Con il supporto
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ACTELION

MILANO

30 novembre
1 dicembre 2017

ACTION

Pneumologi in azione nell'ipertensione arteriosa polmonare (PAH)

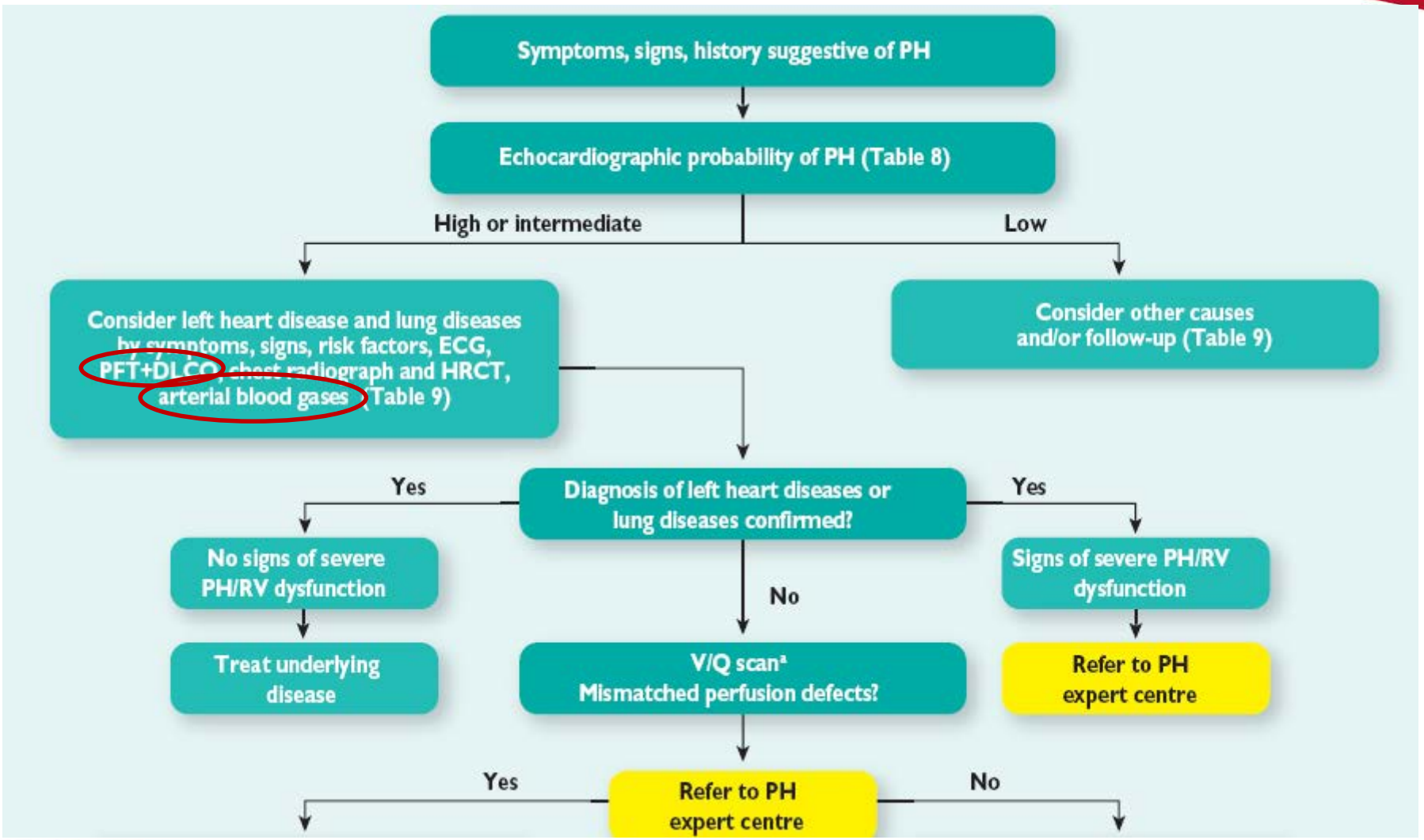
MILANO, Palazzo delle Stelline

ACTION

Pneumologi in azione
nell'ipertensione arteriosa polmonare (PAH)

Prove di funzionalità respiratoria: un aiuto alla diagnosi

Dr.ssa Maria Rosa Mirenda


Symptoms, signs, history suggestive of PH
Echocardiographic probability of PH (Table 8)
High or intermediate
Low
Consider left heart disease and lung diseases by symptoms, signs, risk factors, ECG, PFT+DLCO, chest radiograph and HRCT, arterial blood gases (Table 9)
Consider other causes and/or follow-up (Table 9)
Diagnosis of left heart diseases or lung diseases confirmed?
Yes
Yes
No
No signs of severe PH/RV dysfunction
Signs of severe PH/RV dysfunction
Treat underlying disease
V/Q scan[a] Mismatched perfusion defects?
Refer to PH expert centre
Yes
No
Refer to PH expert centre

2015 ESC/ERS

- ✓Spirometria semplice
- ✓Spirometria globale (pletismografia)
- ✓DLCO (singolo respiro)

Lung function in pulmonary hypertension

A.T. Low [a,*], A.R.L. Medford [b], A.B. Millar [c], R.M.R. Tulloh [a]

[a] University Hospitals Bristol NHS Foundation Trust, Upper Maudlin Street, Bristol, United Kingdom
[b] North Bristol Lung Centre, Southmead Hospital, Southmead Road, Bristol, United Kingdom
[c] Academic Respiratory Unit, Southmead Hospital, Southmead Road, Bristol, United Kingdom

Age: 50 Height(cm): 164 Weight(kg): 55.0 Gender: Femm. RaceCaucasica

		Ref	Pre Meas	Pre % Ref	Post Meas	Post % Ref	Post % Chg
Spirometry							
VC	Litri	3.06	2.67	87			
FVC	Litri	3.08	2.67	87			
FEV1	Litri	2.63	2.16	82			
FEV1/FVC	%	80	81				
FEV1/SVC	%		81				
PEF	L/sec	6.41	5.57	87			
FEF25-75%	L/sec	3.27	2.16	66			
FEF25%	L/sec	5.63	5.52	98			
FEF50%	L/sec	3.93	3.66	93			
FEF75%	L/sec	1.58	0.83	53			
Lung Volumes							
TLC	Litri	5.03	4.34	86			
RV	Litri	1.77	1.68	95			
RV/TLC	%	36	39				
FRC PL	Litri	2.72	3.07	113			
FRC N2	Litri	2.72					
Raw	cmH2O/L/sec	<2.24	2.14				
sRaw	cmH2O/L/s/L		7.19				
Diffusion							
DLCO	mL/mmHg/min	24.6	11.3	46			
DL Adj	mL/mmHg/min	24.6	11.3	46			
DLCO/VA	mL/mHg/min/L	4.88	2.88	59			
DL/VA Adj	mL/mHg/min/L	4.88	2.88	59			
VA	Litri	5.03	3.91	78			

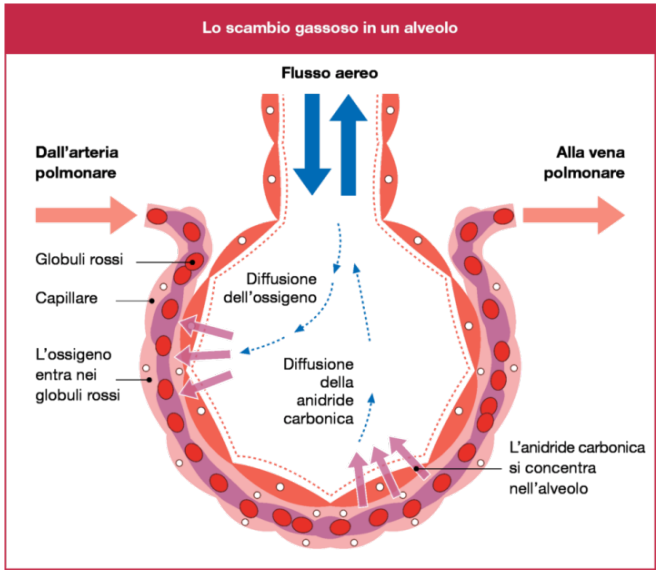
Flusso

Respiratory Medicine, 2015

Il ruolo della DLCO

- ✓ **Consente di valutare la capacità di diffusione dei gas O2 e CO2 attraverso la membrana alveolo-capillare. Il test di diffusione valuta l'integrità di tale membrana.**

- ✓ **Si sfrutta monossido di carbonio, gas che ha un'elevata affinità per l'emoglobina e il cui trasferimento è limitato quindi unicamente dalla diffusione**



- ✓ **Il test di diffusione del monossido di carbonio viene effettuato facendo inalare al soggetto una miscela con CO a bassissime concentrazioni (0.3%) ed elio (He) ad una concentrazione del 10% mediante respiro singolo.**

SERIES "ATS/ERS TASK FORCE: STANDARDISATION OF LUNG FUNCTION TESTING"

Interpretative strategies for lung function tests

R. Pellegrino, G. Viegi, V. Brusasco, R.O. Crapo, F. Burgos, R. Casaburi, A. Coates, C.P.M. van der Grinten, P. Gustafsson, J. Hankinson, R. Jensen, D.C. Johnson, N. MacIntyre, R. McKay, M.R. Miller, D. Navajas, O.F. Pedersen and J. Wanger

Alterazione	DLCO (% del teorico)
lieve	< 80% e ≥ 60%
media	< 60% e ≥ 40%
elevata	< 40%

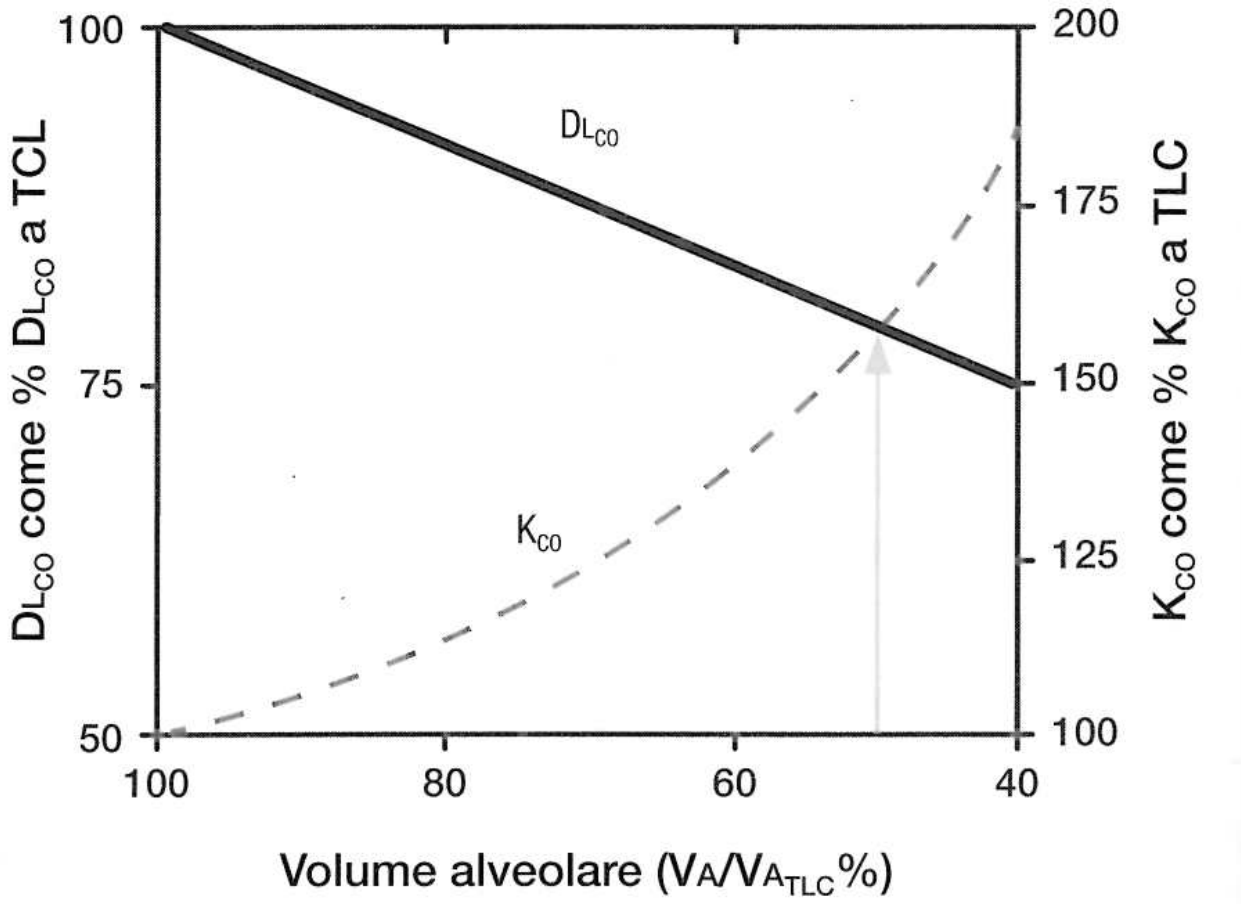
75% dei pazienti con PAH ha una DLCO < 80%

DLCO 59-71%

ATS/ERS, 2005

Respiratory Medicine, 2015

DLCO= Kco x VA ml/min/mmHg



~~DLCO/VA~~

Loss of alveolar membrane diffusing capacity and pulmonary capillary blood volume in pulmonary arterial hypertension

Samar Farha[1*], Daniel Laskowski[1,2], Deepa George[2], Margaret M Park[2,3], WH Wilson Tang[3], Raed A Dweik[1,2] and Serpil C Erzurum[1,2]

