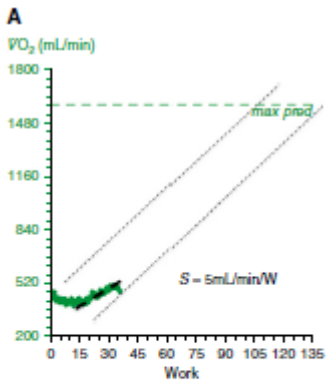
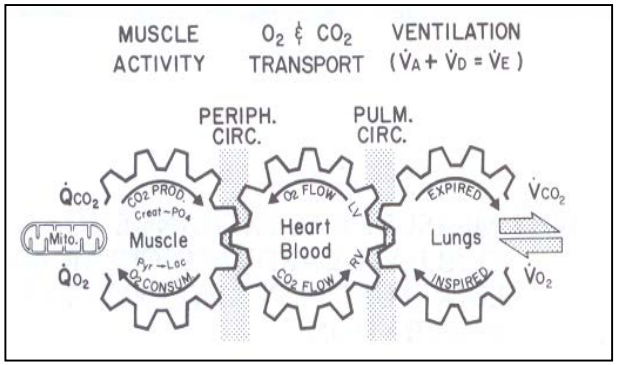
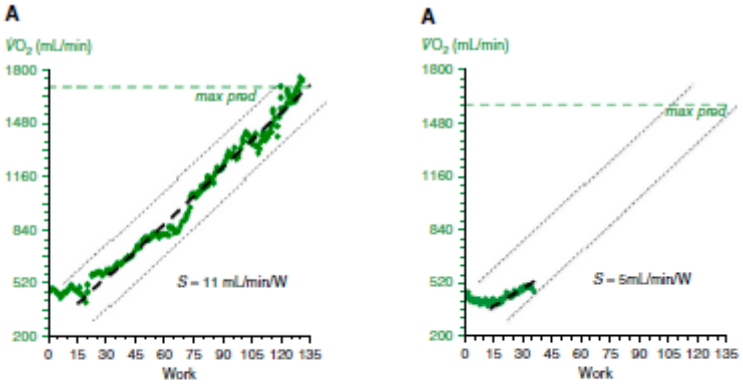


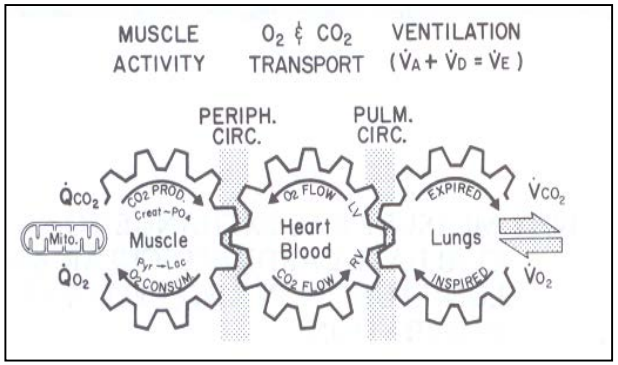




Wasserman K et al. Principles of Exercise Testing and Interpretation

Test da sforzo cardiopolmonare: peakVO_2





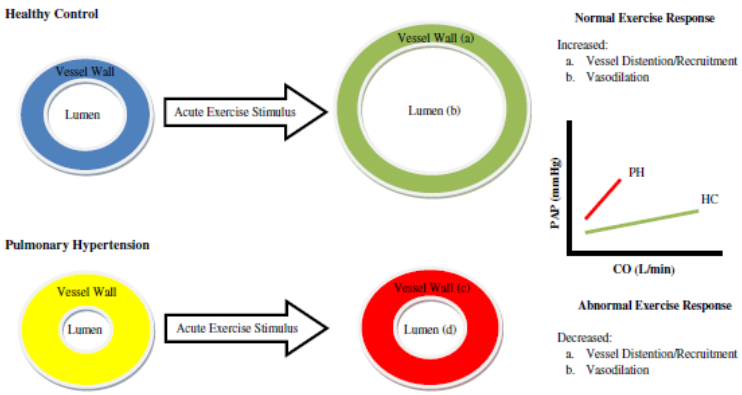


Fig 1 – Comparison between normal and abnormal pulmonary arterial vessel response to acute exercise. *Abbreviations:* CO, cardiac output; HC, healthy control; PAP, pulmonary artery pressure; PH, pulmonary hypertension.

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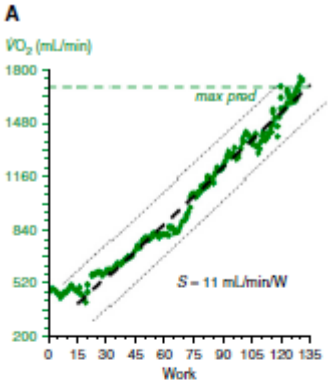
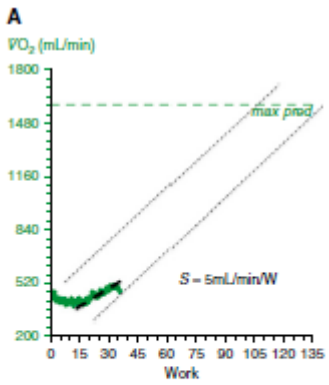
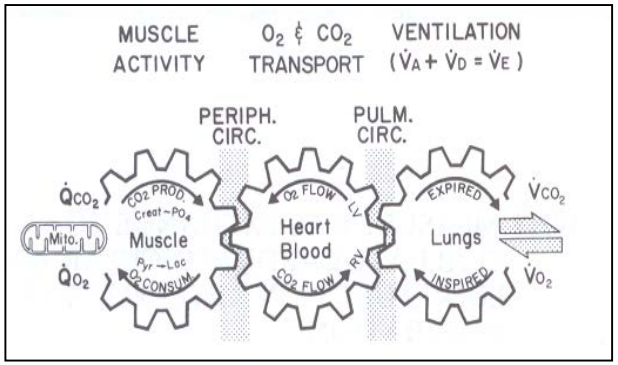
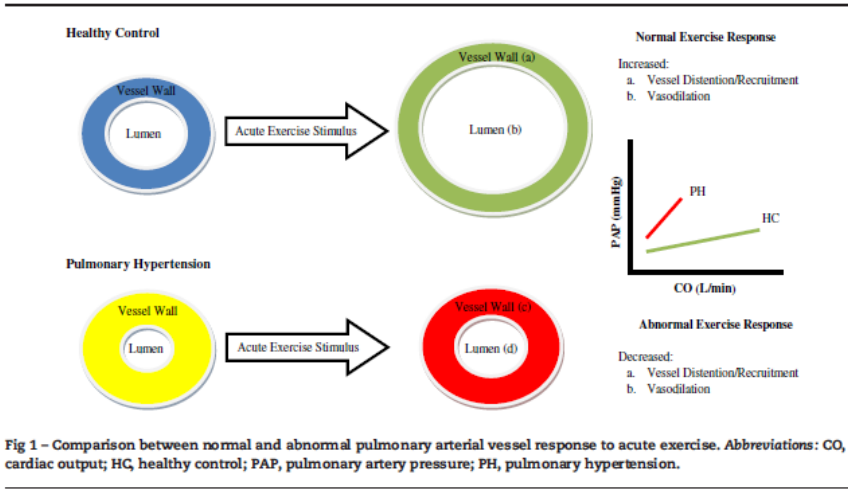
Arena et al. Progr Cardiovasc Dis 2015; 57: 480-8

Test da sforzo cardiopolmonare: peakVO_2









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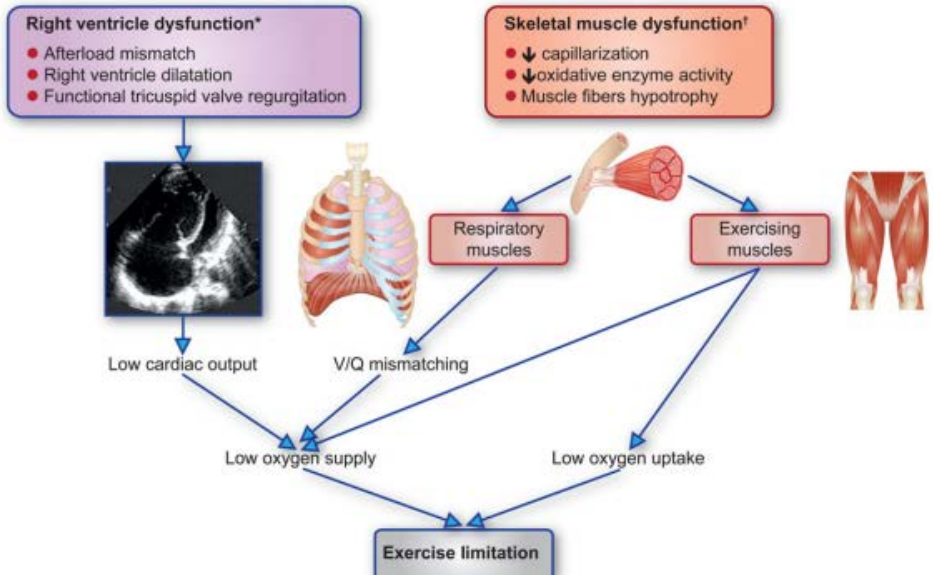
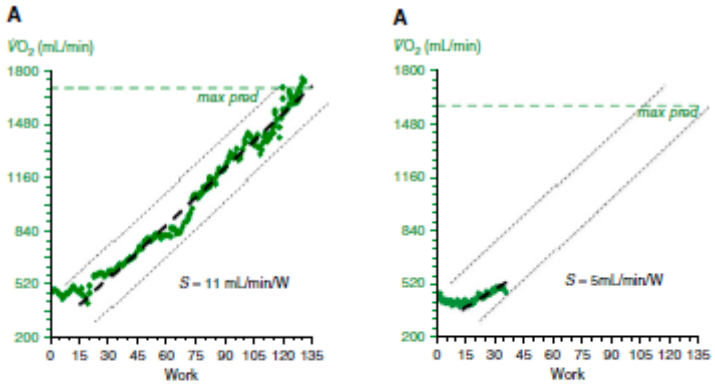


Gruppo MultiMedica

Galiè N., Manes A, Palazzini M. Eur Heart J 2016; 37; 45-48

Test da sforzo cardiopolmonare: polso O_2

PAH



Legge di Fick
$CO=VO_2/C(a\text{-}v)O_2$

$CO=SVxHR$

VO_2/HR (polsoO_2)=
$SV \times C(a–v)O_2$

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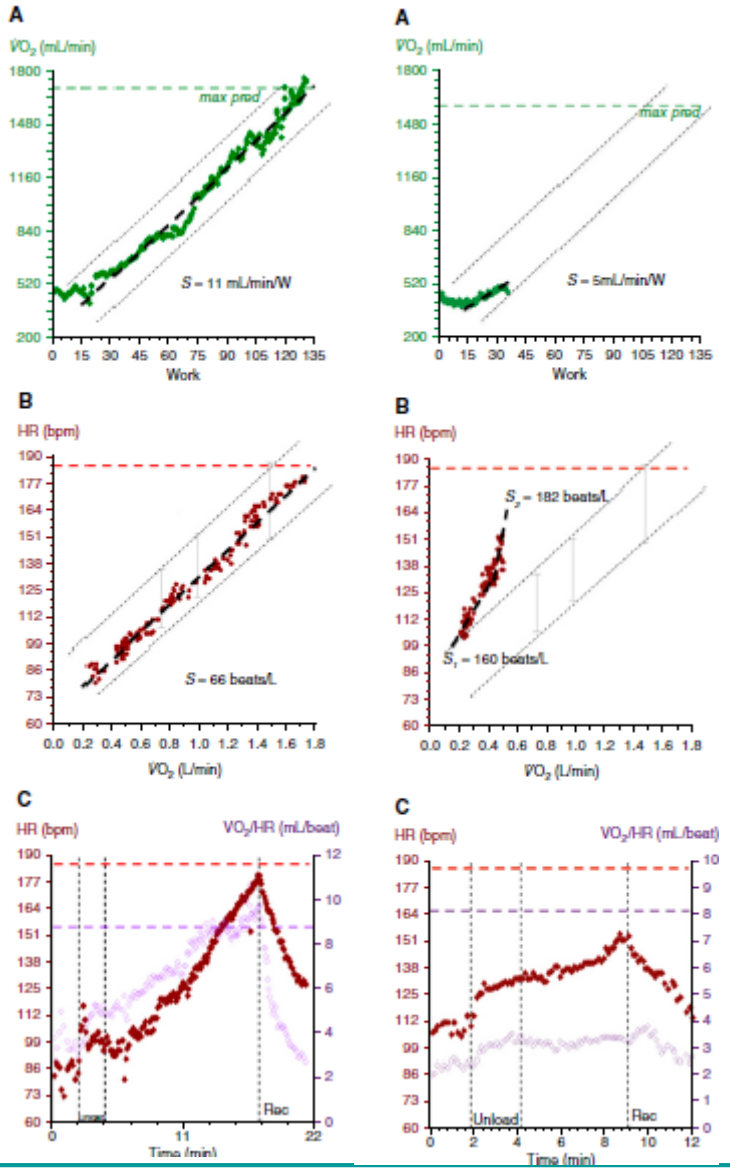
Neder et al. AnnalsATS Vol 12 n.4 April 2015

