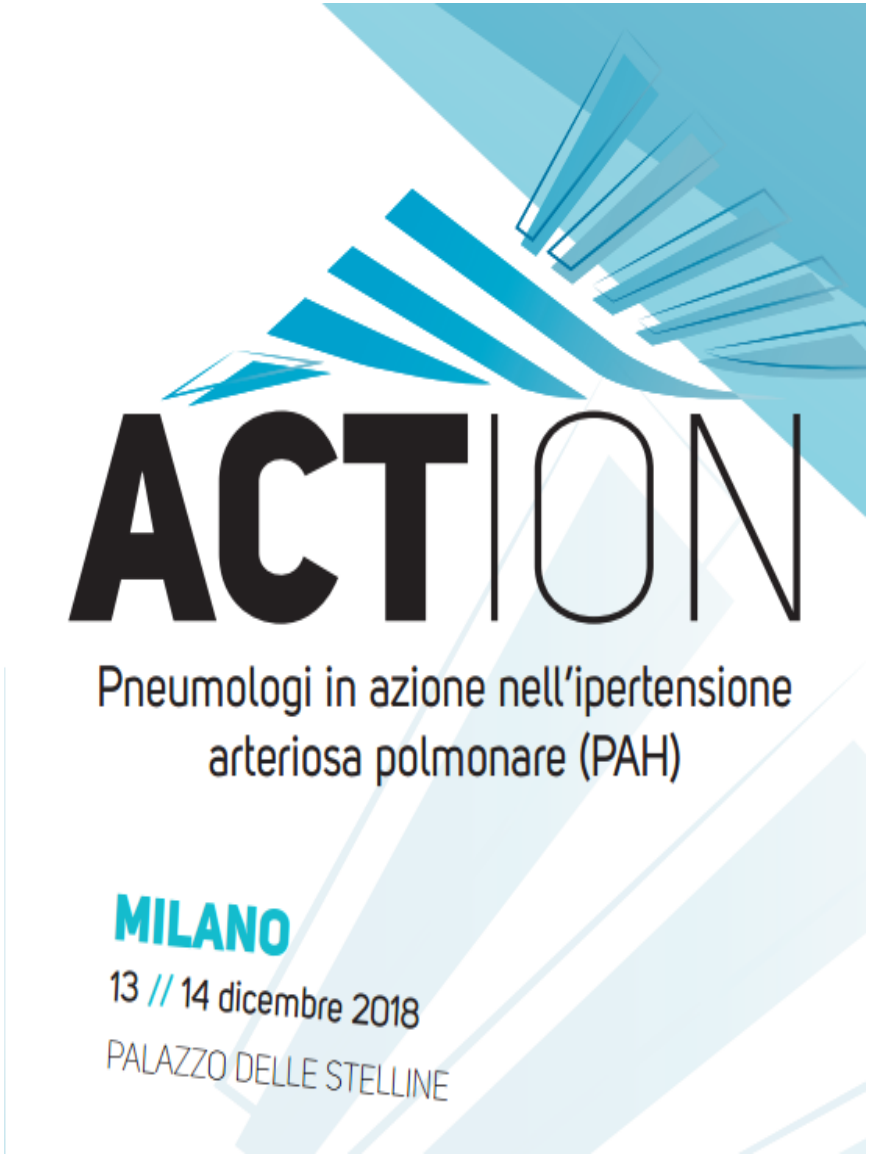

IL RUOLO DELLA RIABILITAZIONE NELL'IPERTENSIONE POLMONARE

Dott.ssa Gaia Cattadori
UO Cardiologia Riabilitativa
H San Giuseppe
IRCCS - Multimedica
MILANO

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Table 1: Different components of the rehabilitation programme in patients with pulmonary arterial hypertension (PAH).

Intervention	Comment
Expert education and supervision	It is a prerequisite for training in PAH to perform this in collaboration with a PAH expert centre with programmes specifically tailored to groups of PAH patients.
Aerobic exercise training	Low workload, e.g., aerobic bicycle training (40–80% of peak exercise capacity). Monitoring oxygen saturation (>90%) and heart rate (<120/min). For 10 to 25 minutes. Frequency: daily.
Resistance training	Dumbbell with low weights for 30 minutes. Frequency: 5 times/week.
Mental walking training	Guidance in exploring individual physical limits and pacing. Frequency: several times/week.
Respiratory therapy	For 30 minutes. Frequency: 5 times/week.
Psychological support	If needed.
Nutritional support	If needed.
Social service	If needed.
Instruction in inhalation device	If needed.