Equazione di Roughton e Forster:

$1/DL = 1/Dm + 1/\theta xVc$

DL = DLCO
Dm= capacità di diffusione di membrana
Vc = volume capillare
Θ = reazione del CO con il sangue (corretta per la concentrazione emoglobinica)

Respiratory Research 2013

Variable	Healthy N = 41	PAH N = 28	p-value
Age (years)	34 ±2	45 ±2	<0.01
Gender (M/F)	17/24	6/22	0.09
Smoking history (never/current/ ex smoker)	40/0/1	24/1/3	0.1
Height (cm)	169 ±1	167 ±3	0.3
Weight (kg)	79 ±3	89 ±7	0.2
O_2 Saturation (% of Hgb)	98 ±0.2	96 ±0.4	<0.01
FE_{NO} (ppb)	19 ±2	18 ±2	0.7
FVC (%)	98 ±2	91 ±3	0.2
FEV_1 (%)	93 ±2	80 ±4	<0.01
FEV_1/FVC	81 ±1	75 ±1	<0.01
TLC (%)	85 ±2	82 ±2	0.4
V_A (L)	4.9 ±0.2	4.3 ±0.2	0.1
DL_{CO} (ml/min/mmHg)	24 ±1	17 ±1	<0.01
DL_{NO} (ml/min/mmHg)	94 ±4	66 ±5	<0.01
D_m (ml/min/mmHg)	48 ±2	33 ±2	<0.01
V_c (ml)	78 ±4	63 ±5	<0.01
D_m/V_c (1/min/mmHg)	0.6 ±0.02	0.6 ±0.04	0.8
Hgb (g/dl)	13.3 ±0.3	13.5 ±0.4	0.9

↓ Dm

- ✓ **ispessimento della membrana alveolocapillare per processi fibrotici e proliferativi**
- ✓ **edema interstiziale**

↓ Vc

- ✓ **↑ resistenze vascolari**
- ✓ **↓ output cardiaco**
- ✓ **trombosi locale**

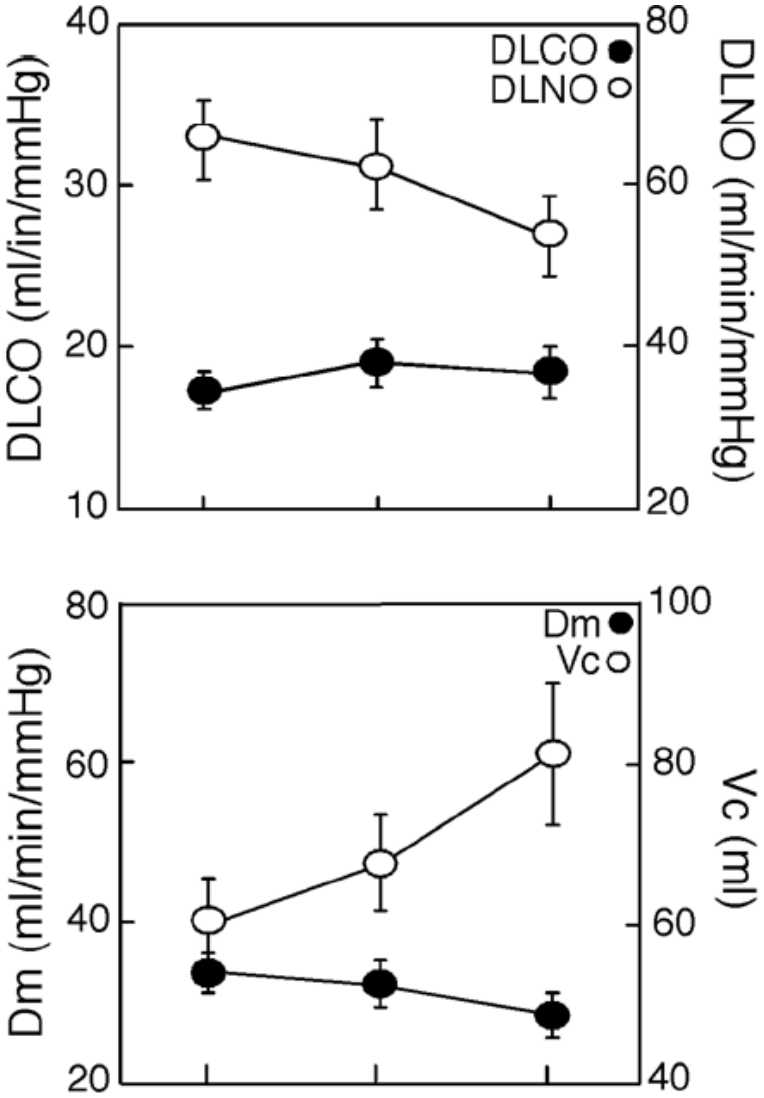


Table 3 Changes over time in the PAH group

Variable	Estimated unit/year change	Wilcoxon SR p-value
FEV_1 (ml)	−144	0.1
FEV_1 (%)	−3	0.12
FVC (ml)	−190	0.2
FVC (%)	−5	0.2
FEV_1/FVC	0.8	0.4
V_A (ml)	20	0.4
FE_{NO} (ppb)	0.5	0.4
TLC (%)	0.7	0.5
DL_{CO} (ml/min/mmHg)	−1.2	0.7
DL_{NO} (ml/min/mmHg)	−24	0.01
D_m (ml/min/mmHg)	−12	0.01
V_c (ml)	11	0.07
D_m/V_c (1/min/mmHg)	−0.4	0.04
Hgb (g/dl)	0.05	0.6

Severely reduced diffusion capacity in idiopathic pulmonary arterial hypertension: patient characteristics and treatment responses

Pia Trip[1], Esther J. Nossent[1], Frances S. de Man[1,2], Inge A.H. van den Berk[3], Anco Boonstra[1], Herman Groepenhoff[1], Edward M. Leter[4], Nico Westerhof[1,2], Katrien Grünberg[5], Harm-Jan Bogaard[1] and Anton Vonk-Noordegraaf[1]

	D_{LCO} <45% pred	D_{LCO} ⩾45% pred	p-value
Survival years			0.002¶
1	87	95	
3	54	86	
5	38	80	

Eur Respir J, 2013

Demographics	D_{LCO} <45% pred	D_{LCO} ⩾45% pred	p-value
Patients n	48	118	
Age at diagnosis years	67 (53–75)	46 (35–60)	<0.001
Sex male	24 (50)	22 (19)	0.013
Body mass index kg·m^{-2}	26±4	27±6	0.035
Smoking	33 (77)	54 (48)	0.033
Current smoker	8 (19)	20 (18)	0.765
Former smoker	25 (58)	34 (30)	0.065
Pack years	25 (0–40)	0 (0–13)	0.009
Medical history			
Coronary disease	13 (27)	1 (1)	0.008
Hypertension	14 (29)	26 (22)	0.207
Diabetes mellitus	12 (25)	11 (9)	0.513
Thyroid disease	4 (8)	12 (10)	0.701
Pulmonary disease			
COPD (GOLD I-II)	5 (10)	6 (5)	0.845

TABLE 2 Computed tomography findings in patients according to the diffusing capacity of the lung for carbon monoxide (D_{LCO})

Presence of fibrosis	Presence of emphysema					
	D_{LCO} <45% pred#			D_{LCO} ⩾45% pred¶		
	None	Mild	Moderate	None	Mild	Moderate
None	14 (32)	9 (21)	8 (18)	64 (67)	24 (25)	4 (4)
Mild	3 (7)	4 (9)	4 (9)	1 (1)	1 (1)	1 (1)
Moderate	0 (0)	2 (5)	0 (0)	1 (1)	0 (0)	0 (0)
WHO functional class					0.050#	
I		0 (0)		6 (6)		
II		9 (21)		32 (29)		
III		27 (61)		61 (56)		
IV		8 (18)		10 (9)		
Pulmonary function						
FEV1 % pred		85±16		91±16	0.010¶	
FVC % pred		99±16		102±17	0.206¶	
FEV1/FVC %		68±9		74±9	<0.001¶	
TLC % pred		92±16		99±12	0.004¶	
VA % pred		78±14		85±11	0.001¶	

Eur Respir J, 2013

Lung function in pulmonary hypertension

A.T. Low [a,*], A.R.L. Medford [b], A.B. Millar [c], R.M.R. Tulloh [a]

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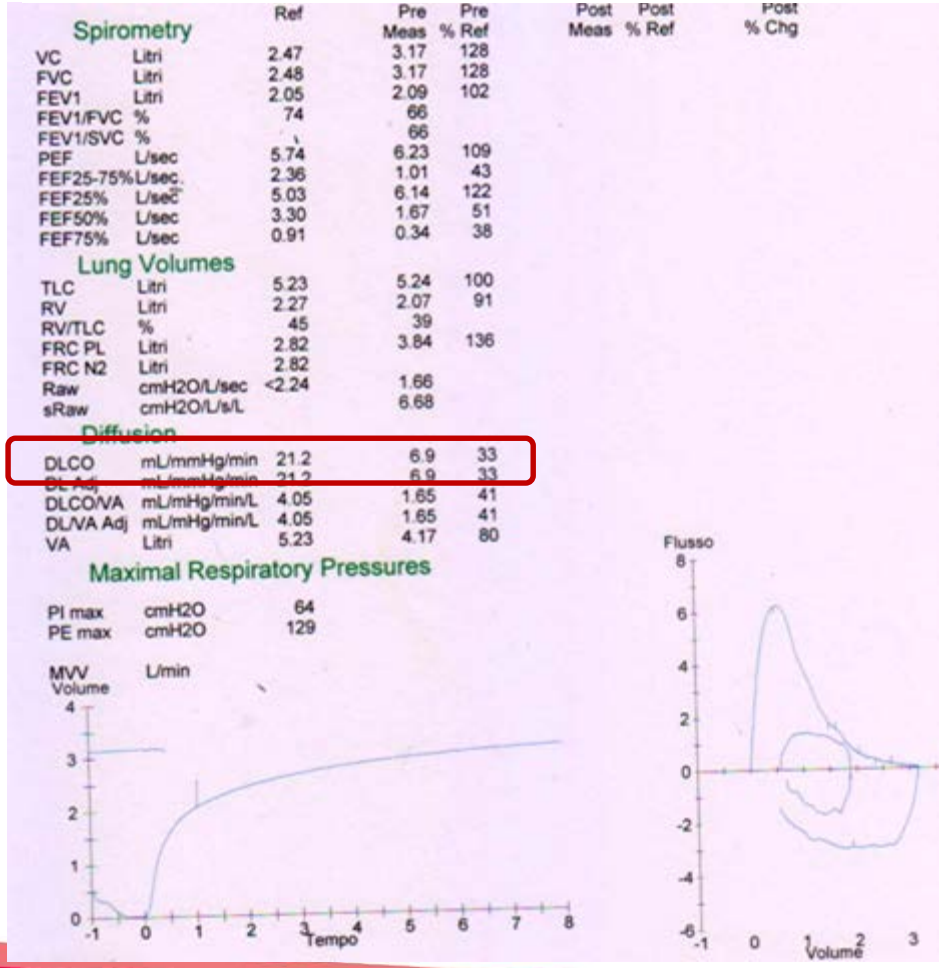


Spirometry		Ref	Pre Meas	Pre % Ref	Post Meas	Post % Ref	Post % Chg
VC	Litri	2.47	3.17	128			
FVC	Litri	2.48	3.17	128			
FEV1	Litri	2.05	2.09	102			
FEV1/FVC	%	74	66				
FEV1/SVC	%		66				
PEF	L/sec	5.74	6.23	109			
FEF25-75%	L/sec	2.36	1.01	43			
FEF25%	L/sec	5.03	6.14	122			
FEF50%	L/sec	3.30	1.67	51			
FEF75%	L/sec	0.91	0.34	38			
Lung Volumes							
TLC	Litri	5.23	5.24	100			
RV	Litri	2.27	2.07	91			
RV/TLC	%	45	39				
FRC PL	Litri	2.82	3.84	136			
FRC N2	Litri	2.82					
Raw	cmH2O/L/sec	<2.24	1.66				
sRaw	cmH2O/L/s/L		6.68				
Diffusion							
DLCO	mL/mmHg/min	21.2	6.9	33			
DL Adj	mL/mmHg/min	21.2	6.9	33			
DLCO/VA	mL/mHg/min/L	4.05	1.65	41			
DL/VA Adj	mL/mHg/min/L	4.05	1.65	41			
VA	Litri	5.23	4.17	80			
Maximal Respiratory Pressures							
PI max	cmH2O	64					
PE max	cmH2O	129					
MVV	L/min						