Test da sforzo cardiopolmonare: polso O_2

PAH



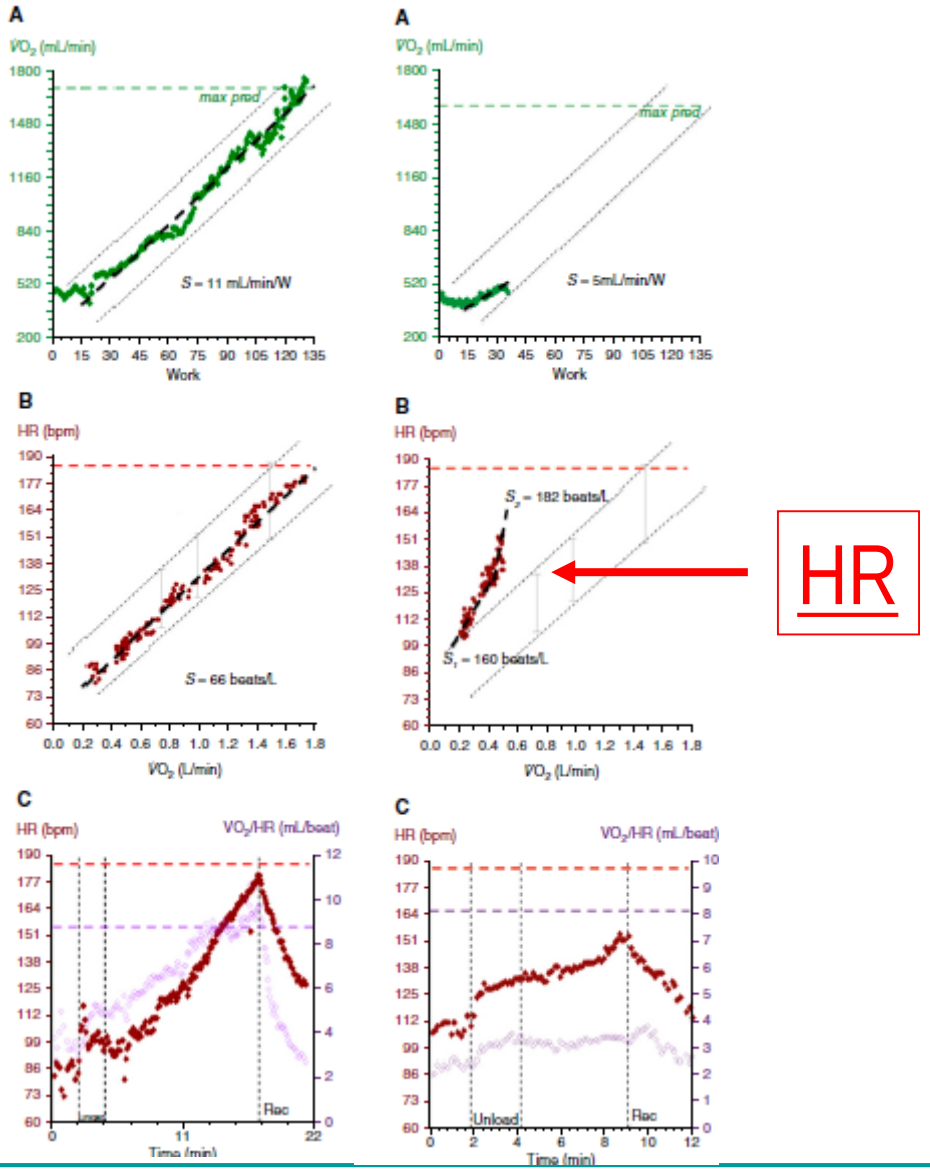
VO_2/HR (polsoO_2)=
SV x C(a–v)O_2

polsoO_2

Neder et al. AnnalsATS Vol 12 n.4 April 2015

Test da sforzo cardiopolmonare: HR

PAH



HR

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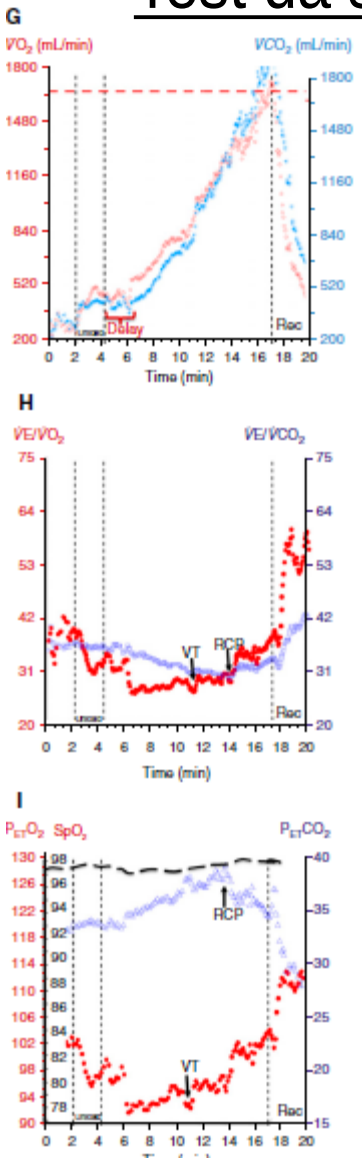
Neder et al. AnnalsATS Vol 12 n.4 April 2015

Test da sforzo cardiopolmonare: soglia anaerobica

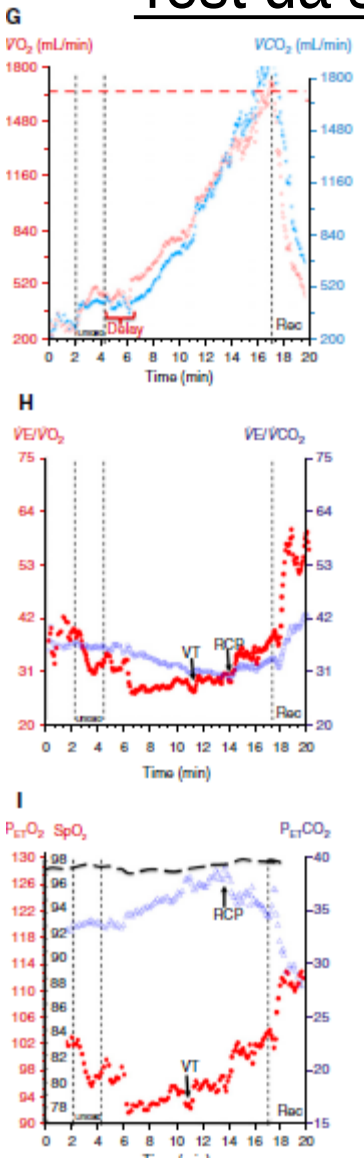
NORMALE

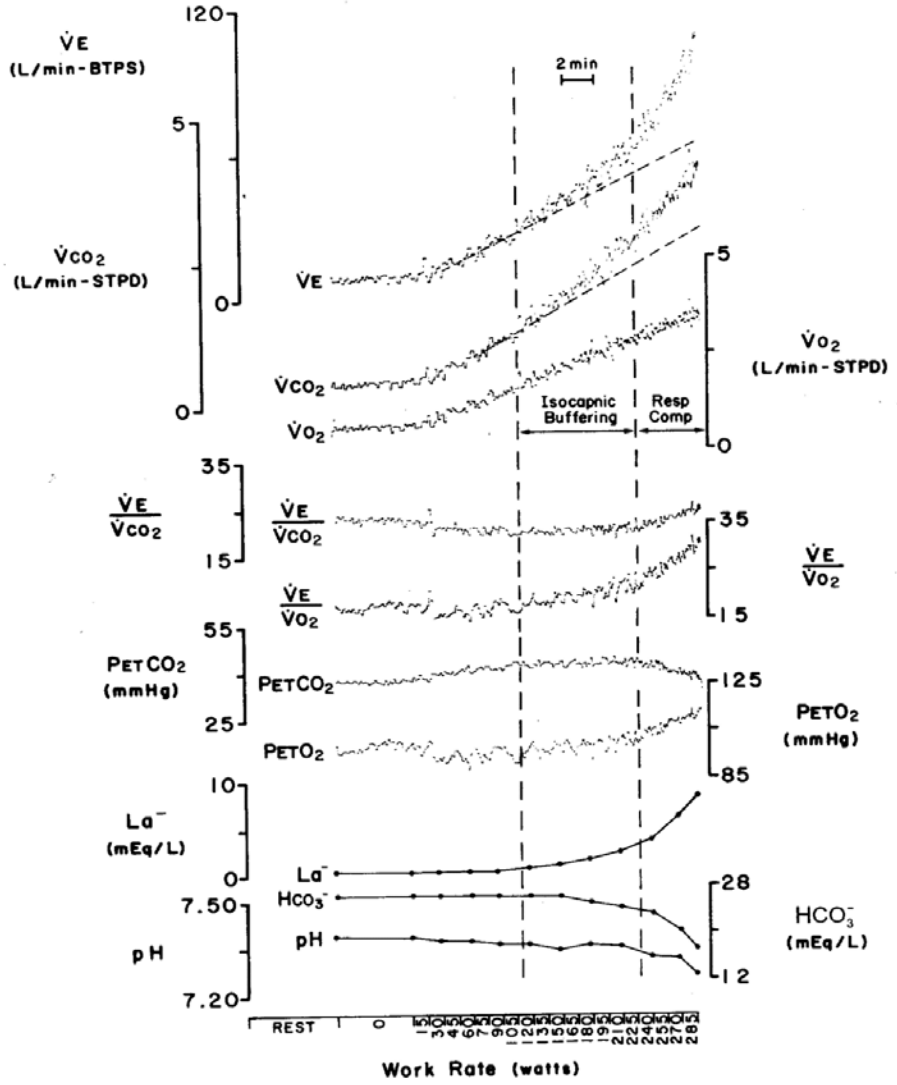


Neder et al. AnnalsATS Vol 12 n.4 April 2015

Test da sforzo cardiopolmonare: soglia anaerobica

NORMALE



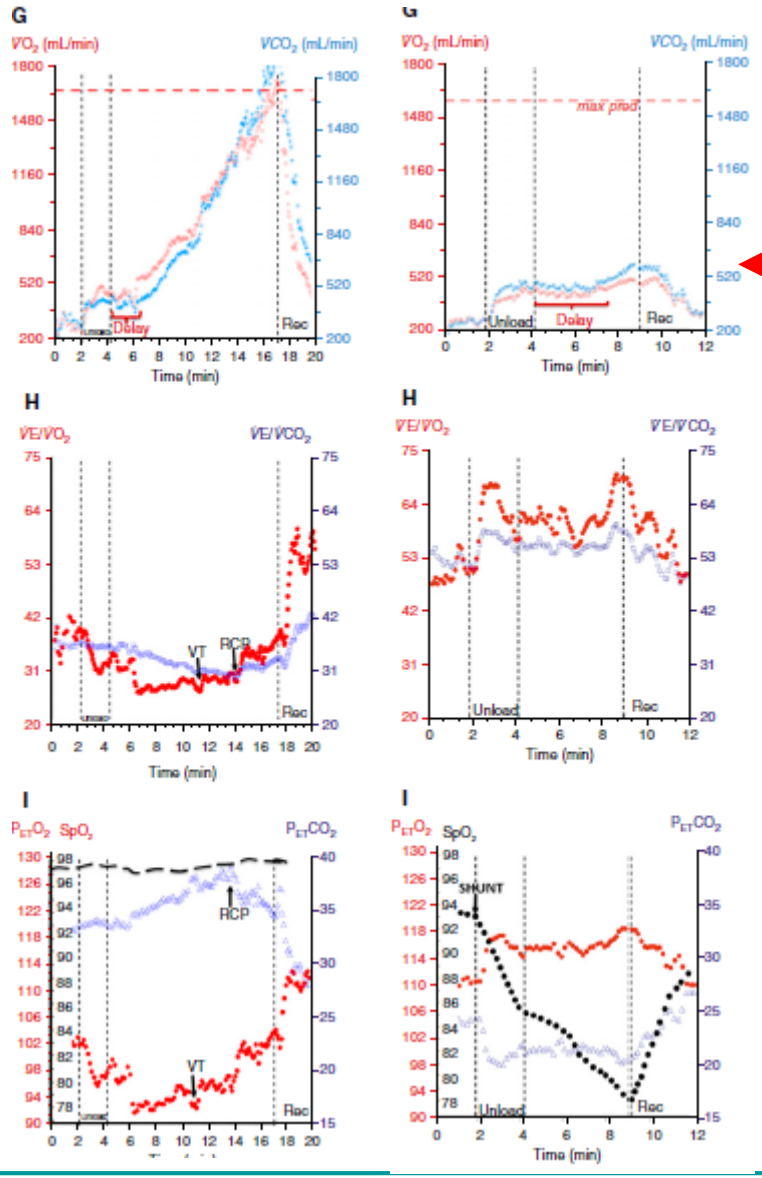


Gruppo MultiMedica

Wasserman K et al. Principles of Exercise Testing and Interpretation

Test da sforzo cardiopolmonare: soglia anaerobica

PAH

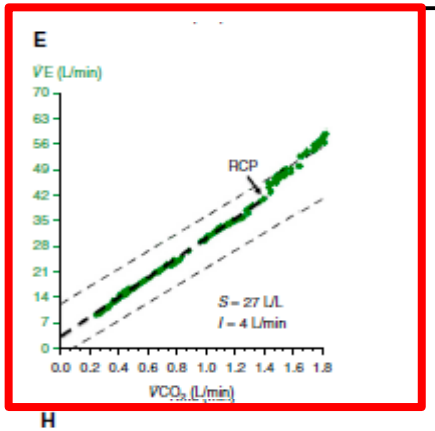


Soglia anaerobica

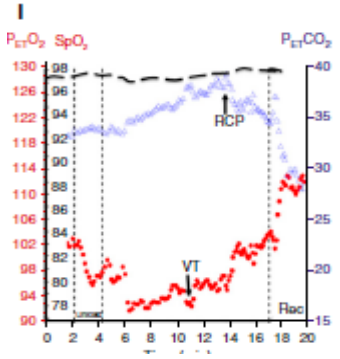
Neder et al. AnnalsATS Vol 12 n.4 April 2015

Test da sforzo cardiopolmonare: ventilazione

NORMALE



$$VE = \frac{VCO_2 \times 863}{[PaCO_2 \times (1 - VD/VT)]}$$

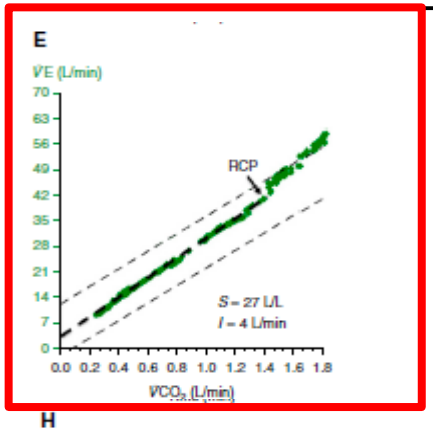


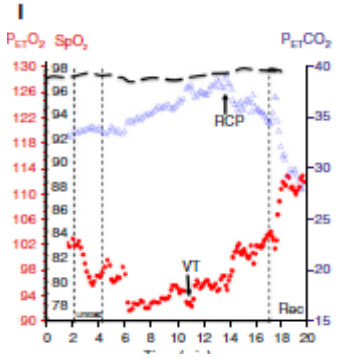
Gruppo MultiMedica

Wasserman K et al. Principles of Exercise Testing and Interpretation

Test da sforzo cardiopolmonare: ventilazione

NORMALE





tamponamento acidosi

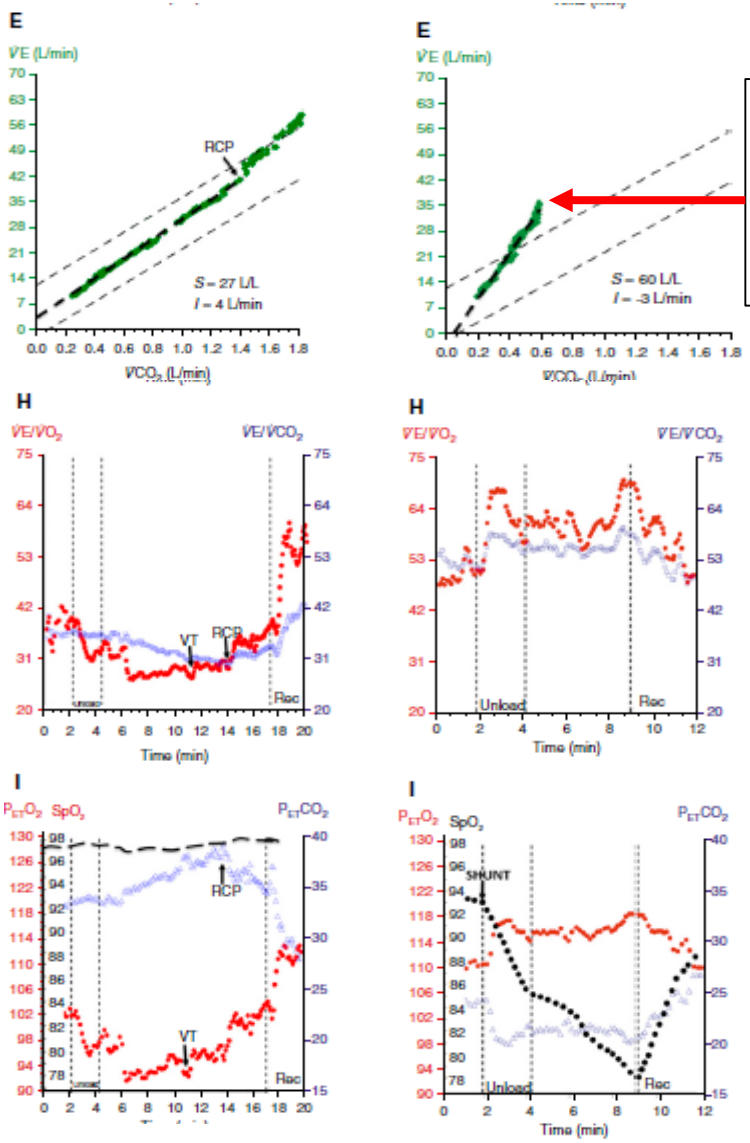
$$VE = \frac{VCO2 \times 863}{\text{set-point } CO_2 [PaCO2 \times (1 - VD/VT)]}$$