20-50% dei pazienti
Deficit restrittivo
↓TLC fino al 64%

20-40% deficit ostruttivo
FEV1/FVC < 70%
76% vs 84% p < 0.001

Respiratory Medicine, 2015

Scambi gassosi nella IPAH

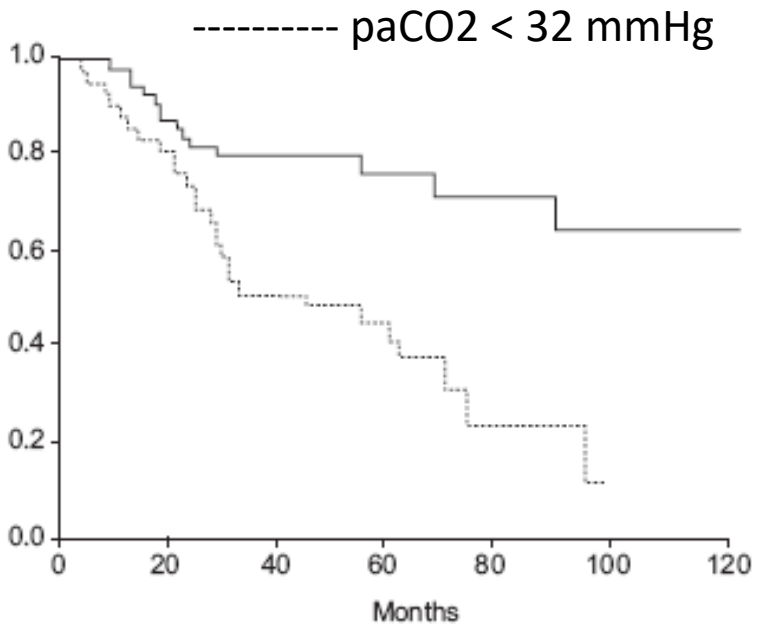
Ipossiemia lieve moderata	**paO2 72 ± 13 mmHg nelle donne**
	paO2 70 ± 13 mmHg negli uomini
Ipocapnia lieve moderata	**paCO2 31 ± 5 mmHg nelle donne**
	paCO2 30 ± 6 mmHg negli uomini

Hoeper, Eur Respir J, 2007

Prognostic value of blood gas analyses in patients with idiopathic pulmonary arterial hypertension

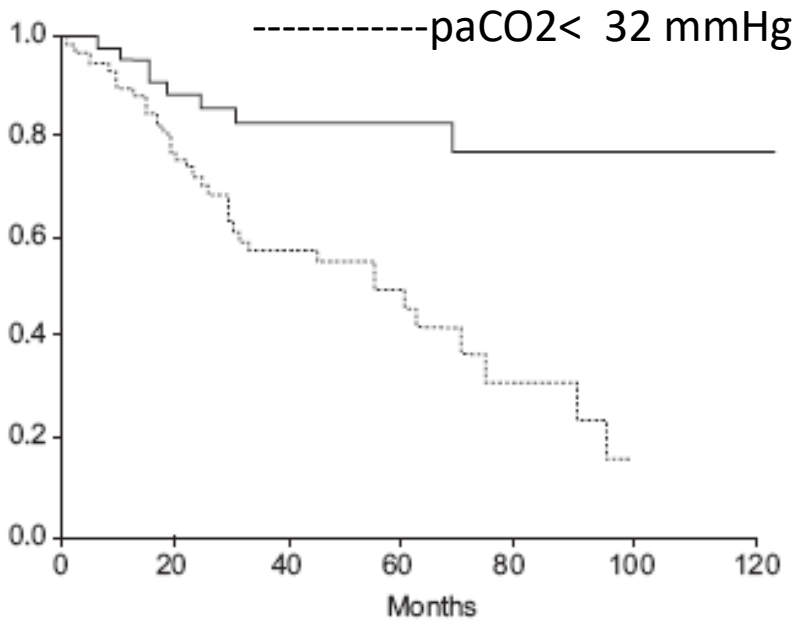
M.M. Hoeper, M.W. Pletz, H. Golpon and T. Welte

	paCO2 ≥ 32	paCO2 < 32 (p<0,001)
1 anno	98	86
2 anni	82	69
3 anni	80	51
5 anni	77	41
8 anni	65	12



Eur Respir J, 2007

	paCO2 ≥ 32	paCO2 < 32 (p<0,001)
1 anno	95	88
2 anni	86	70
3 anni	83	57
5 anni	83	46
8 anni	78	15



Hoeper, Eur Respir J 2007

TABLE 2 Correlations between blood gases at rest, haemodynamics and 6-min walking distance (6MWD)

	6MWD	RAP	mPAP	Cardiac index	PVR	S_{v,O_2}
P_{a,O_2}						
r	0.298	-0.269	0.108	0.008	0.161	0.227
p-value	0.001	0.007	NS	NS	NS	0.026
P_{a,CO_2}						
r	0.104	-0.054	-0.049	0.235	-0.185	0.226
p-value	NS	NS	NS	0.019	NS	0.026

Hoeper, Eur Respir J 2007

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 (Table 6)
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

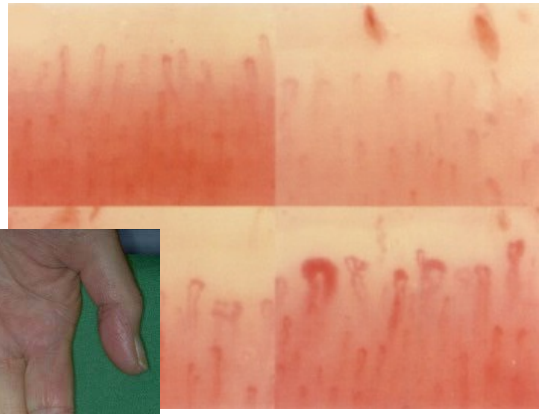
ATS/ERS, 2015

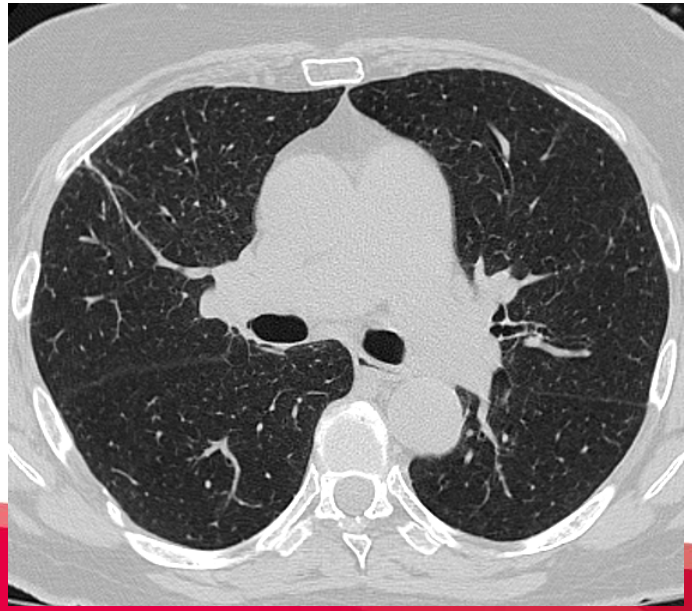
Sclerodermia

↓ DLCO

✓Secondaria all' interessamento isolato della componente vascolare

→ Volumi nella norma





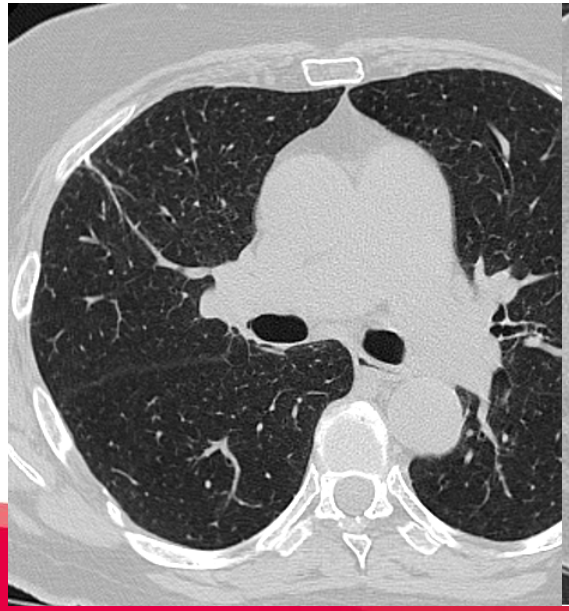
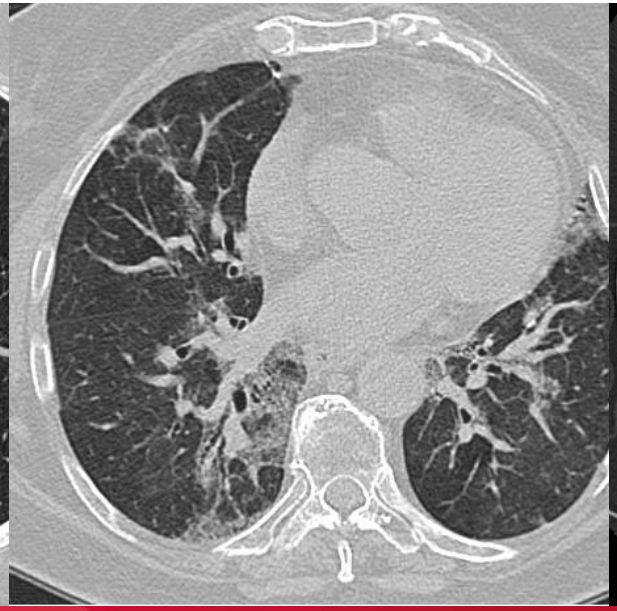
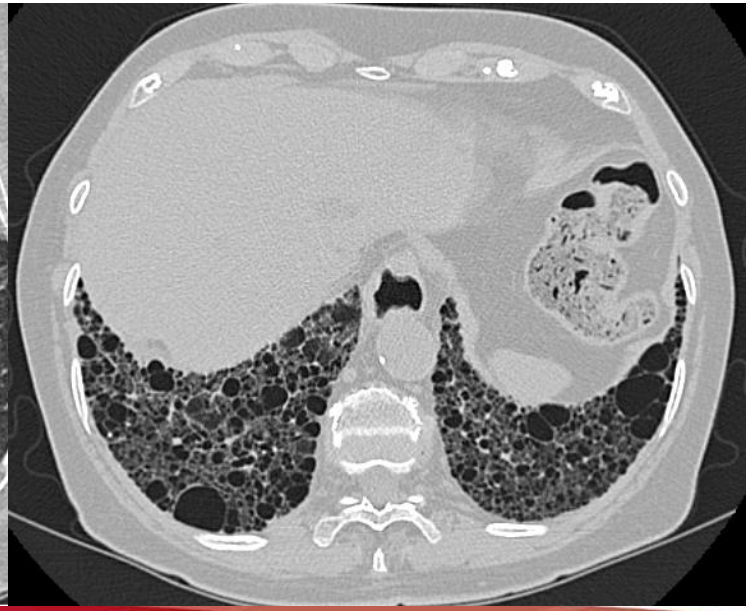
Test immunosierologici

Sclerodermia

↓ DLCO

✓Secondaria all' interessamento isolato della componente vascolare → Volumi nella norma

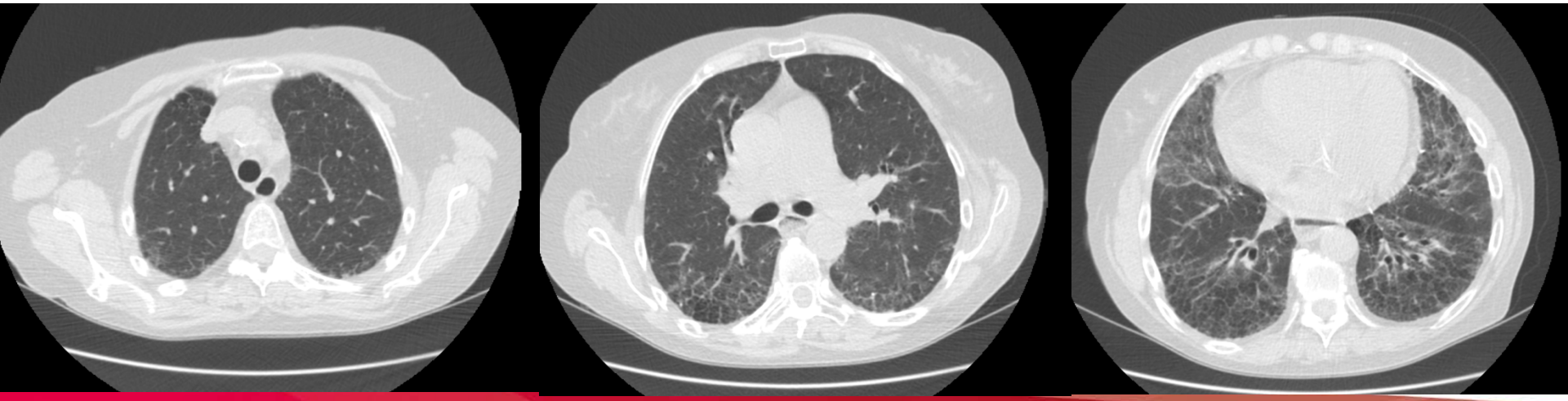
✓secondaria all'interessamento parenchimale → Volumi nella norma
Sindrome restrittiva

Age: 58 Height(cm): 157 Weight(kg): 58.5 Gender: Femm. RaceCaucasica Birth Date 13/03/1956

		Ref	Pre Meas	Pre % Ref	Post Meas	Post % Ref	Post % Chg
Spirometry							
VC	Litri	2.53	2.29	91			
FVC	Litri	2.56	2.13	83			
FEV1	Litri	2.15	1.71	80			
FEV1/FVC	%	78	81				
FEV1/SVC	%		75				
PEF	L/sec	5.78	4.93	85			
FEF25-75%	L/sec	2.91	1.94	67			
FEF25%	L/sec	5.21	4.91	94			
FEF50%	L/sec	3.56	4.20	118			
FEF75%	L/sec	1.31	0.54	42			
Lung Volumes							
TLC	Litri	4.57	3.31	73			
RV	Litri	1.77	1.02	58			
RV/TLC	%	39	31				
FRC PL	Litri	2.57	1.60	62			
FRC N2	Litri	2.57					
Raw	cmH2O/L/sec	<2.24	1.31				
sRaw	cmH2O/L/s/L		2.96				
Diffusion							
DLCO	mL/mmHg/min	21.7	5.6	26			
DL Adj	mL/mmHg/min	21.7	5.6	26			
DLCO/VA	mL/mHg/min/L	4.75	2.05	43			
DL/VA Adj	mL/mHg/min/L	4.75	2.05	43			
VA	Litri	4.57	2.72	60			