ridotta perfusione in zone ventilate

Wasserman K et al. Principles of Exercise Testing and Interpretation

Test da sforzo cardiopolmonare: ventilazione

PAH

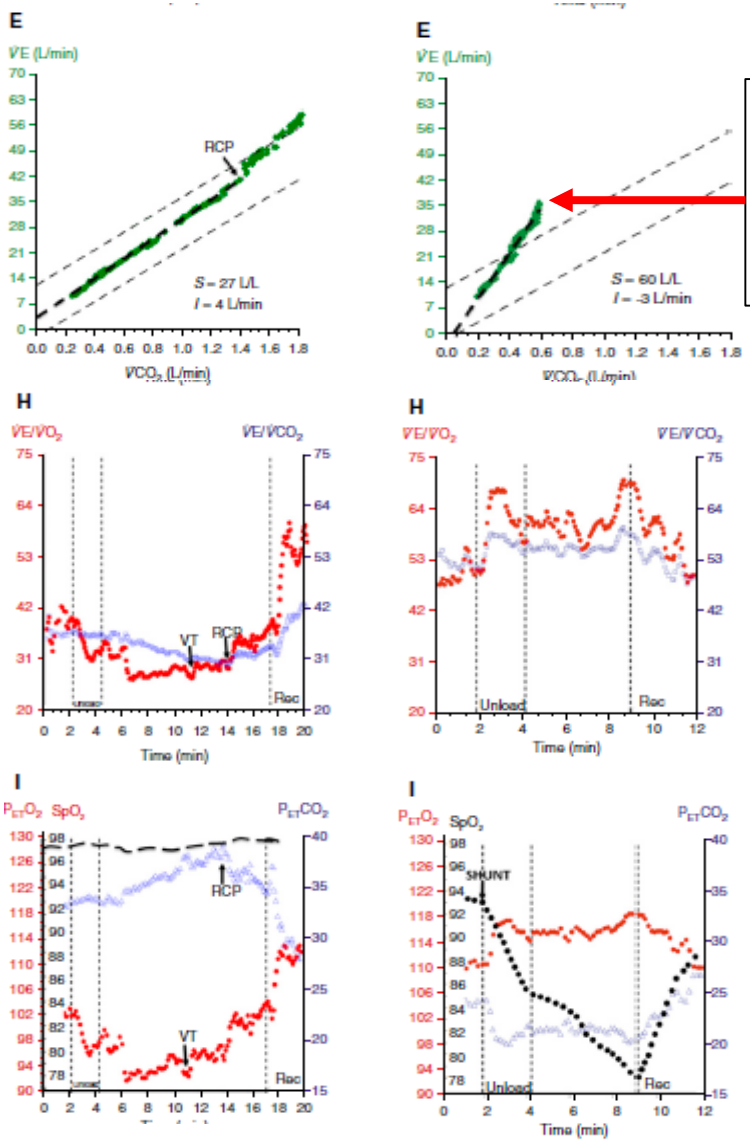


$$VE = \frac{VCO2 \times 863}{[PaCO2 \times (1 - VD/VT)]}$$

Neder et al. AnnalsATS Vol 12 n.4 April 2015

Test da sforzo cardiopolmonare: ventilazione

PAH

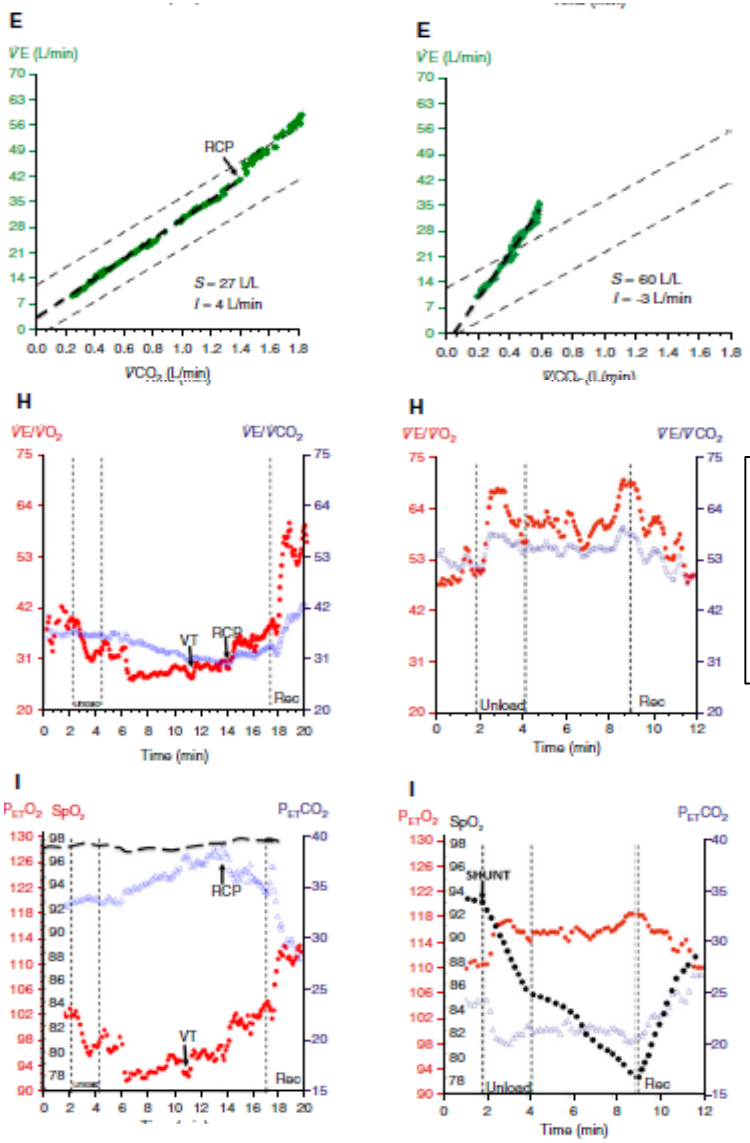


$$VE = \frac{VCO_2 \times 863}{[PaCO_2 \times (1 - VD/VT)]}$$

Neder et al. AnnalsATS Vol 12 n.4 April 2015

Test da sforzo cardiopolmonare: ventilazione

PAH



slope VE/VCO_2

$$VE = \frac{VCO2 \times 863}{[PaCO2 \times (1 - VD/VT)]}$$

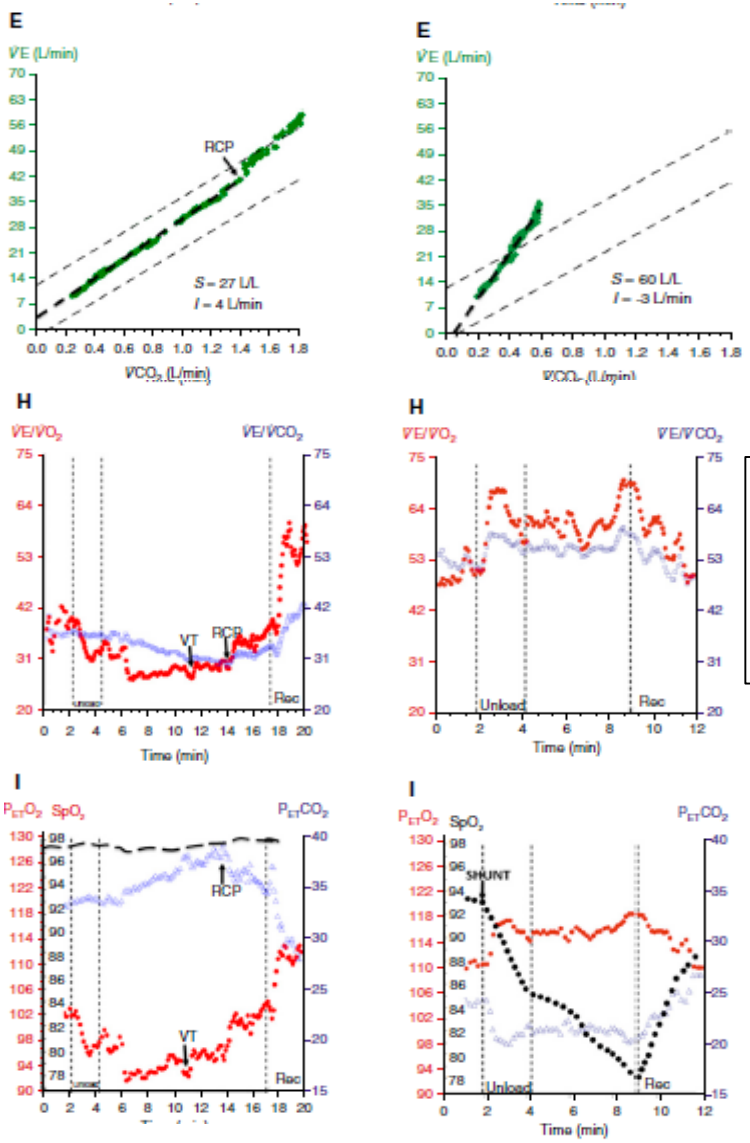
Neder et al. AnnalsATS Vol 12 n.4 April 2015