Flusso



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

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  - 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 (Web Table III)

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

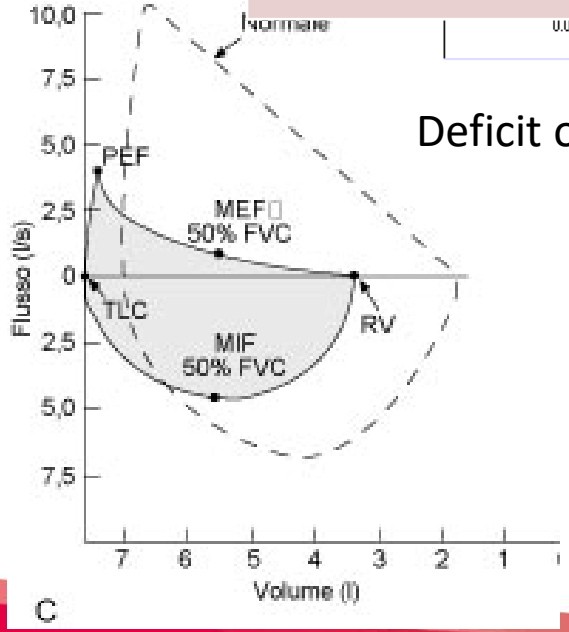
- 5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders, sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: pulmonary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

Kco ridotto /VA normale		Kco ridotto/ VA ridotta	
Meccanismi fisiopatogenetici	**Condizioni cliniche**	**Meccanismi fisiopatologici**	**Condizioni cliniche**
Distruzione del microcircolo	**Ipertensione polmonare idiopatica**	**Distruzione alveolare**	**Enfisema (ridotto volume alveolare accessibile)**
	vasculiti	**Distruzione alveolare**	**Malattia interstiziale diffusa del polmone con fibrosi**
Rimodellamento e dilatazione del microcircolo	Sindrome epatopolmonare	Distruzione del microcircolo	Bronchiolite obliterante
	MAV		Grave SCC

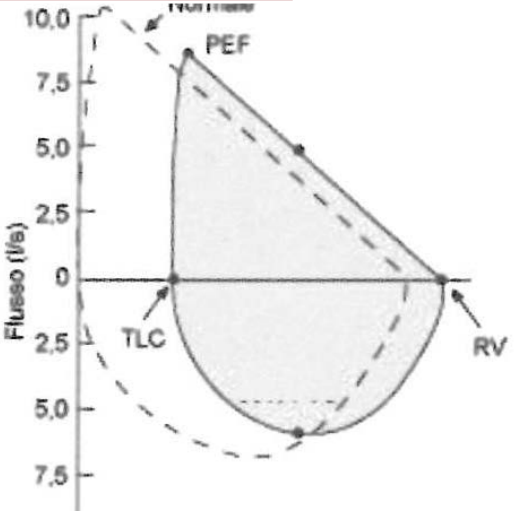
DLCO = Kco x VA

	Rif	Migl.	% Rif	1
DLCO	20.6	15.7	76	15.7
DL Adj	20.6	15.7	76	15.7
DLCO/VA	5.99	3.28	55	3.28
VA		4.78		4.78
DL/VA Adj		3.28		3.28

Severità	FEV1 % del predetto
Lieve	>70
Moderata	60-69
Moderata-severa	50-59
Severa	35-49
Molto severa	<35



Deficit ostruttivo



Deficit restrittivo

ATS/ERS 2005

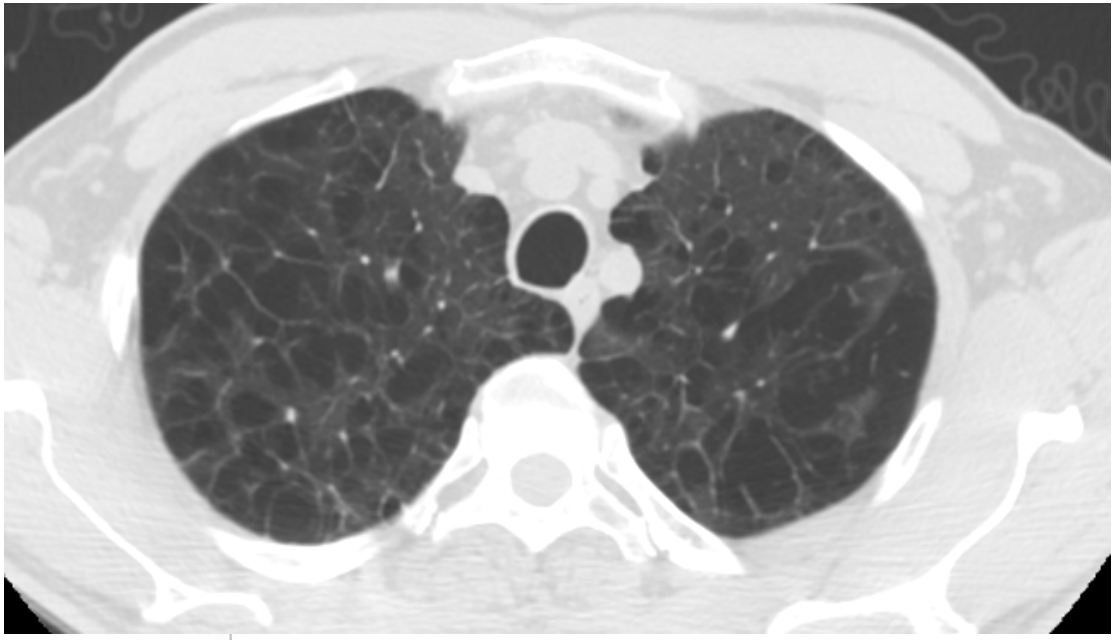
Age: 66 Height(cm): 165 Weight(kg): 85.0 Gender: Femm. RaceCaucasica Birth Date 27/06/1949

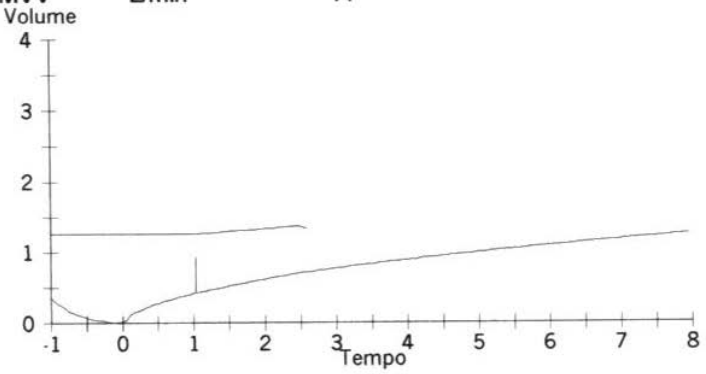
Spirometry		Ref	Pre Meas	Pre % Ref	Post Meas	Post % Ref	Post % Chg
VC	Litri	2.69	1.58	59			
FVC	Litri	2.70	1.56	58			
FEV1	Litri	2.27	1.22	54			
FEV1/FVC	%	77	78				
FEV1/SVC	%		77				
PEF	L/sec	5.98	5.84	98			
FEF25-75%	L/sec	2.74	1.43	52			
FEF25%	L/sec	5.26	4.07	77			
FEF50%	L/sec	3.55	5.23	147			
FEF75%	L/sec	1.19	0.46	38			
Lung Volumes							
TLC	Litri	5.10	2.88	57			
RV	Litri	2.04	1.30	64			
RV/TLC	%	41	45				
FRC PL	Litri	2.76	1.55	56			
FRC N2	Litri	2.76					
Raw	cmH2O/L/sec	<2.24	3.35				
sRaw	cmH2O/L/s/L		6.72				
Diffusion							
DLCO	mL/mmHg/min	22.5	5.8	26			
DL Adj	mL/mmHg/min	22.5	5.8	26			
DLCO/VA	mL/mHg/min/L	4.41	3.28	74			
DLVA Adj	mL/mHg/min/L	4.41	3.28	74			

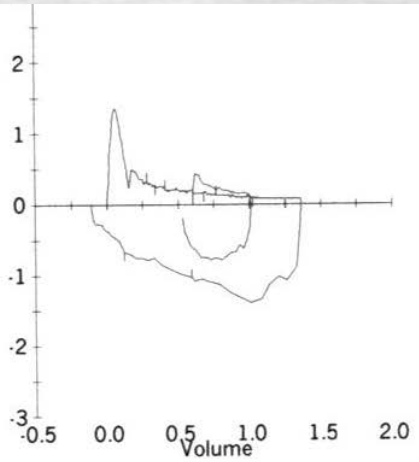
IPF

Age: 73 Height(cm): 163 Weight(kg): 43.0 Gender: Masch. Race: Caucasica Hb:

Spirometry		Ref	Pre Meas	Pre % Ref	Post Meas	Post % Ref	Post % Chg
VC	Liters	3.25	1.47	45			
FVC	Liters	3.15	1.36	43			
FEV1	Liters	2.40	0.42	18			
FEV1/FVC	%	74	31				
FEV1/SVC	%	82	29				
PEF	L/sec	7.02	1.67	24			
FEF25-75%	L/sec	2.72	0.15	6			
FEF25%	L/sec	6.31	0.27	4			
FEF50%	L/sec	3.56	0.17	5			
FEF75%	L/sec	1.02	0.09	9			
Lung Volumes							
TLC	Liters	5.94	7.61	128			
RV	Liters	2.51	6.14	244			
RV/TLC	%	42	81				
FRC PL	Liters	3.38	6.87	203			
Raw	cmH2O/L/sec	<2.24	13.49				
sRaw	cmH2O/L/s/L		87.29				
Diffusion							
DLCO	mL/mmHg/min	21.7	3.2	15			
DL Adj	mL/mmHg/min	21.7	3.2	15			
DLCO/VA	mL/mHg/min/L	3.65	1.65	45			
DL/VA Adj	mL/mHg/min/L	3.65	1.65	45			
VA	Liters	5.94	1.95	33			
Maximal Respiratory Pressures							
PI max	cmH2O	103					
PE max	cmH2O	193					
MVV	L/min	77					







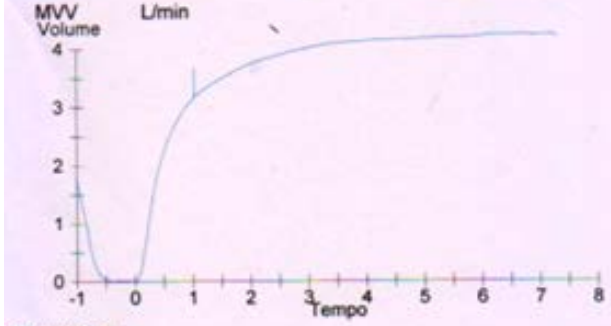
Comments:

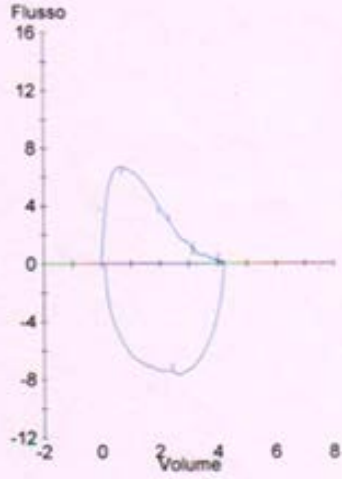
Pseudormalizzazione spirometrica

Spirometry		Ref	Pre Meas	Pre % Ref	Post Meas	Post % Ref	Post % Chg
VC	Litri	3.73	4.31	115			
FVC	Litri	3.61	4.31	119			
FEV1	Litri	2.76	3.19	116			
FEV1/FVC	%	74	74				
FEV1/SVC	%		74				
PEF	L/sec	7.53	8.00	106			
FEF25-75%	L/sec	2.95	2.63	89			
FEF25%	L/sec	6.75	6.49	96			
FEF50%	L/sec	3.89	3.75	96			
FEF75%	L/sec	1.25	1.00	80			
Lung Volumes							
TLC	Litri	6.50	5.82	90			
RV	Litri	2.56	1.51	59			
RV/TLC	%	42	26				
FRC PL	Litri	3.53	3.25	92			
FRC N2	Litri	3.53					
Raw	cmH2O/L/sec	<2.24	1.04				
sRaw	cmH2O/L/s/L		4.46				
Diffusion							
DLCO	mL/mmHg/min	24.4	5.9	24			
DL Adj	mL/mmHg/min	24.4	5.9	24			
DLCO/VA	mL/mHg/min/L	3.76	1.05	28			
DL/VA Adj	mL/mHg/min/L	3.76	1.05	28			
VA	Litri	6.50	5.62	86			