CPET e prognosi in 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%

Test da sforzo cardiopolmonare: ventilazione

PAH



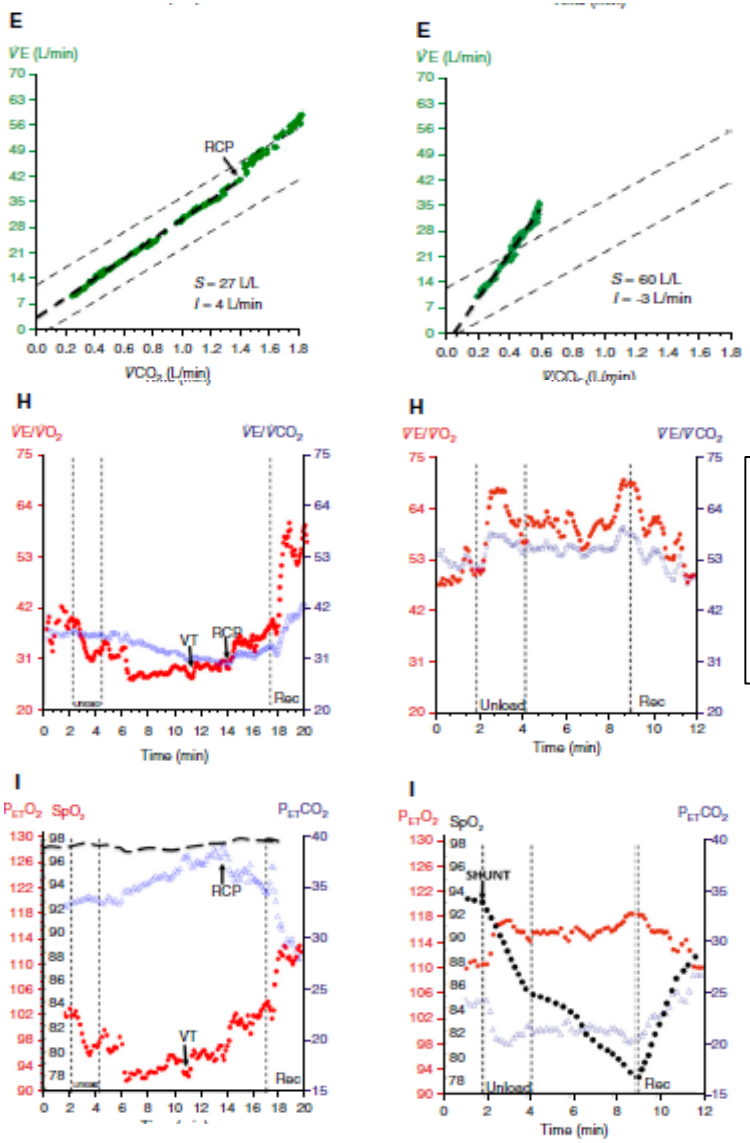
slope VE/VCO_2

$$VE = \frac{VCO2 \times 863}{[PaCO2 \times (1 - VD/VT)]}$$

Neder et al. AnnalsATS Vol 12 n.4 April 2015

Test da sforzo cardiopolmonare: ventilazione

PAH



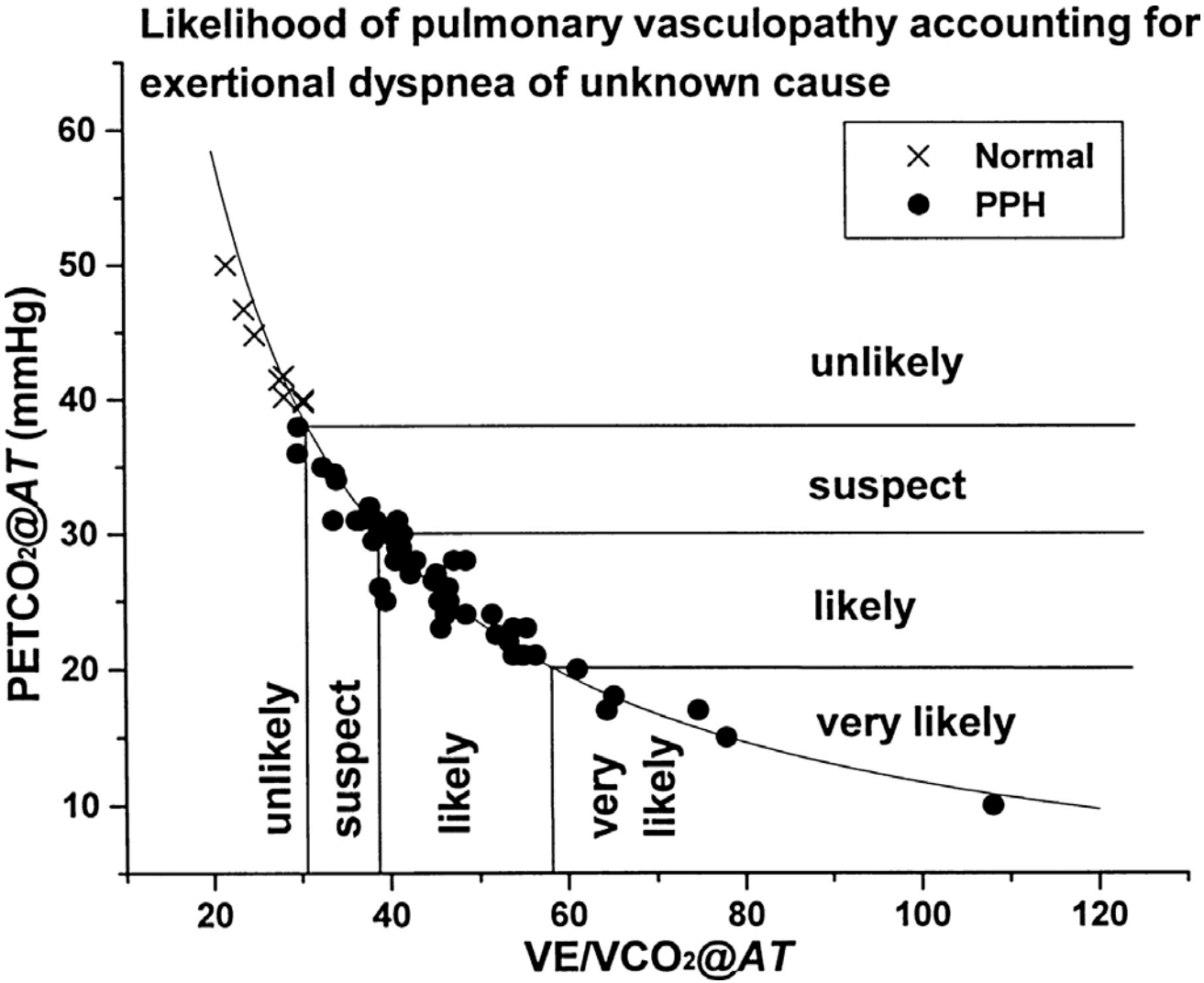
slope VE/VCO_2

$$VE = \frac{VCO2 \times 863}{[PaCO2 \times (1 - VD/VT)]}$$

$pETCO_2$

Neder et al. AnnalsATS Vol 12 n.4 April 2015

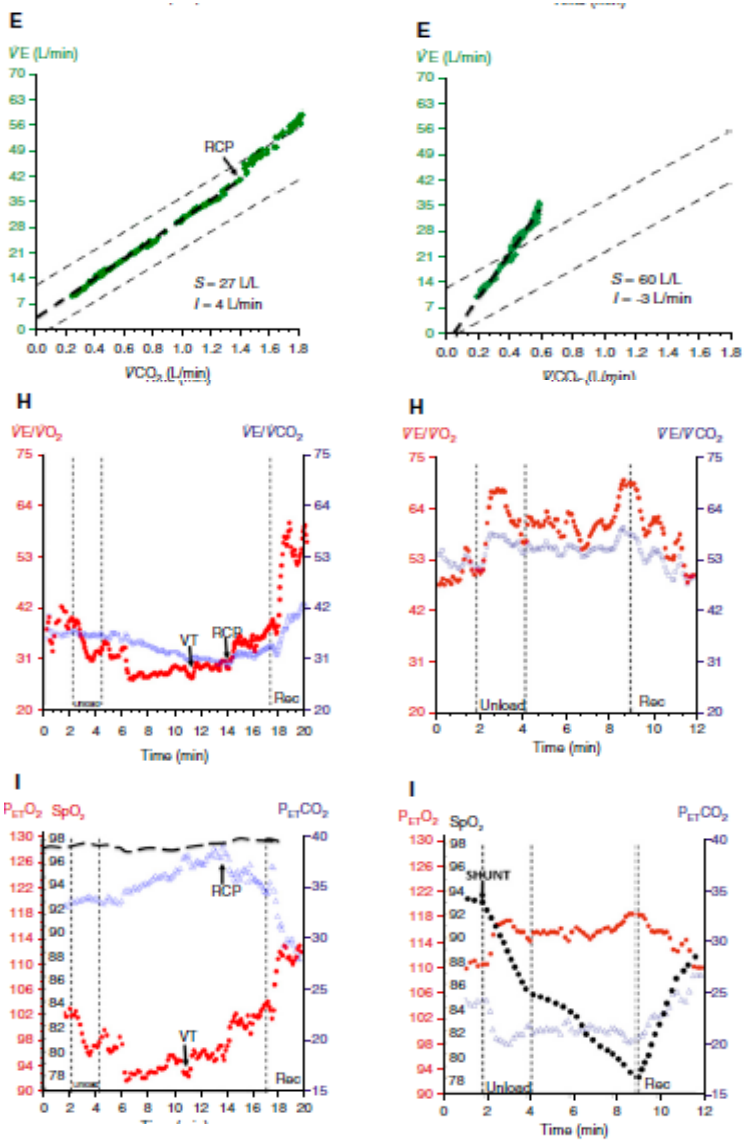
Test da sforzo cardiopolmonare: ventilazione



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

Test da sforzo cardiopolmonare: shunt dx-sin

PAH



shunt dx-sin

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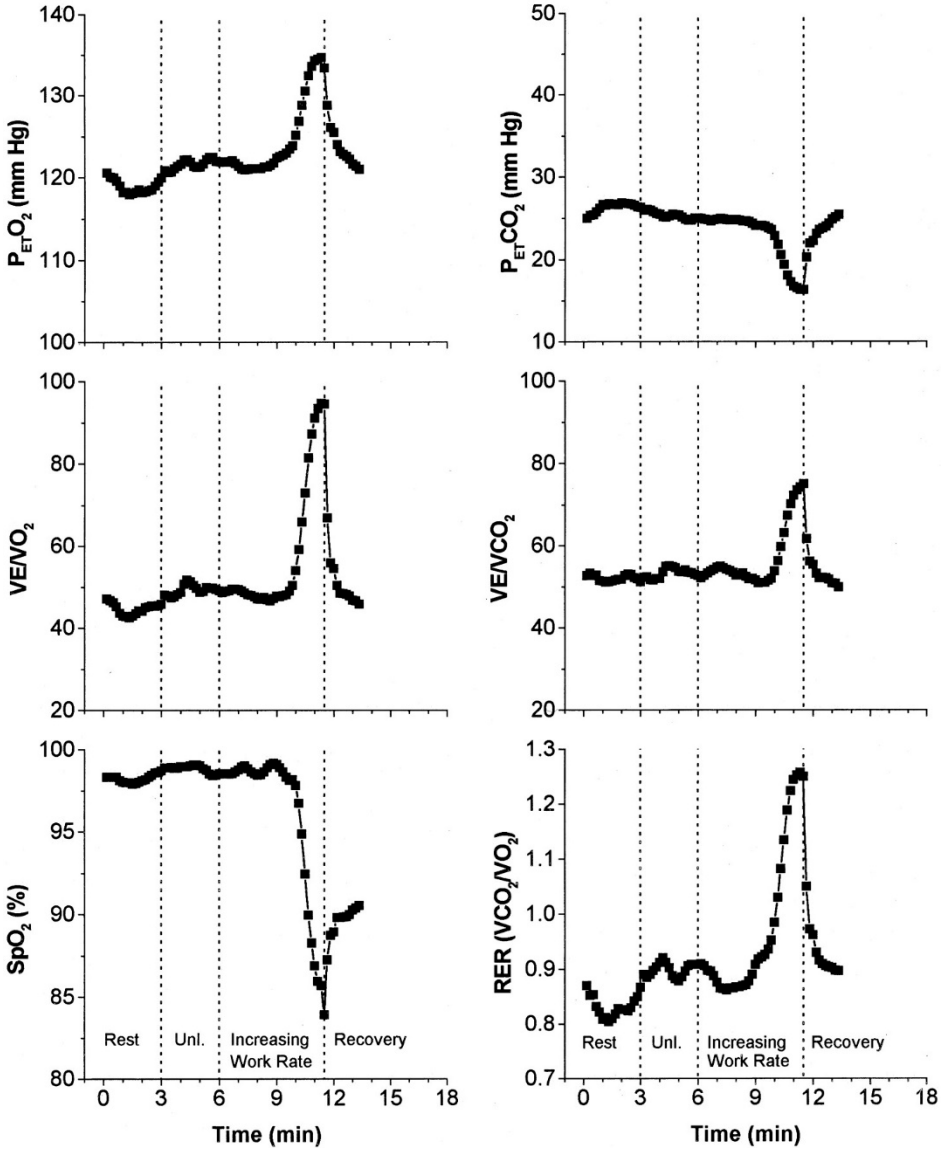
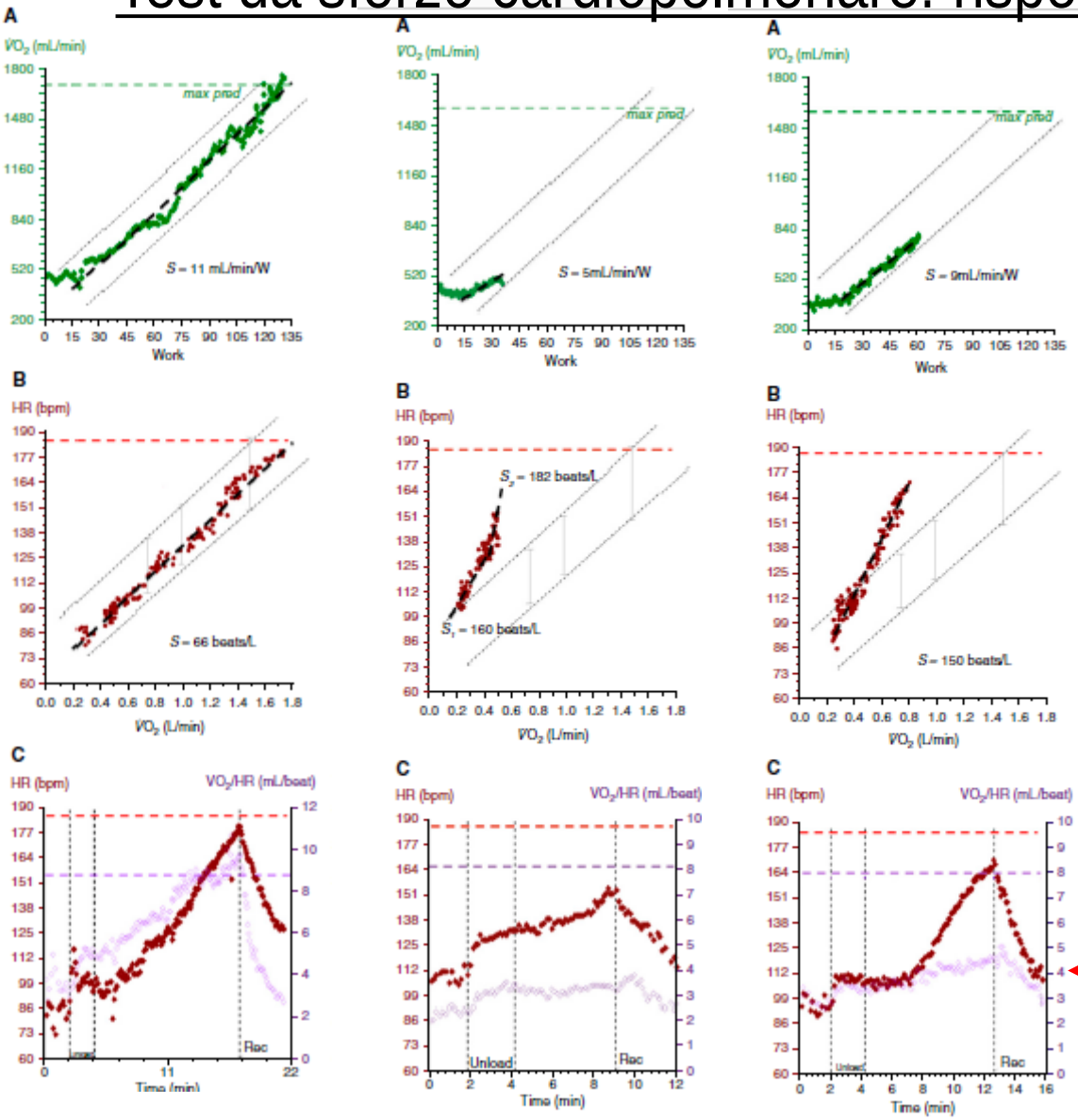
Neder et al. AnnalsATS Vol 12 n.4 April 2015