Maximal Respiratory Pressures

PI max	cmH2O	104
PE max	cmH2O	195
MVV	L/min	

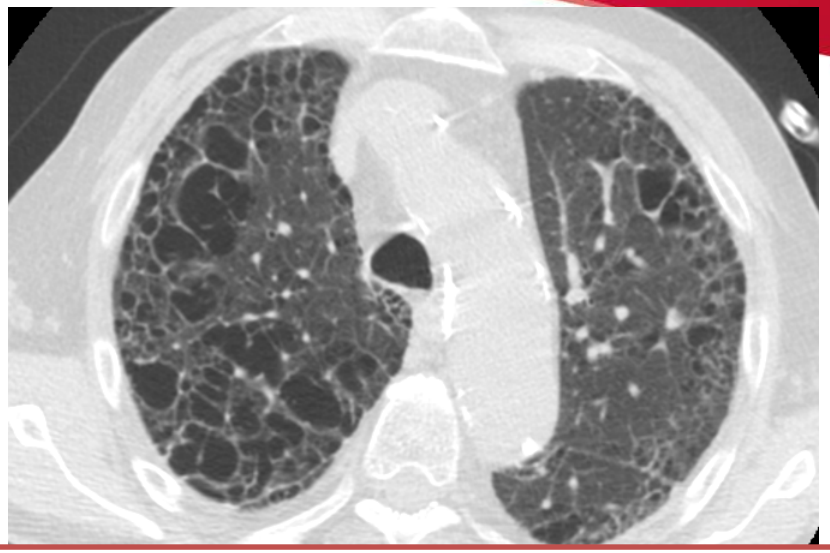




Comments:

Volumi statici e dinamici nella norma
Severa riduzione della DLCO

CEPF



Necessità di interpretare le prove funzionali alla luce delle immagini TC

Test da sforzo: severità e prognosi 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]
It is recommended to evaluate the severity of PAH patients with a panel of data derived from clinical assessment, exercise tests, biochemical markers and echocardiographic and haemodynamic evaluations (*Tables 13* and *14*)	I	C	96,97, 99
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
Achievement/maintenance of an intermediate-risk profile (*Table 13*) should be considered an inadequate treatment response for most patients with PAH	IIa	C	96–99

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: severità e follow up 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]
It is recommended to evaluate the severity of PAH patients with a panel of data derived from clinical assessment, exercise tests, biochemical markers and echocardiographic and haemodynamic evaluations (*Tables 13* and *14*)	I	C	96,97, 99
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
Achievement/maintenance of an intermediate-risk profile (*Table 13*) should be considered an inadequate treatment response for most patients with PAH	IIa	C	96–99

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]

6MWT

- Semplice, poco costoso, accettato da autorità regolatorie (sintomi e capacità funzionale)
- Primo end-point utilizzato in primo trial su terapia PAH-specifica (epoprostenolo)
- End-point primario più usato (bosentan, ambrisentan, sildenafil, tadalafil, treprostinil….)
- Dati basali associati a prognosi

6MWT e prognosi in PAH

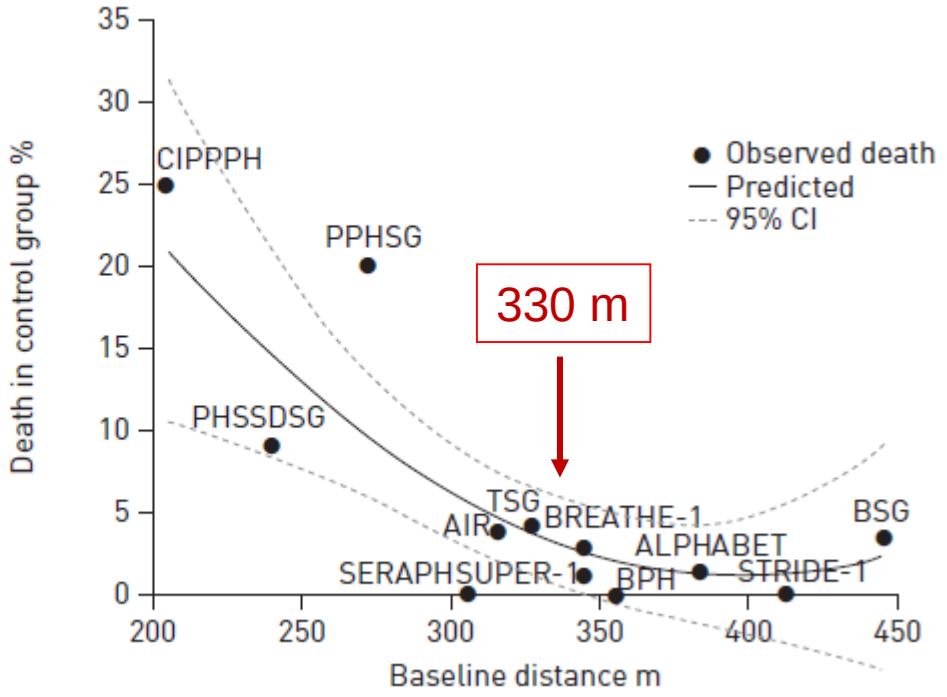


FIGURE 1 Relationship between the mean 6-min walk distance at baseline and the rate of fatal events during follow-up. Reproduced from [24] with permission from the publisher.

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

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%

Predicting Survival in Pulmonary Arterial Hypertension

Insights From the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL)

Raymond L. Benza, MD; Dave P. Miller, MS; Mardi Gomberg-Maitland, MD, MSc; Robert P. Frantz, MD; Aimee J. Foreman, MA; Christopher S. Coffey, PhD; Adaani Frost, MD; Robyn J. Barst, MD; David B. Badesch, MD; C. Gregory Elliott, MD; Theodore G. Liou, MD; Michael D. McGoon, MD

McLaughlin al. JACC 2015; 65: 1976-97

The need to move from 6-minute walk distance to outcome trials in pulmonary arterial hypertension

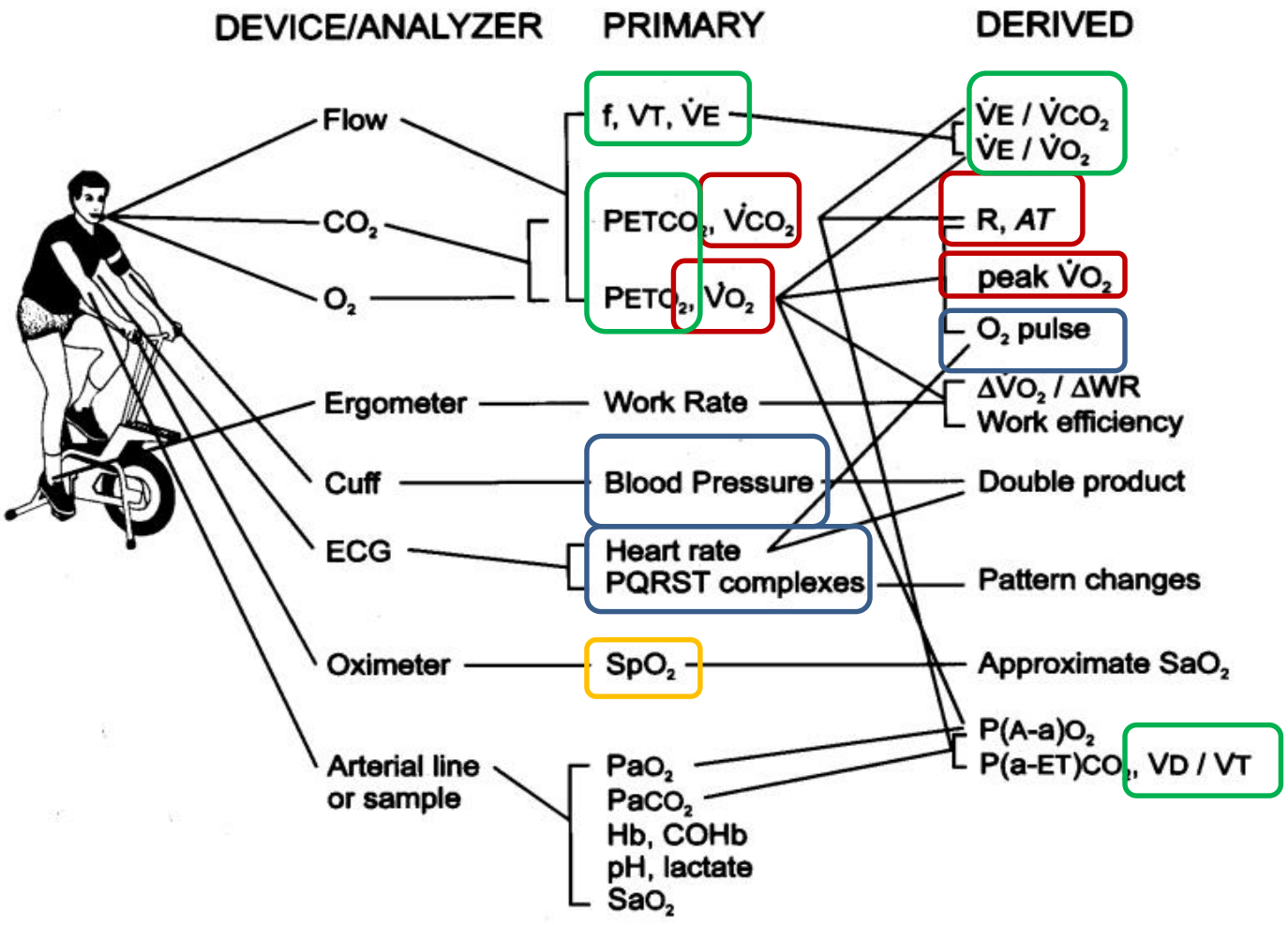
Sean Gaine[1] and Gérald Simonneau[2]

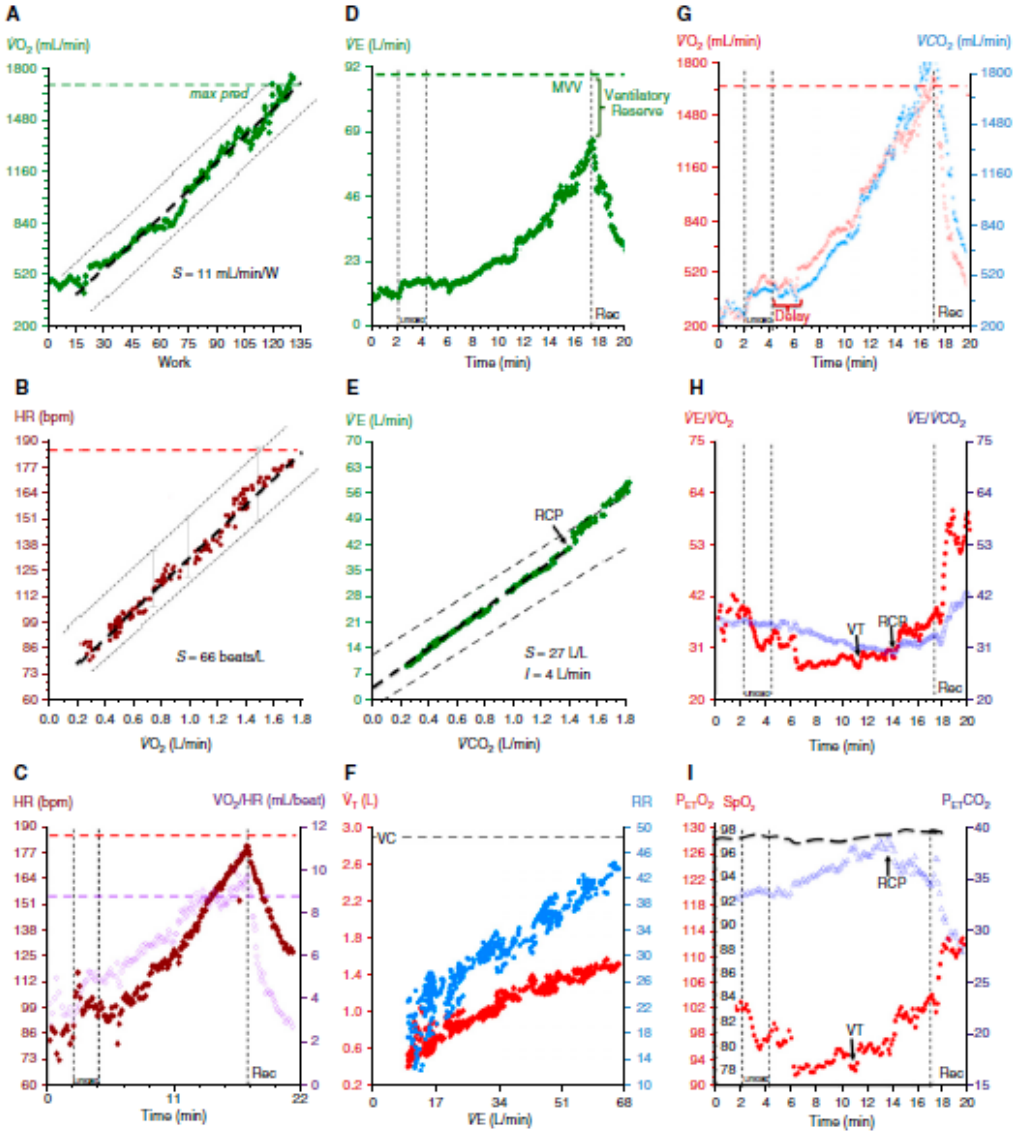
- **«ceiling effect»**
- **Poco specifico (frailty, decondizionamento,…)**
- **Poco utile in «add-on» terapia**
- ***Nessuna informazione sulla fisiopatologia***

CPET

PARAMETRI:

- **metabolici**
- **cardiaci**
- **respiratori**



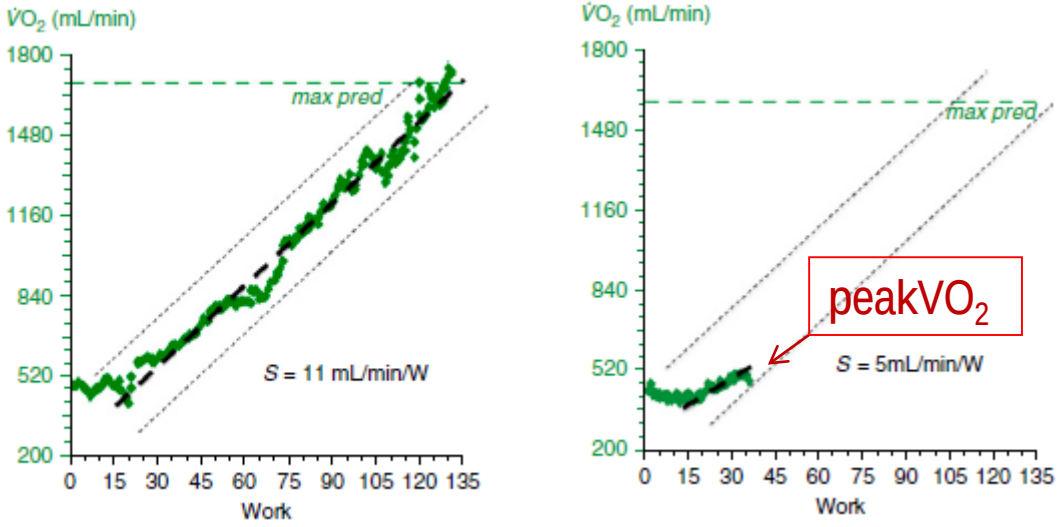

A
V̇O2 (mL/min)
max pred
S = 11 mL/min/W
Work
D
V̇E (L/min)
MVV
Ventilatory Reserve
Rec
Time (min)
G
V̇O2 (mL/min)
V̇CO2 (mL/min)
Delay
Rec
Time (min)
B
HR (bpm)
S = 66 beats/L
V̇O2 (L/min)
E
V̇E (L/min)
RCP
S = 27 L/L
I = 4 L/min
V̇CO2 (L/min)
H
V̇E/V̇O2
V̇E/V̇CO2
VT
RCP
Rec
Time (min)
C
HR (bpm)
V̇O2/HR (mL/beat)
Rec
Time (min)
F
V̇T (L)
RR
VC
V̇E (L/min)
I
PETO2 SpO2
PETCO2
RCP
VT
Rec
Time (min)

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

Exercise Intolerance in Pulmonary Arterial Hypertension

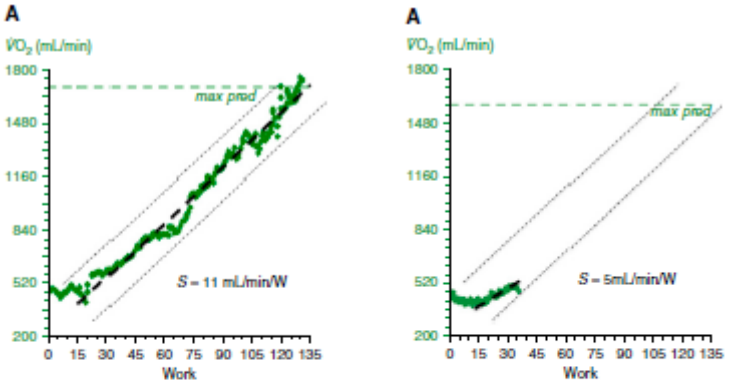
The Role of Cardiopulmonary Exercise Testing

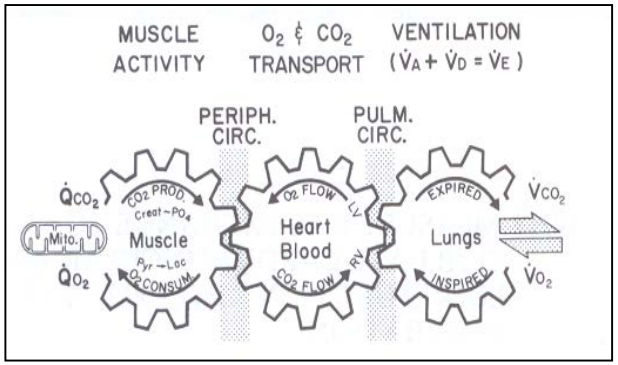
J. Alberto Neder[1,3], Roberta P. Ramos[1,2], Jaquelina S. Ota-Arakaki[2], Daniel M. Hirai[1,3], Christine L. D'Arsigny[4], and Denis O'Donnell[4]



Test da sforzo cardiopolmonare: peakVO_2

PAH





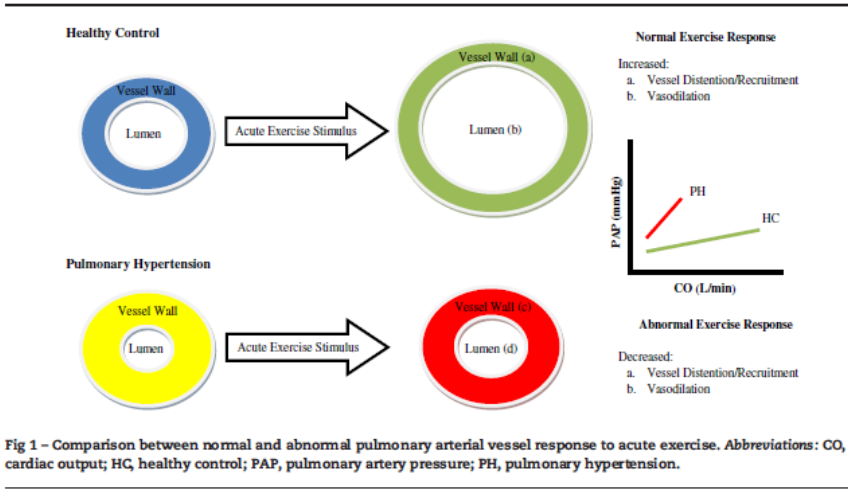
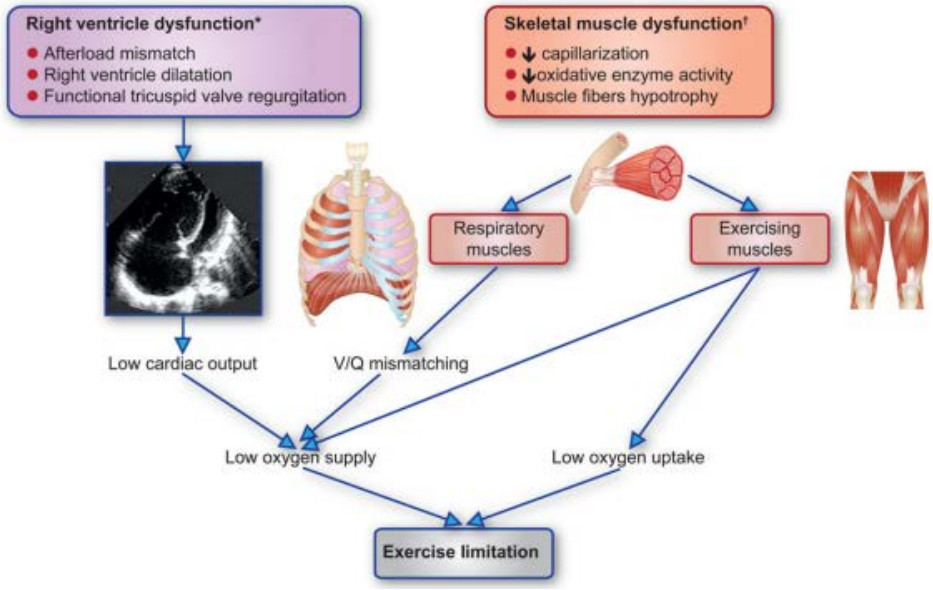


Fig 1 – Comparison between normal and abnormal pulmonary arterial vessel response to acute exercise. *Abbreviations:* CO, cardiac output; HC, healthy control; PAP, pulmonary artery pressure; PH, pulmonary hypertension.



Gruppo MultiMedica

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

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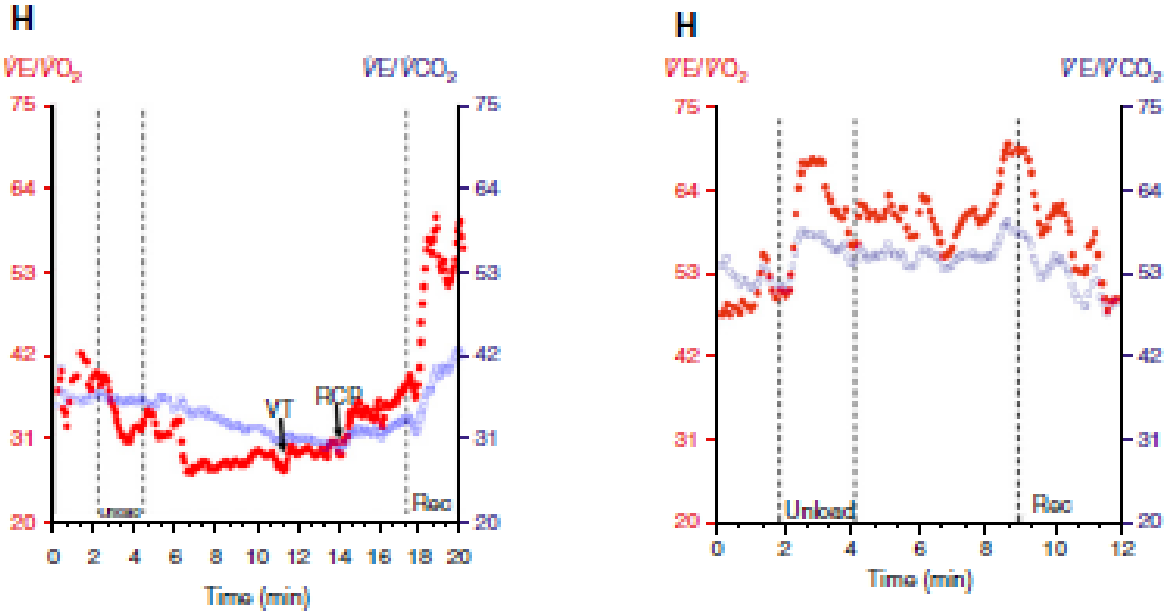

AnnalsATS Volume 12 number 4 April 2015

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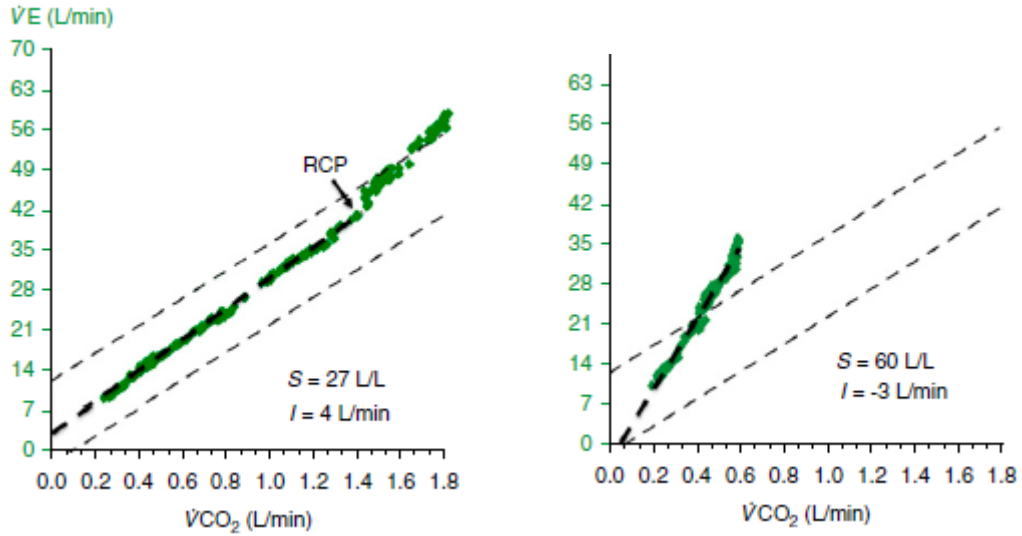
$$VE = \frac{VCO2 \times 863}{[PaCO2 \times (1 - VD/VT)]}$$



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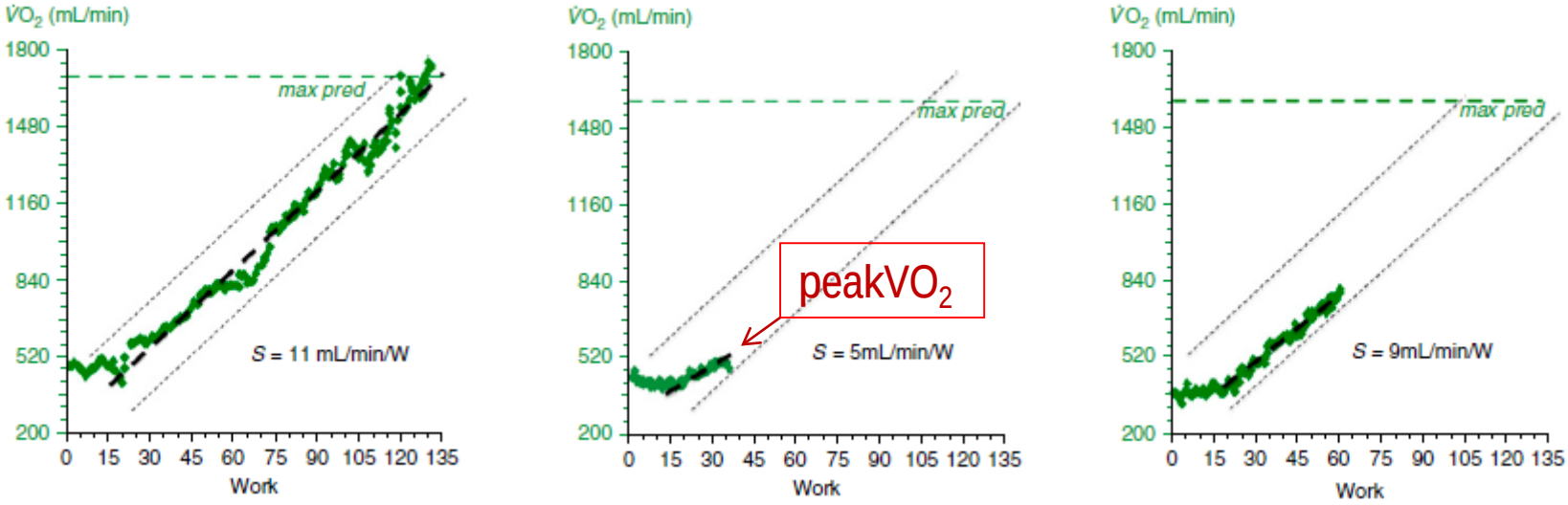