Test da sforzo cardiopolmonare: shunt dx-sin



Sun, X.-G. et al. Circulation 2002;105:54-60

Test da sforzo cardiopolmonare: risposta alla terapia



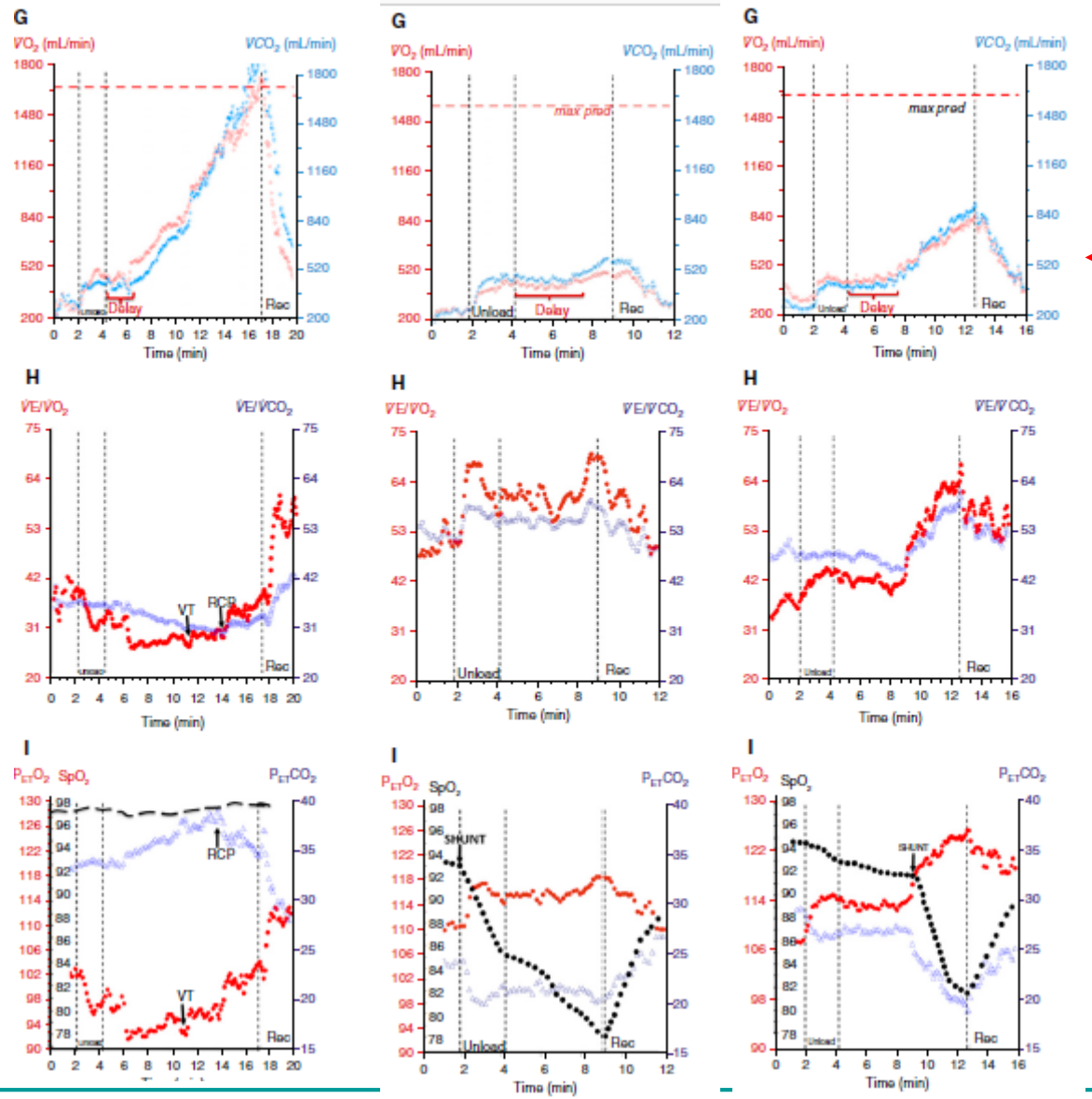
peakVO_2

$PolsoO_2$

Gruppo MultiMedica

Neder et al. AnnalsATS Vol 12 n.4 April 2015

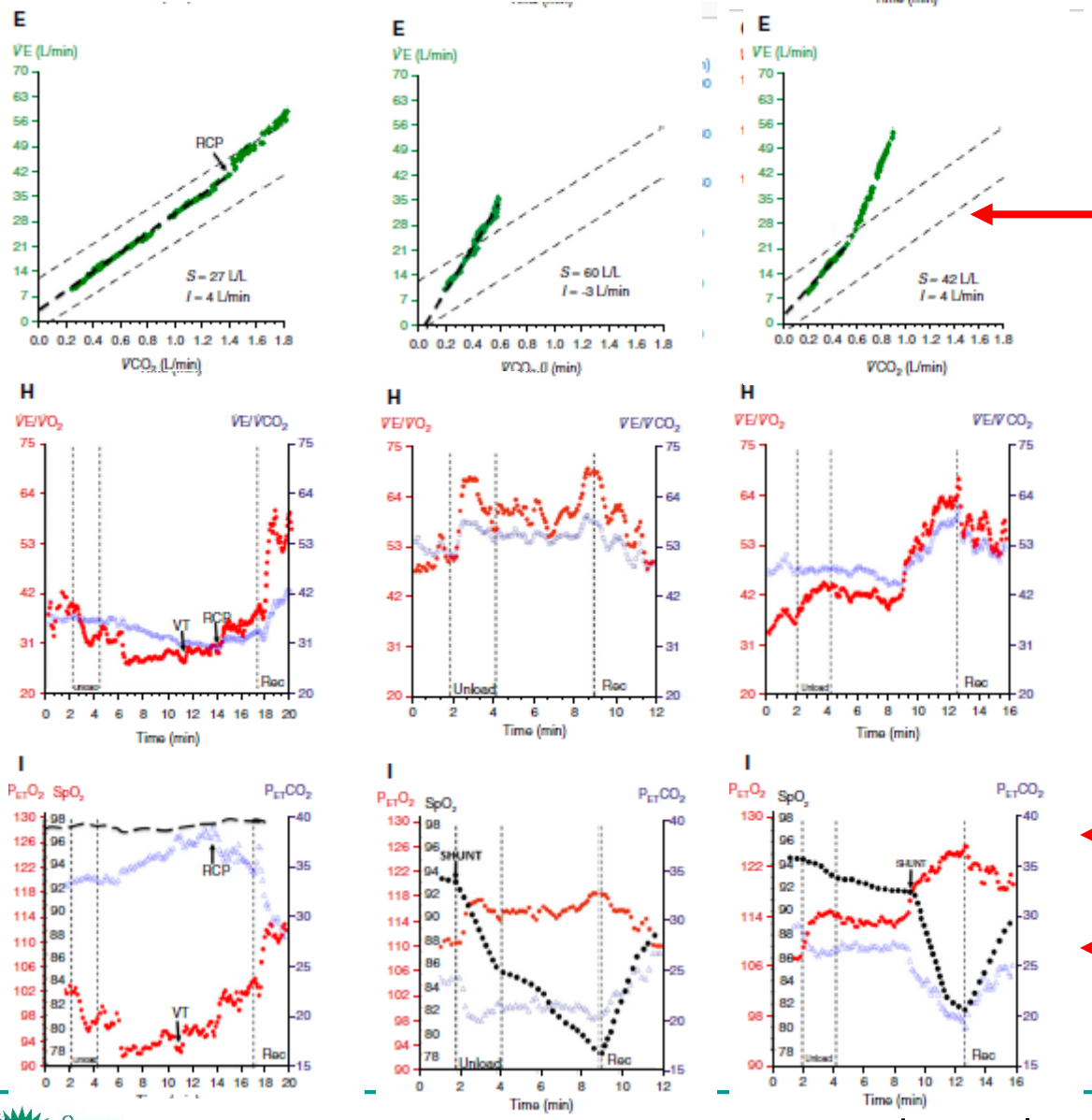
Test da sforzo cardiopolmonare: risposta alla terapia



Soglia anaerobica

Neder et al. AnnalsATS Vol 12 n.4 April 2015

Test da sforzo cardiopolmonare: risposta alla terapia



slope VE/VCO_2

Shunt dx-sin

$petCO_2$

Neder et al. AnnalsATS Vol 12 n.4 April 2015

Gruppo MultiMedica

Use of exercise testing in the evaluation of interventional efficacy: an official ERS statement

TABLE 4 Responsiveness of the different tests to bronchodilators for chronic obstructive pulmonary disease (COPD), vasodilators for pulmonary arterial hypertension (PAH) or pirfenidone for idiopathic pulmonary fibrosis (IPF)

	Variable	COPD	PAH	IPF
IET	V'_{O_2peak}	Modest and inconsistent ↑; few studies	1.5–2 mL·min^{-1}·kg^{-1} or ↑ 9–14%	
	V'_E–V'_{CO_2} indices	Anecdotal evidence	↑ 3–6 units/10–30%	
CWRET	t_{LIM}	14/26 (54%) and 3/11 (27%) of reviewed studies on long- and short-acting bronchodilators, respectively, showed ↑ >MCID (105 s) Limited comparative evidence suggest that it is more responsive than other tests		
	Isotime IC and dyspnoea	Most studies show ↑ >0.2 L and are associated with improvements in dyspnoea intensity of ⩾1 unit on a Borg scale		
ISWT	Time/distance	Inconsistent ↑; few studies		
ESWT	Time/distance	Inconsistent ↑; few studies	No ↑; few studies	
6MWT	Distance	Most studies report increases <MCID (33 m)	Pooled mean effect 38 m	↑ 24 m with pirfenidone

IET: incremental exercise test; CWRET: constant work-rate exercise test; ISWT: incremental shuttle walk test; ESWT: endurance shuttle walk test; 6MWT: 6 min walk test; V'_{O_2peak}: peak oxygen uptake; ↑: significant improvement; V'_E–V'_{CO_2}: ventilation–carbon dioxide output indices; t_{LIM}: time to the limit of tolerance, typically for constant work-rate tests; MCID: minimal clinically important difference; IC: inspiratory capacity.

Puente-Maestu et al. Eur Resp J 2016; 47: 429-460

Use of exercise testing in the evaluation of interventional efficacy: an official ERS statement

TABLE 3 Responsiveness of the tests to rehabilitation

	Variable	COPD	PAH	ILD	Cystic fibrosis/ bronchiectasis
IET	$V'O_{2peak}$	Mean ↑ of 11%	Mean ↑ of 1–1.5 mL·min^{-1}·kg^{-1}	Mean ↑ of 1.2 mL·min^{-1}·kg^{-1}	Limited evidence suggests that it is responsive
	WR_{peak}	Mean ↑ of 6.8 W	No		Limited evidence suggests that it is responsive
	$V'E$-$V'CO_2$ indices				Yes
CWRET	t_{LIM}	Yes; several studies; usually large effects Most studies show ↑ > MCID (105 s) Limited comparative evidence suggests that it is more responsive than other tests	Limited evidence suggests that it is responsive	Limited evidence suggests that it is responsive	Limited evidence suggests that it is responsive
	Isotime IC	Yes		Limited comparative evidence suggests that it is more responsive than other tests	
	Isotime dyspnoea	Yes			
ISWT	Time or distance	Yes Mean ↑ of 38 m	No available information	Limited evidence suggests that it is responsive	No available information
ESWT	Time or distance	Yes Several studies report ↑ of 100–400 s	No available information	Limited evidence suggests that it is responsive	Limited evidence suggests that it is responsive
6MWT	Distance	Mean ↑ of 44 m	Improvements of 50–80 m	Yes Mean ↑ of 39 m	

COPD: chronic obstructive pulmonary disease; PAH: pulmonary arterial hypertension; ILD: interstitial lung disease; IET: incremental exercise test; CWRET: constant work-rate exercise test; ISWT: incremental shuttle walk test; ESWT: endurance shuttle walk test; 6MWT: 6-min walk test; $V'O_{2peak}$: peak oxygen uptake; ↑: significant improvement; WR_{peak}: peak work-rate (or peak power); $V'E$-$V'CO_2$: ventilation–carbon dioxide output indices; t_{LIM}: time to the limit of tolerance, typically for constant work-rate tests; MCID: minimal clinically important difference; IC: inspiratory capacity.

novich[13], Vard[18]

Puente-Maestu et al. Eur Resp J 2016; 47: 429-460

Training cardio-respiratorio in PAH

Seminar

Lancet 1998; **352:** 719–25

Primary pulmonary hypertension

Sean P Gaine, Lewis J Rubin

Primary pulmonary hypertension (PPH) is a progressive disease characterised by raised pulmonary vascular resistance, which results in diminished right-heart function due to increased right ventricular afterload. PPH occurs most commonly in young and middle-aged women; mean survival from onset of symptoms is 2–3 years. The aetiology of PPH is unknown, although familial disease accounts for roughly 10% of cases, which suggests a genetic predisposition. Current theories on pathogenesis focus on abnormalities in interaction between endothelial and smooth-muscle cells. Endothelial-cell injury may result in an imbalance in endothelium-derived mediators, favouring vasoconstriction. Defects in ion-channel activity in smooth-muscle cells in the pulmonary artery may contribute to vasoconstriction and vascular proliferation. Diagnostic testing primarily excludes secondary causes. Catheterisation is necessary to assess haemodynamics and to evaluate vasoreactivity during acute drug challenge. Decrease in pulmonary vascular resistance in response to acute vasodilator challenge occurs in about 30% of patients, and predicts a good response to chronic therapy with oral calcium-channel blockers. For patients unresponsive during acute testing, continuous intravenous epoprostenol (prostacyclin, PGI_2) improves haemodynamics and exercise tolerance, and prolongs survival in severe PPH (NYHA functional class III–IV). Thoracic transplantation is reserved for patients who fail medical therapy. We review the progress made in diagnosis and treatment of PPH over the past 20 years.

Management

Although there is no cure for PPH, there have been advances in both medical and surgical treatment. Physical activity should be limited, and medications that can aggravate pulmonary hypertension should be avoided—vasoactive decongestants, cardiodepressant antihypertensive drugs such as β-adrenergic blockers, and agents that interfere with warfarin or potentiate the degree of anticoagulation, such as non-steroidal anti-inflammatory drugs. Places with low concentrations of ambient oxygen, such as high altitudes or unpressurised aircraft, may exacerbate PPH, and some patients may need supplementary oxygen. The haemodynamic stresses of pregnancy, particularly immediately post-partum, are poorly tolerated. The importance of effective contraception should be emphasised, but oral contraceptives should not be taken by patients with PPH since they may increase the risk of thrombosis and may exacerbate PPH.[23] Hormone-replacement therapy appears to have no adverse effects on PPH in postmenopausal women.

Gruppo MultiMedica

Training cardio-respiratorio in PAH

Exercise Physiology

Exercise and Respiratory Training Improve Exercise Capacity and Quality of Life in Patients With Severe Chronic Pulmonary Hypertension

Derliz Mereles, MD*; Nicola Ehlken*; Sandra Kreuscher*; Stefanie Ghofrani, MD; Marius M. Hoeper, MD; Michael Halank, MD; F. Joachim Meyer, MD; Gabriele Karger, MD; Jan Buss, MD; Jana Juenger, MD; Nicole Holzapfel, MA; Christian Opitz, MD; Jörg Winkler, MD; Felix F.J. Herth, MD; Heinrike Wilkens, MD; Hugo A. Katus, MD; Horst Olschewski, MD; Ekkehard Grünig, MD

***Background*—**Pulmonary hypertension (PH) is associated with restricted physical capacity, limited quality of life, and a poor prognosis because of right heart failure. The present study is the first prospective randomized study to evaluate the effects of exercise and respiratory training in patients with severe symptomatic PH.

***Methods and Results*—**Thirty patients with PH (21 women; mean age, 50±13 years; mean pulmonary artery pressure, 50±15 mm Hg; mean World Health Organization [WHO] class, 2.9±0.5; pulmonary arterial hypertension, n=23; chronic thromboembolic PH, n=7) on stable disease-targeted medication were randomly assigned to a control (n=15) and a primary training (n=15) group. Medication remained unchanged during the study period. Primary end points were the changes from baseline to week 15 in the distance walked in 6 minutes and in scores of the Short Form Health Survey quality-of-life questionnaire. Changes in WHO functional class, Borg scale, and parameters of echocardiography and gas exchange also were assessed. At week 15, patients in the primary and secondary training groups had an improved 6-minute walking distance; the mean difference between the control and the primary training group was 111 m (95% confidence interval, 65 to 139 m; $P<0.001$). Exercise training was well tolerated and improved scores of quality of life, WHO functional class, peak oxygen consumption, oxygen consumption at the anaerobic threshold, and achieved workload. Systolic pulmonary artery pressure values at rest did not change significantly after 15 weeks of exercise and respiratory training (from 61±18 to 54±18 mm Hg) within the training group.

Conclusions*—**This study indicates that respiratory and physical training could be a promising adjunct to medical treatment in severe PH. The effects add to the beneficial results of modern medical treatment. (Circulation*. 2006;114:1482-1489.)

Key Words: rehabilitation ■ exercise ■ hypertension, pulmonary ■ pulmonary heart disease ■ quality of life

Training cardio-respiratorio in PAH

Heart, Lung and Circulation (2016) 25, 333–341
1443-9506/04/$36.00
http://dx.doi.org/10.1016/j.hlc.2015.10.015

REVIEW

Effects of Exercise Training on Exercise Capacity in Pulmonary Arterial Hypertension: A Systematic Review of Clinical Trials

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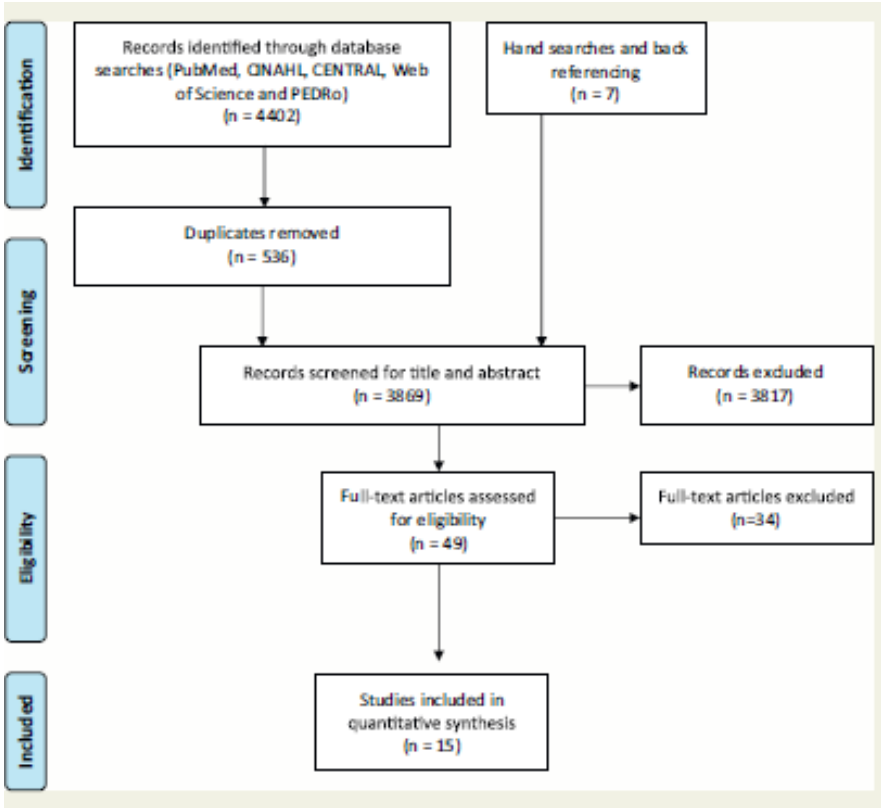
(*Circ Heart Fail.* 2015;8:1032-1043.

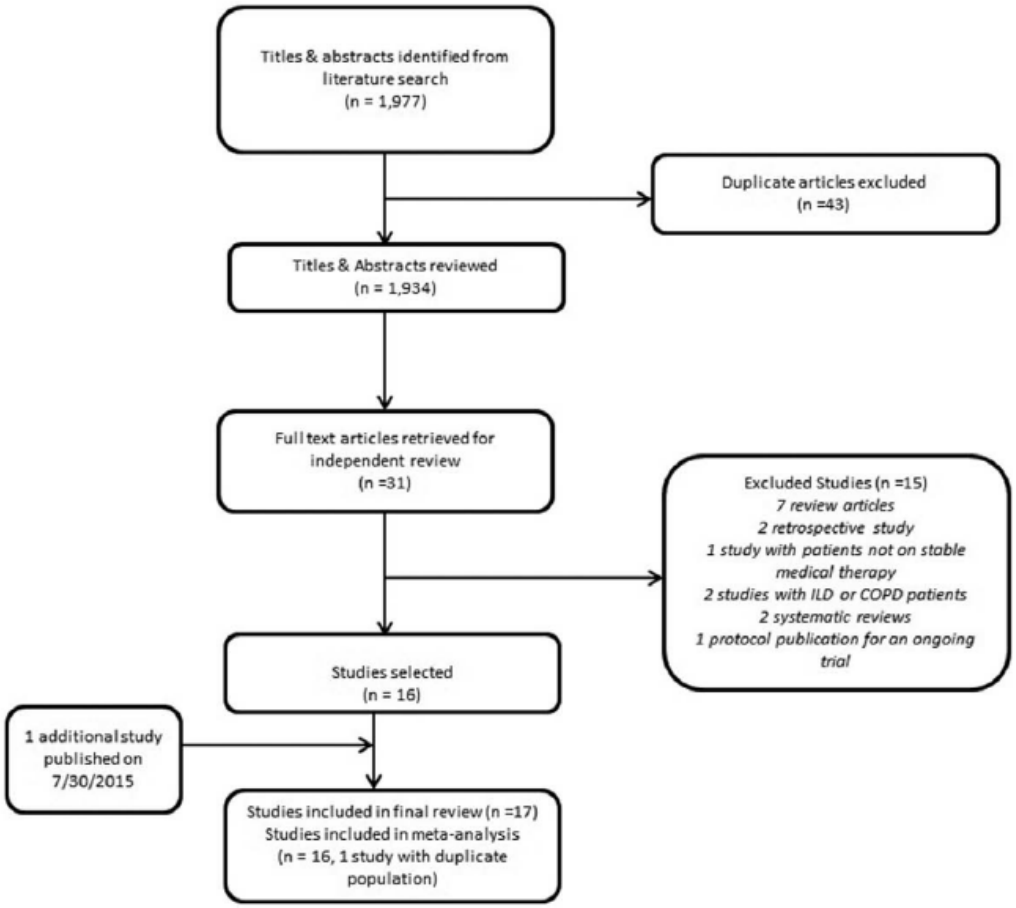
Efficacy and Safety of Exercise Training in Chronic Pulmonary Hypertension

Systematic Review and Meta-Analysis

Ambarish Pandey, MD; Sushil Garg, MD; Monica Khunger, MD; Sonia Garg, MD; Dharam J. Kumbhani, MD, SM; Kelly M. Chin, MD; Jarett D. Berry, MD, MS

Training cardio-respiratorio in PAH





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Babu AS et al. Heart, Lung and Circulation 2016; 25, 333-341

Pandey et al. Circ Heart Fail 2015; 8: 1032-43

Training cardio-respiratorio in PAH

European Heart Journal (2016) 37, 35–44
doi:10.1093/eurheartj/ehv337

CLINICAL RESEARCH
Pulmonary circulation

Exercise training improves peak oxygen consumption and haemodynamics in patients with severe pulmonary arterial hypertension and inoperable chronic thrombo-embolic pulmonary hypertension: a prospective, randomized, controlled trial

Nicola Ehlken[1*†], Mona Lichtblau[1†], Hans Klose[2†], Johannes Weidenhammer[1], Christine Fischer[3], Robert Nechwatal[4], Sören Uiker[4], Michael Halank[5], Karen Olsson[6], Werner Seeger[7], Henning Gall[7], Stephan Rosenkranz[8], Heinrike Wilkens[9], Dirk Mertens[10], Hans-Jürgen Seyfarth[11], Christian Opitz[12], Silvia Ulrich[13], Benjamin Egenlauf[1], and Ekkehard Grünig[1]

Heart Online First, published on May 24, 2016 as 10.1136/heartjnl-2015-309230
Pulmonary vascular disease

OPEN ACCESS

ORIGINAL ARTICLE

Efficacy of cardiac rehabilitation after balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension

Shigefumi Fukui,[1] Takeshi Ogo,[1] Hiroshi Takaki,[1] Jin Ueda,[1] Akihiro Tsuji,[1] Yoshiaki Morita,[2] Reon Kumasaka,[1] Tetsuo Arakawa,[1] Michio Nakanishi,[1] Tetsuya Fukuda,[2] Satoshi Yasuda,[1] Hisao Ogawa,[1] Norifumi Nakanishi,[1] Yoichi Goto[1]

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Training cardio-respiratorio in PAH: sicurezza

Table 5. Training-Associated Adverse Effects Reported in Included Studies

Study	Total No. of Exercise Training Participants	Exercise Training–Related Adverse Events
Mereles et al 2006[14]	15	Dizziness in 2 patients, low oxygen saturation in 1 patient
Martinez-Quintana et al 2010[26]	4	Exercise intolerance with cyanosis in 2 patients
Fox et al 2011[17]	11	None
Chan et al 2013[22]	10	None
Ley et al 2013[23]	10	None
Weinstein et al 2013[30]	11	None
Ehlken et al 2015[29]	46	None
Becker-Grünig et al 2013[21]	20	None
Grünig et al 2012[20]	21	None
Grünig et al 2011[18]	58	Dizziness with training in 2 patients
Grünig et al 2012[19]	183	Presyncope in 1 patient after training Self-limiting tachycardia in 2 patients during exercise
Mainguy et al 2010[16]	5	None
Nagel et al 2012[27]	35	Syncope during exercise in 1 patient Herpes zoster in 1 patient
De Man et al 2009[15]	19	Minor dizziness in 2 patients
Kabitz et al 2014[24]	7	None
Inagaki et al 2014[28]	8	One patient with hypotension during training
Ihle et al 2014[25]	17	None

Training cardio-respiratorio in PAH: capacità funzionale

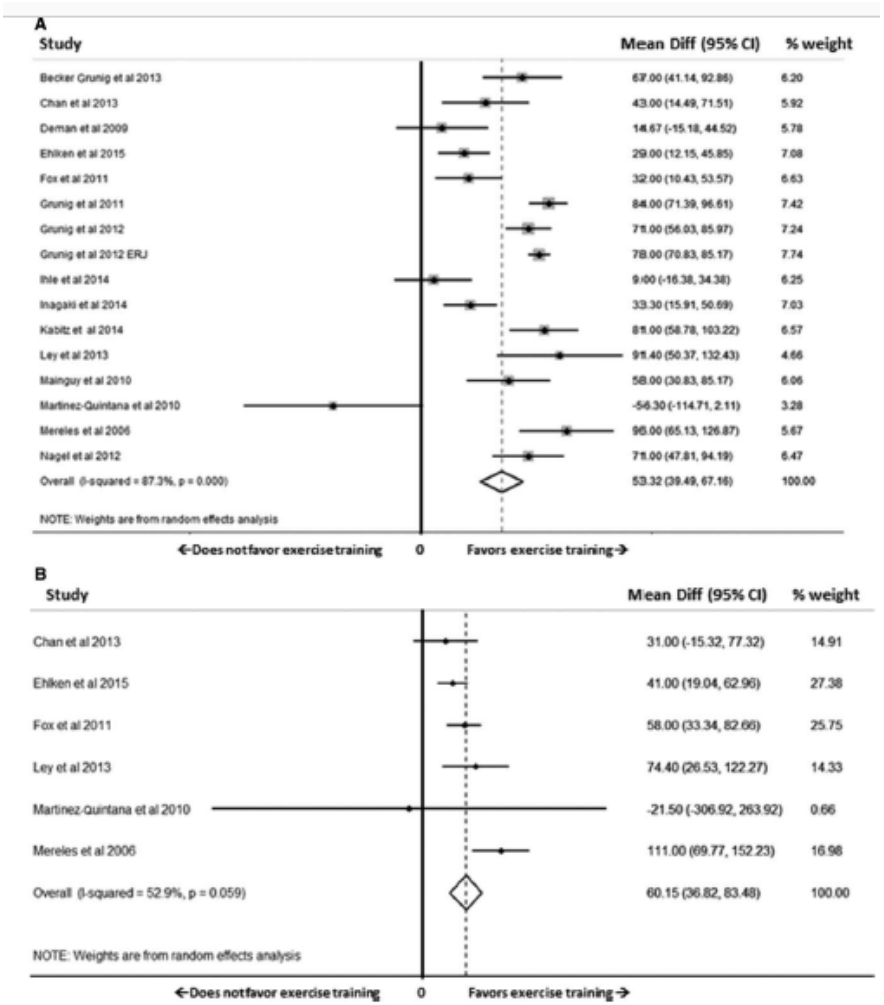

Figure 2. Forest plot showing effect of exercise training on 6-minute walk distance on pooled analysis of all included studies[14–29] (**A**) and parallel group trials with an intervention and control arm only[14,17,20,23,26,29] (n=6; **B**). CI indicates confidence interval.

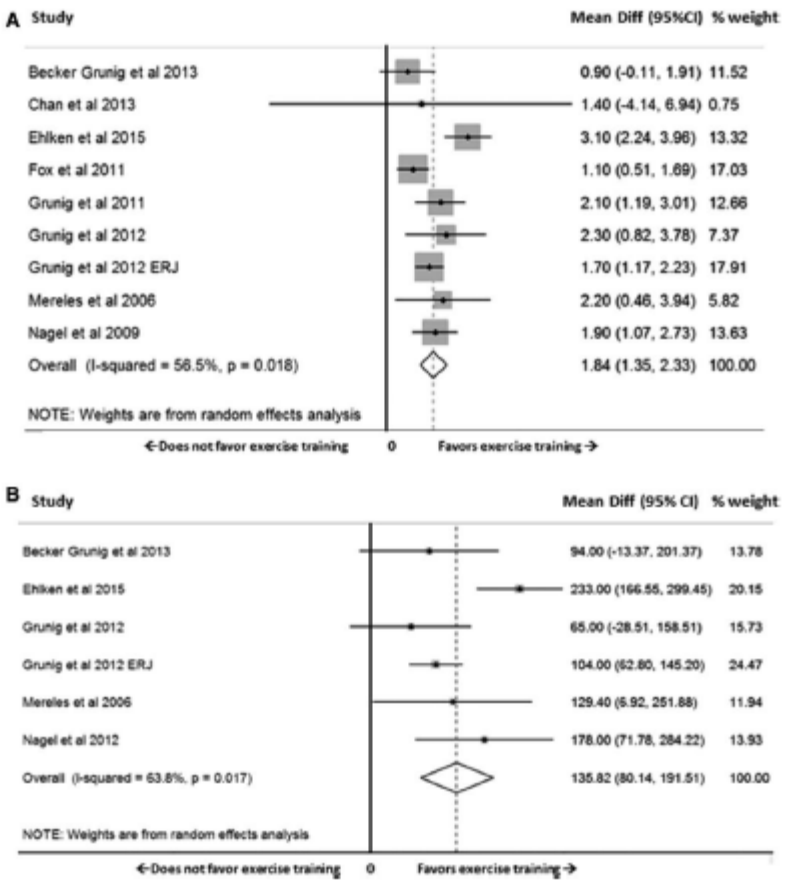

Figure 3. Forest plot showing effect of exercise training on peak relative oxygen uptake (mL/kg per minute; n=9, **A**)[14,17–22,27,29] and peak absolute oxygen uptake (mL/min) on pooled analysis of included studies (n=6, **B**).[14,19–21,27,29] CI indicates confidence interval.