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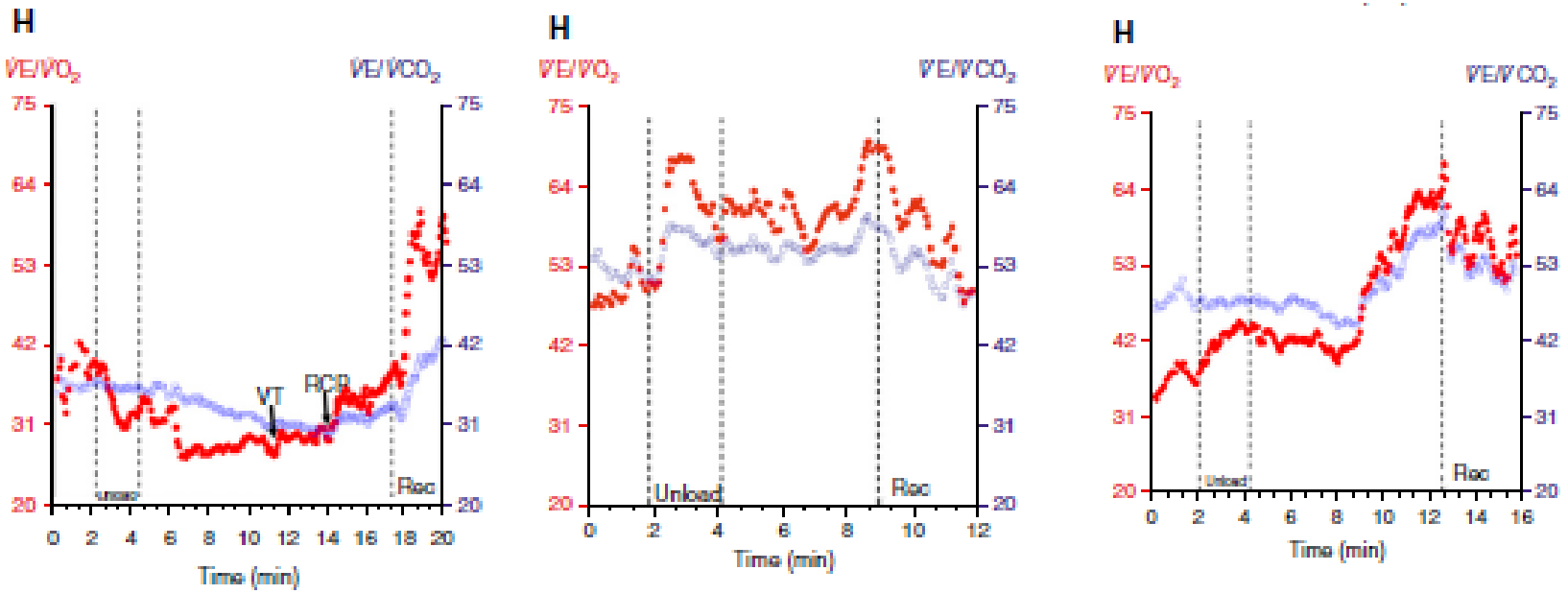

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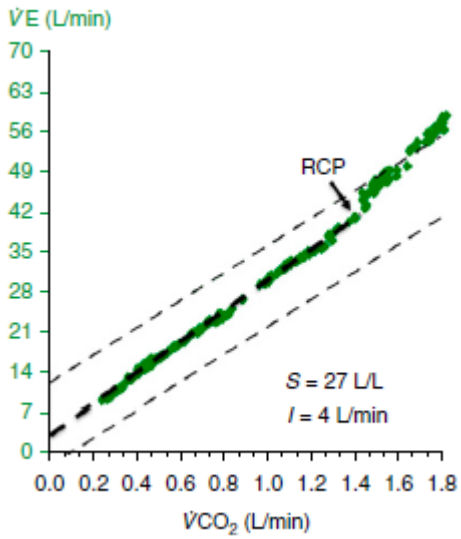

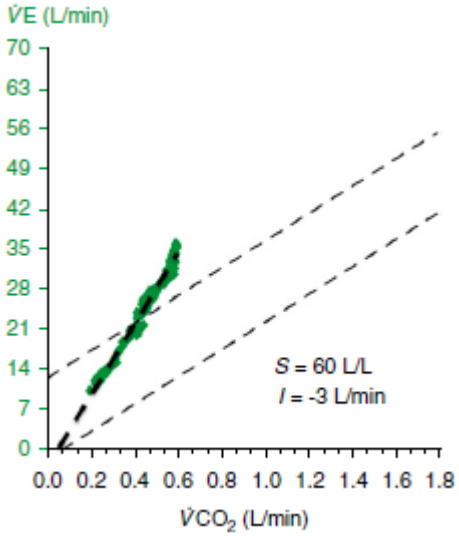

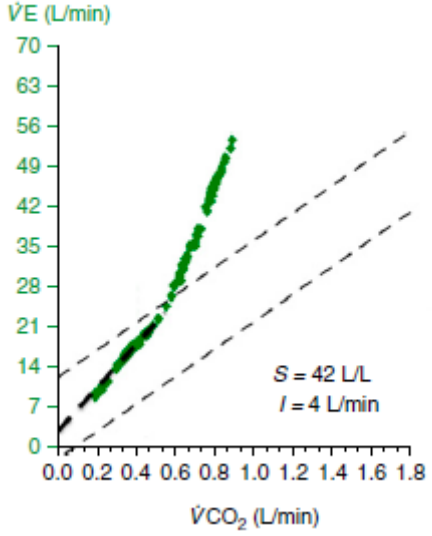

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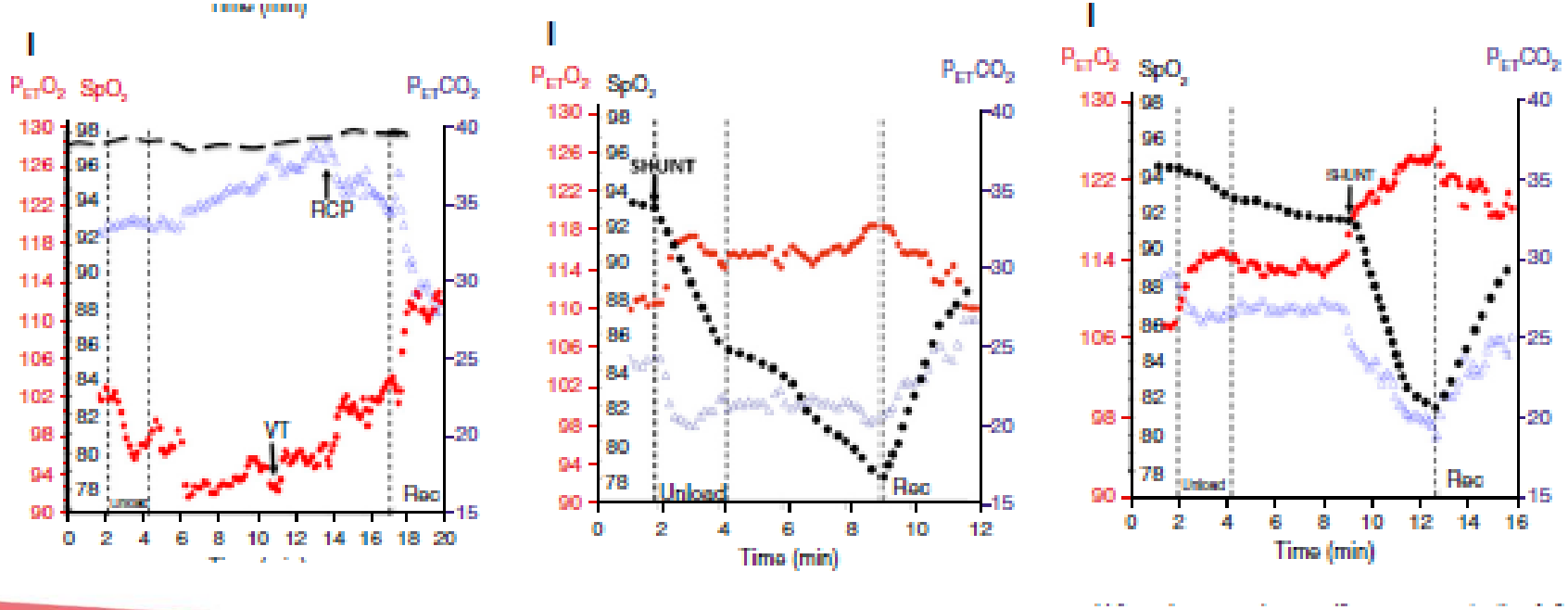

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WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) 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%

McLaughlin al. JACC 2015; 65: 1976-97

European Heart Journal (2016) **37**, 35–44
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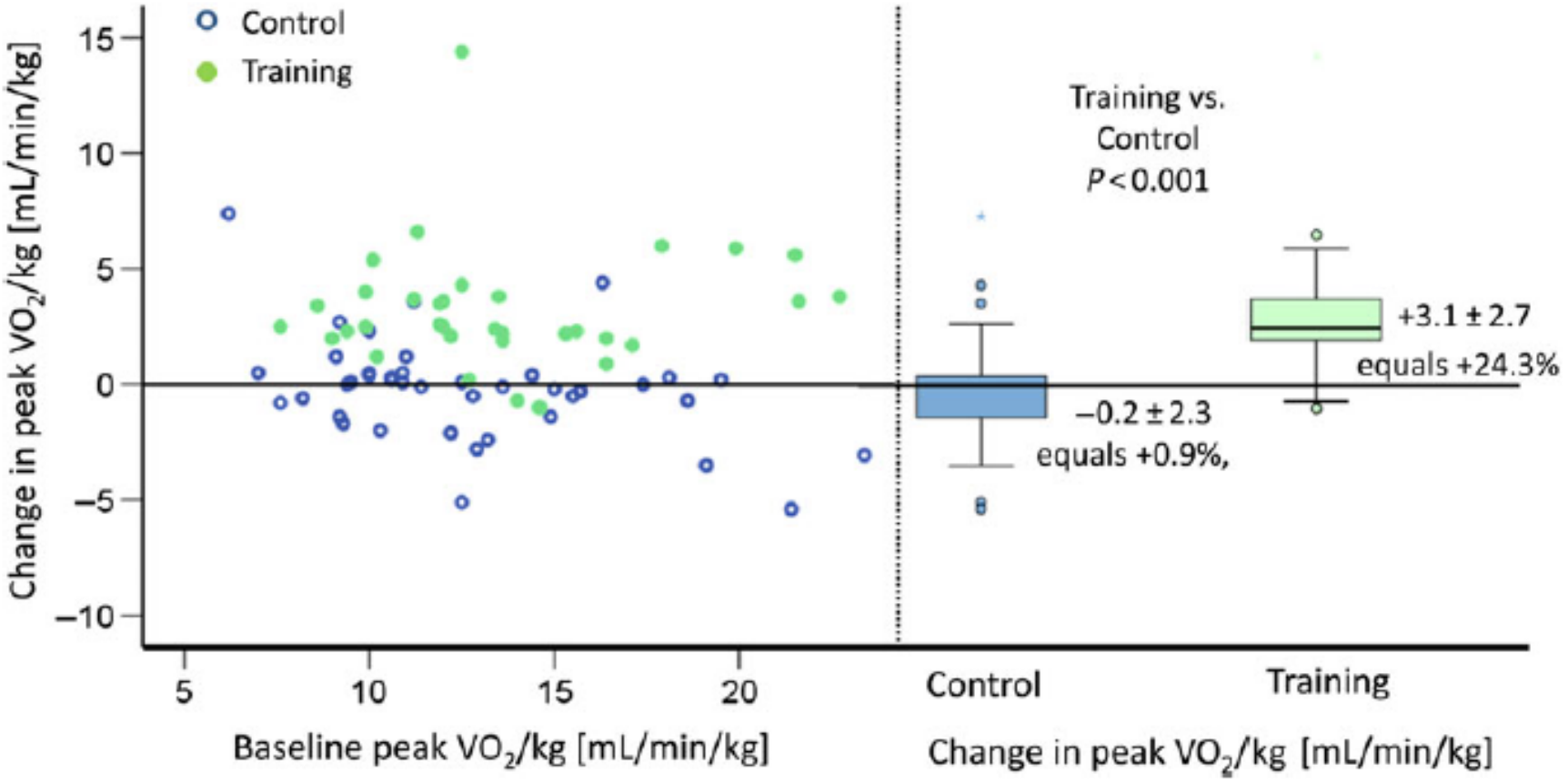
CLINICAL RESEARCH
Pulmonary circulation