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Effetti del Training in HF

Clinical Investigation

Hemodynamic Effects of Exercise Training in Heart Failure

GAIA CATTADORI, MD,[1] JEAN-PAUL SCHMID, MD,[2] NICOLAS BRUGGER, MD,[2] ERICA GONDONI, MD,[1]
PIETRO PALERMO, MD,[1] AND PIERGIUSEPPE AGOSTONI, MD, PhD[1,3,4]

Milan, Italy; Bern, Switzerland; Seattle, Washington

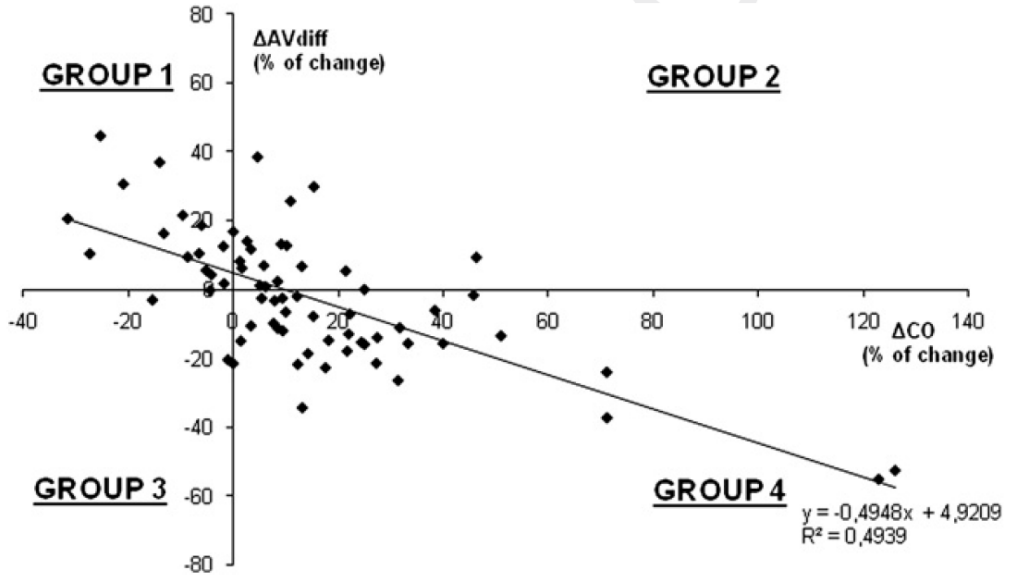

Fig. 2. Correlation between pre- and posttraining variations (Δ) of calculated arteriovenous O_2 differences (a-v O_2diff) vs. variation of peak CO. Data are reported as percentage of changes.

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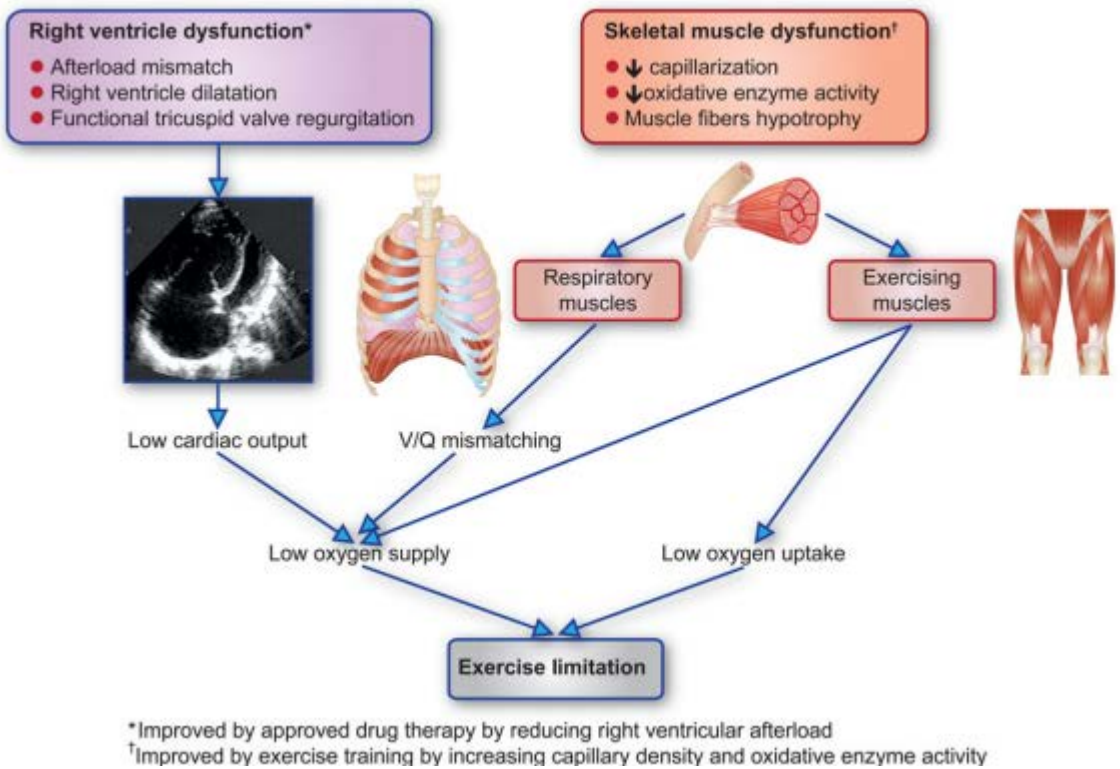
Cattadori G. et al. J Card Fail. 2011; 17:916-22

Effetti del Training in PAH



Galiè N., Manes A, Palazzini M. Eur Heart J 2016; 37; 45-48

Training cardio-respiratorio in PAH

European Heart Journal (2016) **37**, 45–48
doi:10.1093/eurheartj/ehv440

EDITORIAL

Exercise training in pulmonary hypertension: improving performance but waiting for outcome

Nazzareno Galie[1]*, Alessandra Manes[2], and Massimiliano Palazzini[1]

[1]University of Bologna, Department of Experimental, Diagnostic and Specialty Medicine-DIMES, Bologna, Italy; and [2]S. Orsola-Malpighi University Hospital, Bologna, Italy

Training cardio-respiratorio in PAH: Guidelines 2015

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Training cardio-respiratorio in PAH: Guidelines 2015

Table 16 Recommendations for general measures

Recommendations	Class[a]	Level[b]	Ref.[c]
It is recommended that PAH patients avoid pregnancy	I	C	160, 161
Immunization of PAH patients against influenza and pneumococcal infection is recommended	I	C	
Psychosocial support is recommended in PAH patients	I	C	168
Supervised exercise training should be considered in physically deconditioned PAH patients under medical therapy	IIa	B	153–157
In-flight O_2 administration should be considered for patients in WHO-FC III and IV and those with arterial blood O_2 pressure consistently <8 kPa (60 mmHg)	IIa	C	
In elective surgery, epidural rather than general anaesthesia should be preferred whenever possible	IIa	C	
Excessive physical activity that leads to distressing symptoms is not recommended in PAH patients	III	C	

Table 1 Summary of articles included in the review (n=15)

Author (year)	Number	Design	NYHA grade at enrolment	PH cause (n)	Intervention (Intensity)	Duration	Outcome measures	Results
Mereles et al. (2006)	30	RCT	II – IV	CTEPH (6), PAH (24)	Exercise + respiratory muscle training	3 weeks – institution-based and 12 weeks – home-based	6MWD	85m increase after 3 weeks and 96m after 15 weeks (p<0.001)
							SF36	Improved QoL in physical function and vitality (p<0.005)
Shoemaker et al. (2009)	2	Case report		iPH and PAH due to scleroderma	Cycle ergometry (50% peak workload)	6 weeks – institution-based, 3 days/week	peak VO_2	4% and 14% increase
							CAMPHOR	Improved
							SF36	
deMan et al. (2009)	19	Pre-post	II – III	iPH	Cycling and quadriceps muscle training while maintaining SpO2>85% and HR <120 bpm	12 weeks – institution-based	6MWD	4% increase (p=0.13)
							Workload at AT	Increase in workload of AT from 32 to 46 Watt; (p=0.003)
							Quadriceps endurance and strength	13% and 34% increase (p<0.05)
Martinez-Quintana et al. (2010)	8	Non-randomised controlled trial	II – III	Congenital heart disease	Interval training on bicycle and resistance training	2 days a week for 12 weeks – institution-based	6MWD	No significant change in 6MWD and QoL
							SF12	
Mainguy et al. (2010)	5	Case series	II – III	iPH	Aerobic and resisted exercises (60% max workload and 70% MVC)	12 weeks – institution based	6MWD	58m improvement (p=0.01)
Fox et al. (2011)	22	Non-randomised controlled trial	II – III	iPH and CTEPH	Aerobic and resisted exercises + stair climbing (60-80% HRmax)	12 weeks – institution- and home-based	6MWD	32m and 1.1ml/Kg/min improvement (p<0.05)
							peak VO_2	
Grunig et al. (2011)	58	Pre-post	II – IV	iPH	Aerobic and resistance training + respiratory muscle training	3 weeks – institution-based and 12 weeks – home-based	6MWD	87m and 2.1ml/Kg/min improvement (p<0.001)
							peak VO_2	
							SF36	Improvement in all domains of SF36 (p<0.05)
Grunig et al. (2012)	183	Pre-post	II – IV	PAH, CTEPH, PH due to lung and heart disease	Exercise + respiratory muscle training	3 weeks – institution-based and 12 weeks – home-based	6MWD	58m increase after 3 weeks and 78m after 15 weeks (p<0.001)
							SF36	Improved QoL (p<0.05)
Grunig et al. (2012)	21	Pre-post	II – IV	PAH due to CTD	Exercise + respiratory muscle training	3 weeks – institution-based and 12 weeks – home-based	6MWD	67m increase after 3 weeks and by 71m after 15 weeks (p<0.05)
							SF36	Improved QoL (p<0.05)
Nagel et al. (2012)	35	Pre-post	II – IV	CTEPH	Exercise + respiratory muscle training	3 weeks – institution-based and 12 weeks – home-based	6MWD	61m increase after 3 weeks and 71m after 15 weeks
							peak VO2	1.9ml/Kg/min after 15 weeks
							SF36	Improved QoL (p<0.05)
							NT-proBNP	>20% reduction at 3 weeks
							Survival	1,2 and 3year survival rates of 97%, 94% and 86%
Chan et al. (2013)	23	RCT	I-IV	PAH	Education versus exercise training	10 weeks	6MWD	56m increase with exercise training (p=0.002)
							SF36	
							CAMPHOR	Improvements in both QoL measurements (p<0.05)
Becker-Grunig et al. (2013)	20	Pre-post	II – IV	PAH due to CHD	Exercise + respiratory muscle training	3 weeks – institution-based and 12 weeks – home-based	6MWD	63m increase after 3 weeks and 67m increase after 15 weeks (p<0.001)
							peakVO2	Increased from 8.3L /min to 9.02 and 9.25L /min at 3 and 15 weeks respectively
							SF36	
							Survival	Significant improvement only in bodily pain
								100% survival at years 1 and 2. Transplantation free survival 100% and 93% at years 1 and 2
Ley et al. (2013)	20	RCT	II-III	PAH, CTD, CTEPH, Portal hypertension	Exercise + respiratory muscle training	3 weeks	6MWD	91m improvement in the experimental group (p=0.008)
Weinstein et al. (2013)	24	RCT	I-IV	PAH, CTD	Education versus exercise training	10 weeks	6MWD	53m increase (p=0.003) with exercise training
							Fatigue	Improved
Kabitz et al. (2014)	7	Case series	III-IV	PAH		3 weeks – institution-based and 12 weeks – home-based	6MWD	92m increase after 3 weeks and 81m increase after 15 weeks (p<0.001)
							Respiratory muscle strength	Improved PImax by 1 kPa (p=0.086), PEmax by 2.3 kPa (p=0.021), SnPna by 1.3 kPa (p=0.025) at 15 weeks

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Tipo di training:

- Aerobico (approccio prudente: cominciare <50% capacità aerobica/durata 30' fino a 50-75% 30-60'; max 120 bpm e satO2 85%)
- di resistenza
- Respiratorio

Pazienti: classe I e IV

Durata: 3 settimane ricoverati e durata 12 settimane

Vantaggio economico: 657 euro.

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Training cardio-respiratorio in PAH

Eur Respir J 2012; 40: 7–8
DOI: 10.1183/09031936.00070312

EDITORIAL

Exercise training for pulmonary hypertension: another prescription to write?

Lewis J. Rubin

For over 30 years I have been advising my patients with pulmonary hypertension (PH) to be physically active to a level of exertion that does not produce severe dyspnoea persisting post-exercise, dizziness, syncope or chest pain, based on the assumption that inactivity was bad both physically and mentally. This empirical advice meant little in the years before effective medical and surgical methods of treating PH were developed, but gained importance both as a conditioning practice for patients considered for transplantation or pulmonary endarterectomy, and as an adjunct to long-term medical therapy [1]. Only recently, however, has evidence supporting a meaningful benefit of physical activity been generated, dispelling the notion that there may be more harm than good resulting from attempting to increase blood flow through a restricted and presumed noncompliant pulmonary vascular bed [2]. In this issue of the *European Respiratory Journal*, GRÜNIG *et al.* [3] bring our understanding of the effects of exercise in PH a leap forward by demonstrating that an intensive 3-week in-hospital rehabilitation programme followed by a regimented home exercise programme resulted in marked improvements in a variety of exercise parameters, as well as indices of quality of life. Furthermore, these effects persisted in the cohort re-evaluated after 15 weeks of training. These results are even more impressive when one considers that similar results were seen irrespective of the aetiology and functional severity of PH. The authors emphasise, however, that supervision and monitoring are important, since episodes of presyncope and syncope were observed, although no fatalities resulted. Taken together, these data provide guidance for instructing patients on the potential benefits and risks of intensive training.

Not all of the individual results of this study
as the sum of its parts, however. The impro
walk test reported by GRÜNIG *et al.* [3] are
observed in any clinical trial with medical th
even more dramatic when considering that n
already on combination therapy. However, t
is highly subject to a "learning effect", even
training regimen, and the 6-min walk res
trials have typically been much greater than
subsequent double-blind trials [4]. Further
50 m or more have been observed in placebo-treated subjects
in PH clinical trials [5]. In addition, reliably estimating resting pulmonary artery systolic pressure using Doppler echocardiography is dubious, at best, in patients with PH [6]; reliably estimating pressure during exercise should be considered more art than science at present. Similarly, assessing functional class can be quite subjective and susceptible to unblinding bias. Nevertheless, improvement in the more objective parameters, including maximal oxygen consumption, resting and maximal heart rate, are convincing and support benefit. That even those patients who failed to improve exercise capacity nevertheless improved their quality of life indices is strong evidence in support of a programme that incorporates physiotherapy and psychosocial support for PH, along with medical care.