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

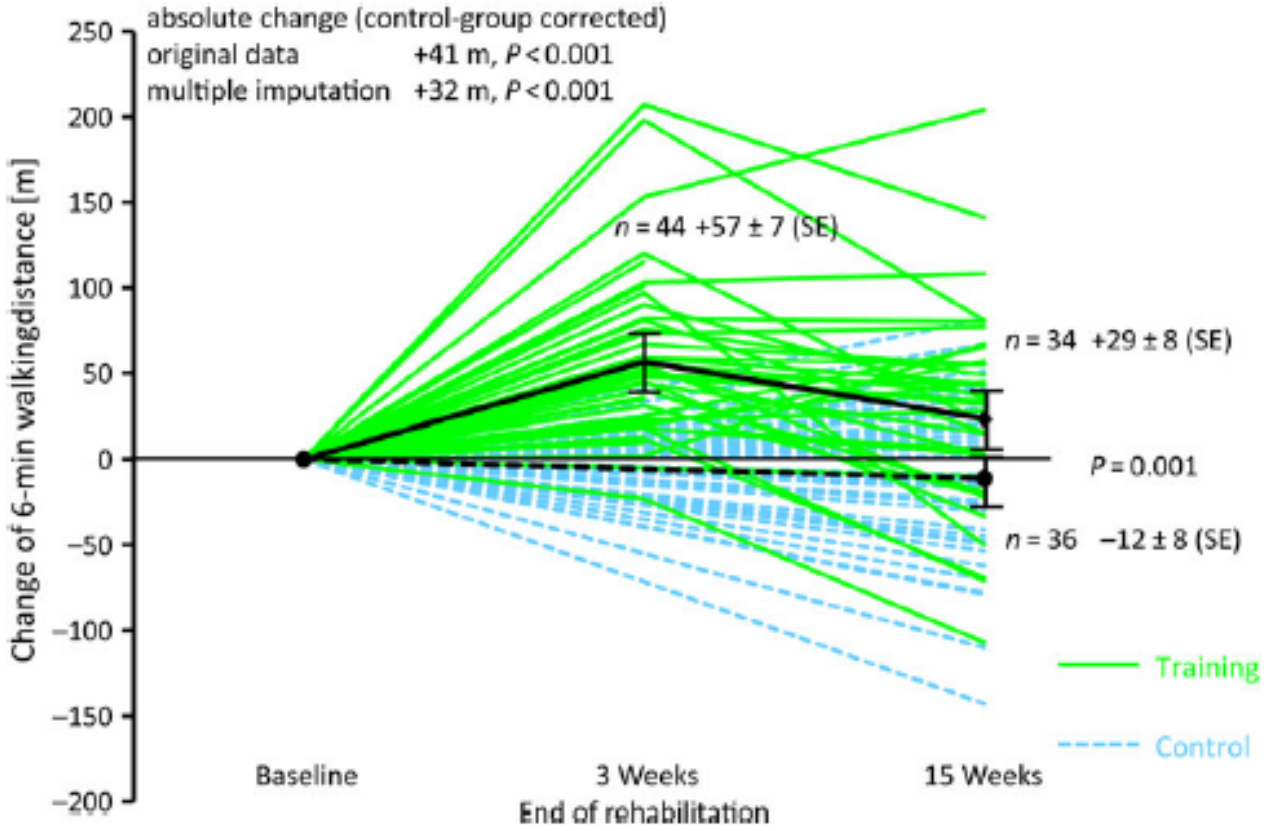
Nicola Ehlken[1*†], Mona Lichtblau[1†], Hans Klose[2†], Johannes Weidenhammer[1], Christine Fischer[3], Robert Nechwatal[4], Sören Uiker[4], Michael Halank[5], Karen Olsson[6], Werner Seeger[7], Henning Gall[7], Stephan Rosenkranz[8], Heinrike Wilkens[9], Dirk Mertens[10], Hans-Jürgen Seyfarth[11], Christian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

Primary endpoint: change in peak oxygen uptake



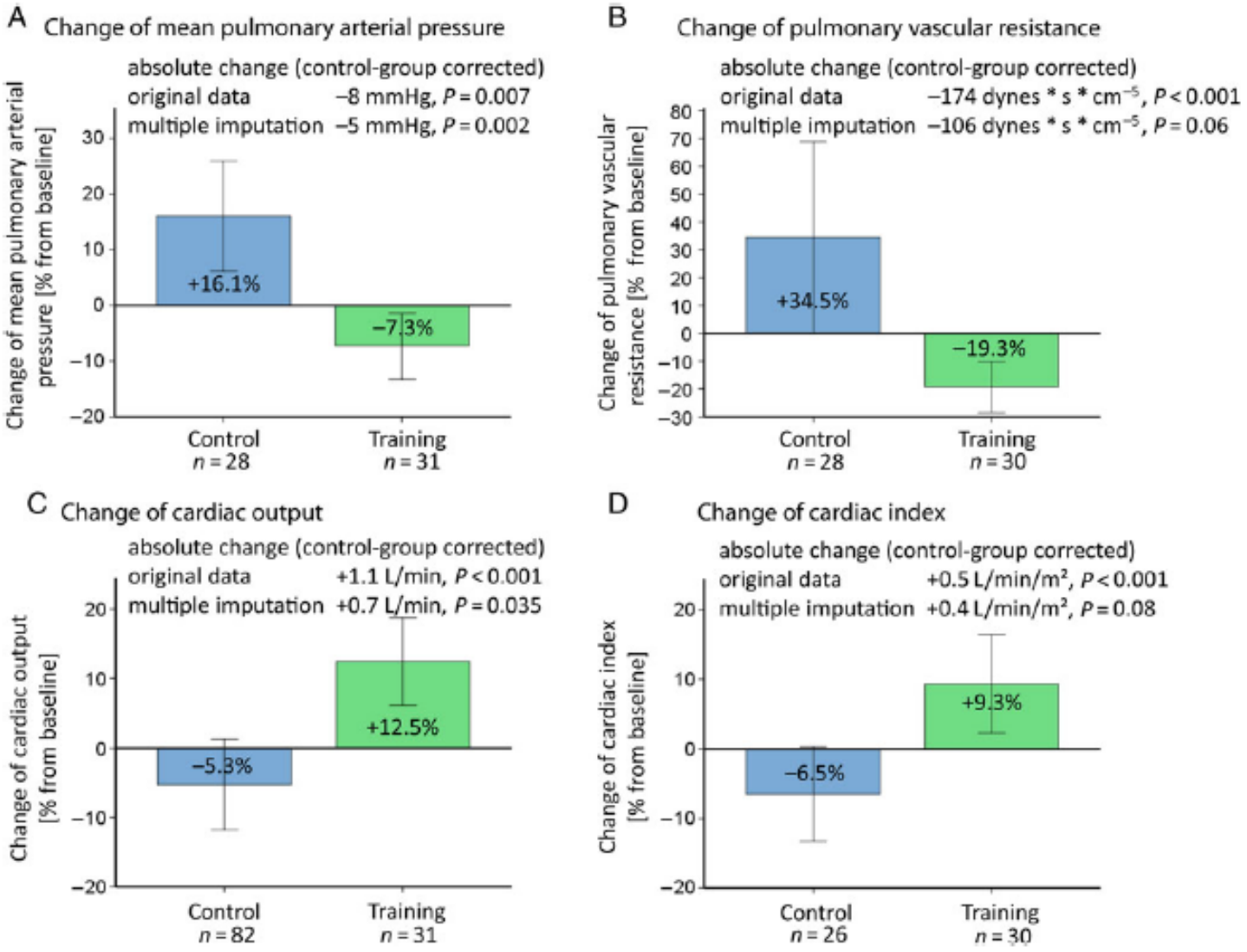
Ehlken et al. Eur Heart J 2016; 37: 35-44

Secondary endpoints: 6MWT



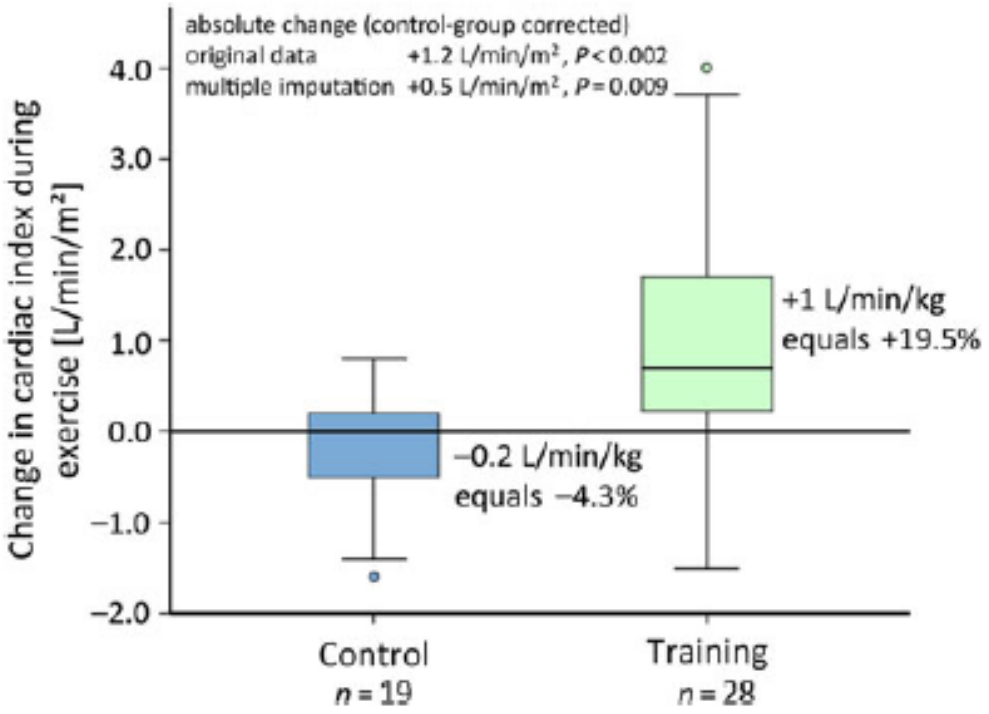
Ehlken et al. Eur Heart J 2016; 37: 35-44

Secondary endpoints: haemodynamics and right heart function



Ehlken et al. Eur Heart J 2016; 37: 35-44

Secondary endpoints: Haemodynamics during exercise



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doi:10.1093/eurheartj/ehv440

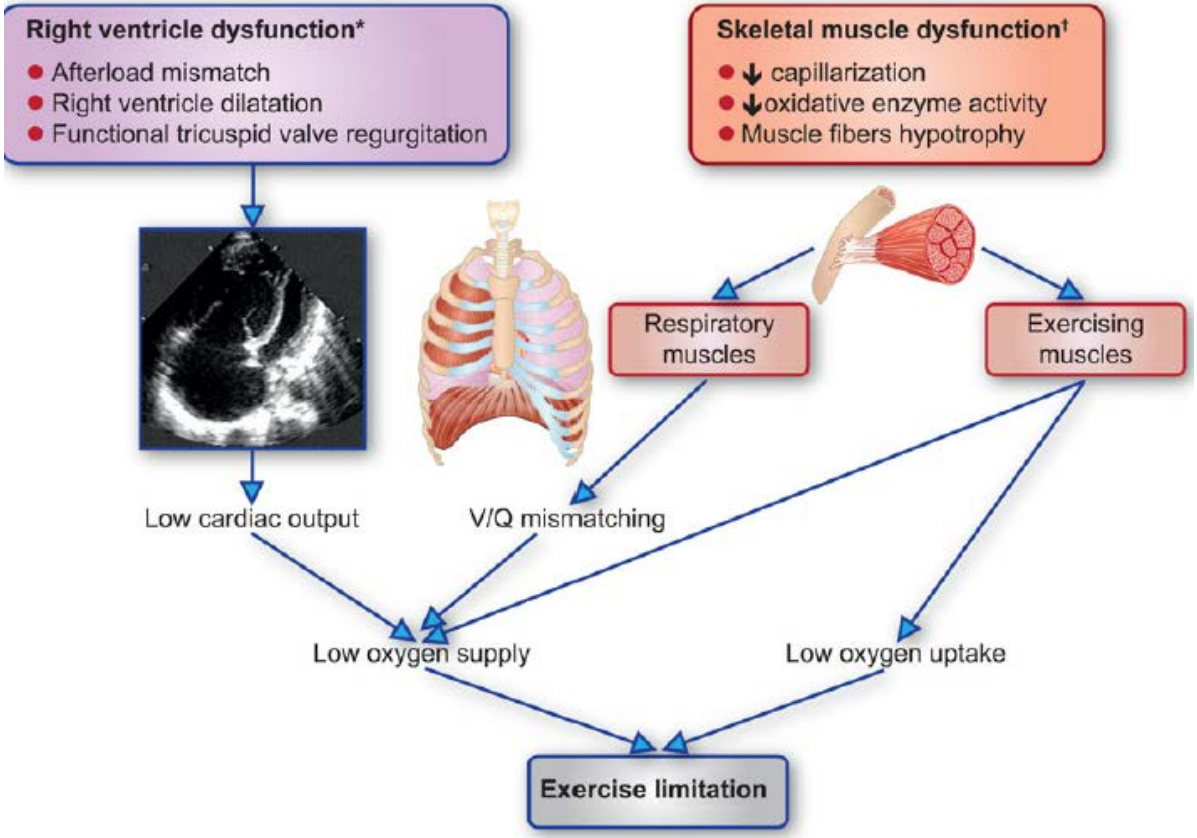
EDITORIAL

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

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

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

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



*Improved by approved drug therapy by reducing right ventricular afterload
†Improved by exercise training by increasing capillary density and oxidative enzyme activity

European Heart Journal 2016; EDITORIAL

Grazie!