GRÜNIG *et al.* [3] point out that this was not a randomised, blinded trial, which would be impossible to achieve with this therapy. It is also worth noting that this is a single centre experience, and duplication of these results from other centres is needed, not only to confirm them, but to demonstrate that this aggressive programme is feasible elsewhere as well, and therefore of potential relevance to many more patients. The expense and need for the 3-week in-hospital phase should also be reconsidered, since this is not feasible in many parts of the world. Additionally, the authors applied the "last observation carried forward (LOCF)" statistical method to analyse the results of patients who did not complete the full 15-week programme. However, the non-completers comprised a large percentage (40%) of the total population, and LOCF would give an overestimate of the "true" treatment effect if those who dropped out did so because of worsening for any cause [3]. Finally, as with medical therapy for PH, it will be important to evaluate the maintenance and durability of these effects over a

In this Olympic year we are enthralled by the gracefulness of trained athletes and reminded of the benefits of physical activity even for those of us who do not compete. GRÜNIG *et al.* [3] now provide evidence that one of the prescriptions that we write for our PH patients should be for physical activity and exercise. I can now look forward to the day when we will hol
a PH Special Olympics.

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IPERTENSIONE POLMONARE: DAL CATETERISMO ALLE NUOVE TERAPIE

Test da sforzo e riabilitazione cardio-respiratoria servono?

Dott.ssa Gaia Cattadori
UO Cardiologia Riabilitativa
H San Giuseppe – Multimedica - MI

IPERTENSIONE POLMONARE: DAL CATETERISMO ALLE NUOVE TERAPIE

Test da sforzo e riabilitazione cardio-respiratoria servono.

Dott.ssa Gaia Cattadori
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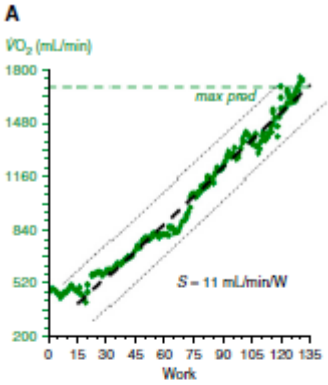
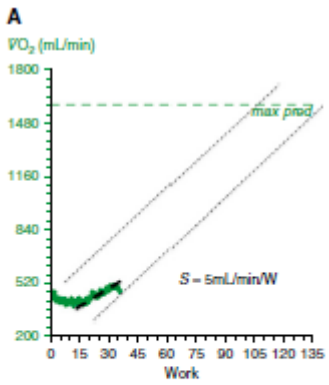
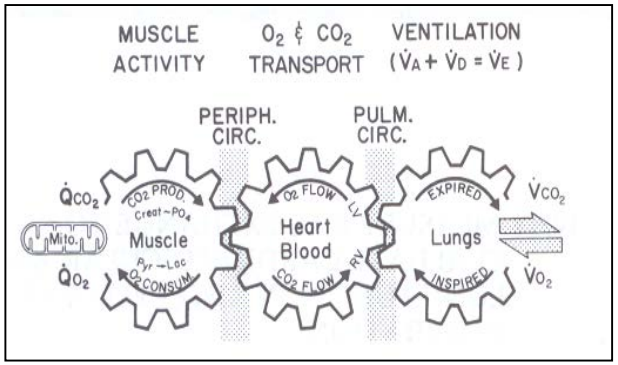
Test da sforzo cardiopolmonare: peakVO_2



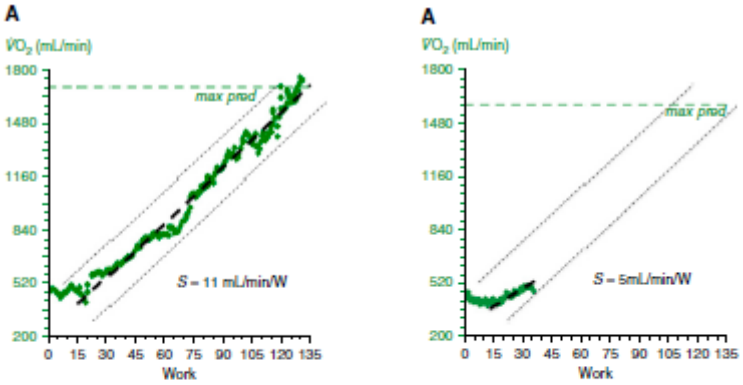


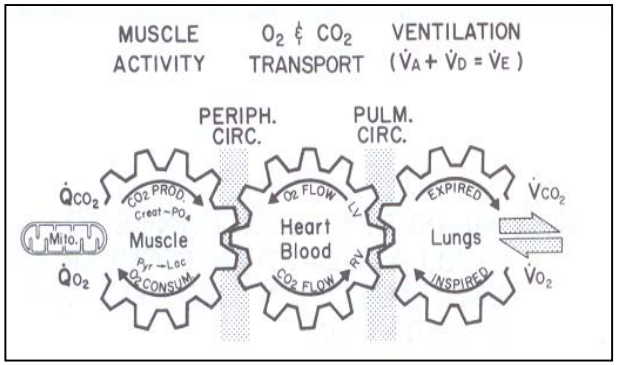


VO_2 = CO x $C(a–v)O_2$

Wasserman K et al. Principles of Exercise Testing and Interpretation

Test da sforzo cardiopolmonare: peakVO_2





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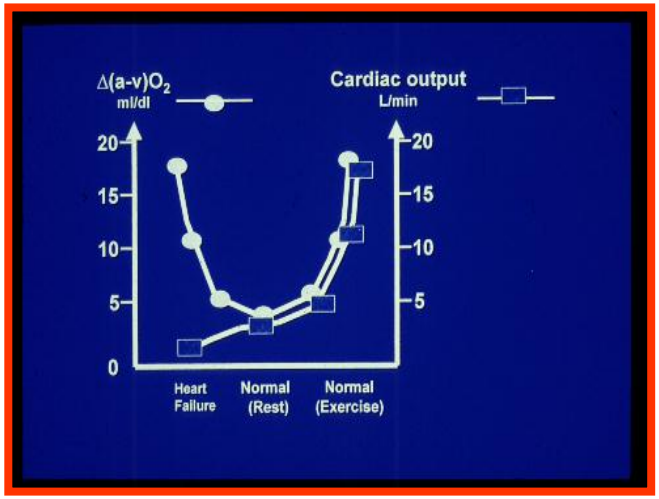

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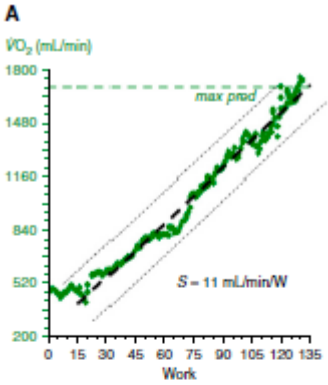
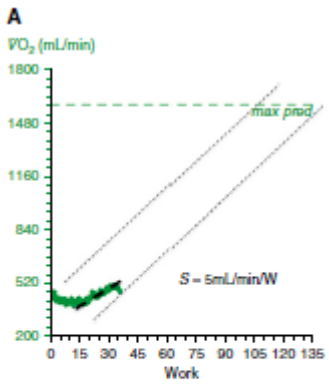
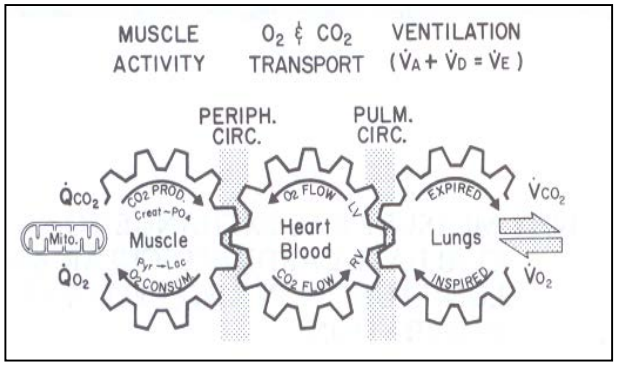
Wasserman K et al. Principles of Exercise Testing and Interpretation

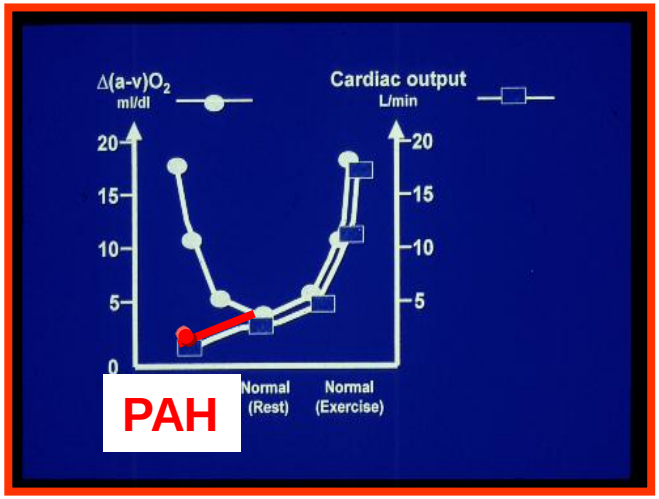
Test da sforzo cardiopolmonare: peakVO_2







VO_2 = CO x $C(a–v)O_2$



Wasserman K et al. Principles of Exercise Testing and Interpretation

Test da sforzo cardiopolmonare + misura CO

Noninvasive Cardiac Output Measurement by Inert Gas Rebreathing in Suspected Pulmonary Hypertension

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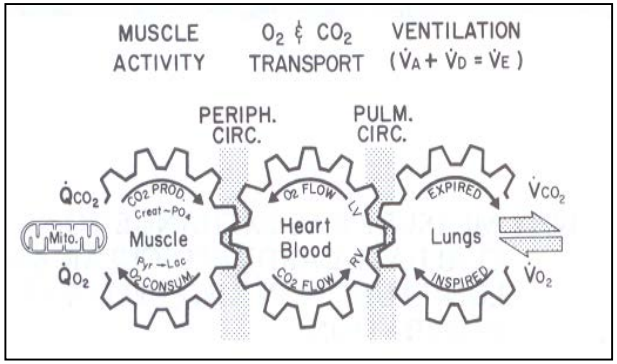
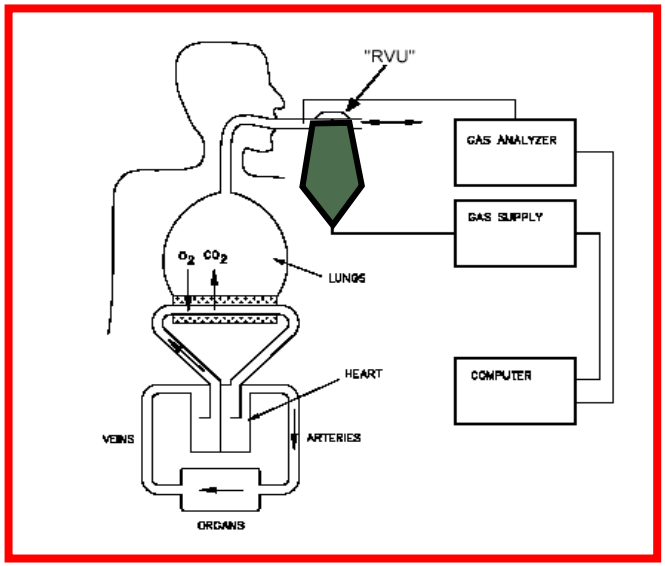
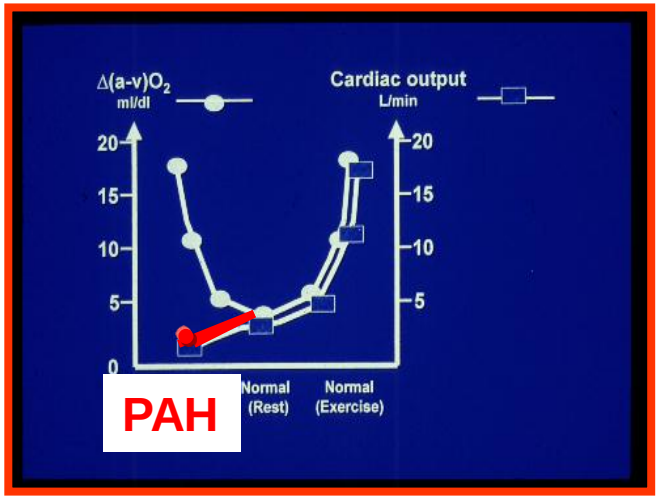
The objective of this study was to evaluate inert gas rebreathing (IGR) reliability in cardiac output (CO) measurement compared with Fick method and thermodilution. IGR is a noninvasive method for CO measurement; CO by IGR is calculated as pulmonary blood flow plus intrapulmonary shunt. IGR may be ideal for follow-up of patients with pulmonary hypertension (PH), sparing the need of repeated invasive right-sided cardiac catheterization. Right-sided cardiac catheterization with CO measurement by thermodilution, Fick method, and IGR was performed in 125 patients with possible PH by echocardiography. Patients were grouped according to right-sided cardiac catheterization–measured mean pulmonary and wedge pressures: normal pulmonary arterial pressure (n = 20, mean pulmonary arterial pressure = 18 ± 3 mm Hg, pulmonary capillary wedge pressure = 11 ± 5 mm Hg), PH and normal pulmonary capillary wedge pressure (PH-NW, n = 37 mean pulmonary arterial pressure = 42 ± 13 mm Hg, pulmonary capillary wedge pressure = 11 ± 6 mm Hg), and PH and high pulmonary capillary wedge pressure (PH-HW, n = 68, mean pulmonary arterial pressure = 37 ± 9 mm Hg, pulmonary capillary wedge pressure = 24 ± 6 mm Hg). Thermodilution and Fick measurements were comparable. Fick and IGR agreement was observed in normal pulmonary arterial pressure (CO = 4.10 ± 1.14 and 4.08 ± 0.97 L/min, respectively), whereas IGR overestimated Fick in patients with PH-NW and those with PH-HW because of intrapulmonary shunting overestimation in hypoxemic patients. When patients with arterial oxygen saturation (SO_2) ≤90% were excluded, IGR and Fick agreement improved in PH-NW (CO = 4.90 ± 1.70 and 4.76 ± 1.35 L/min, respectively) and PH-HW (CO = 4.05 ± 1.04 and 4.10 ± 1.17 L/min, respectively). In hypoxemic patients, we estimated pulmonary shunt as Fick − pulmonary blood flow and calculated shunt as: −0.2423 × arterial SO_2 + 21.373 L/min. In conclusion, IGR is reliable for CO measurement in patients with PH with arterial SO_2 >90%. For patients with arterial SO_2 ≤90%, a new formula for shunt calculation is proposed. (Am J Cardiol 2014;113:546–551)



$$VO_2 = CO \times C(a-v)O_2$$





Farina et al. Am J Cardiol 2014;113:546-551

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