Keusch S et al. Swiss Med Wkly. 2017; 147

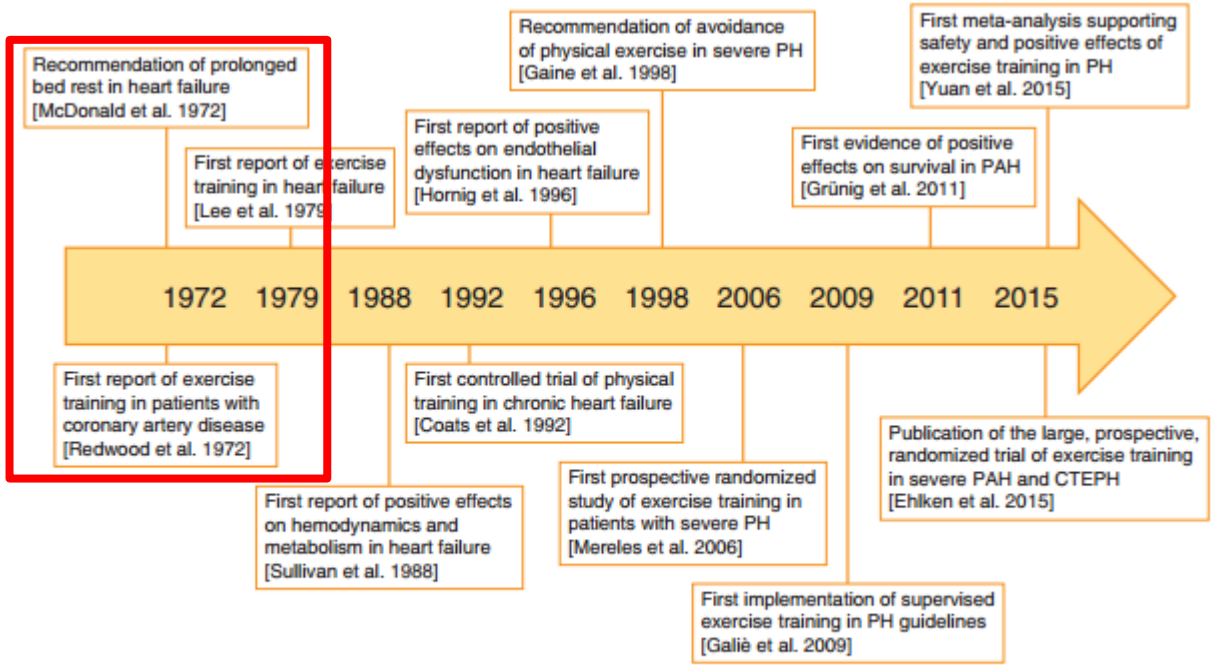

Fig. 1. Timeline of clinical evidence for exercise training in PH.
CTEPH,chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.

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Richter et al. Pulm Circ 2017; 7: 20-37

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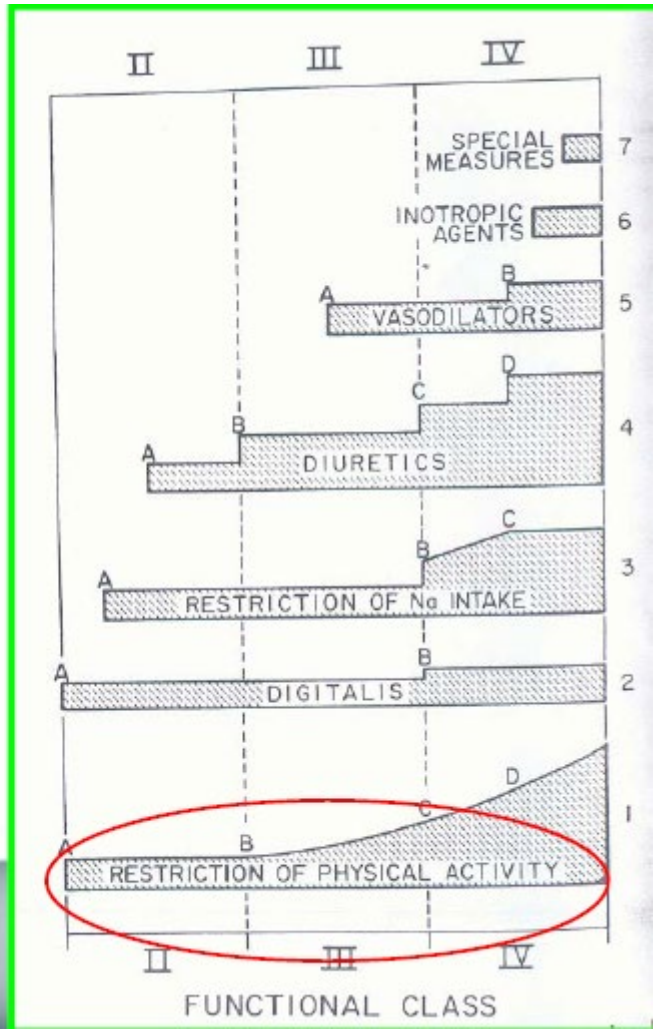
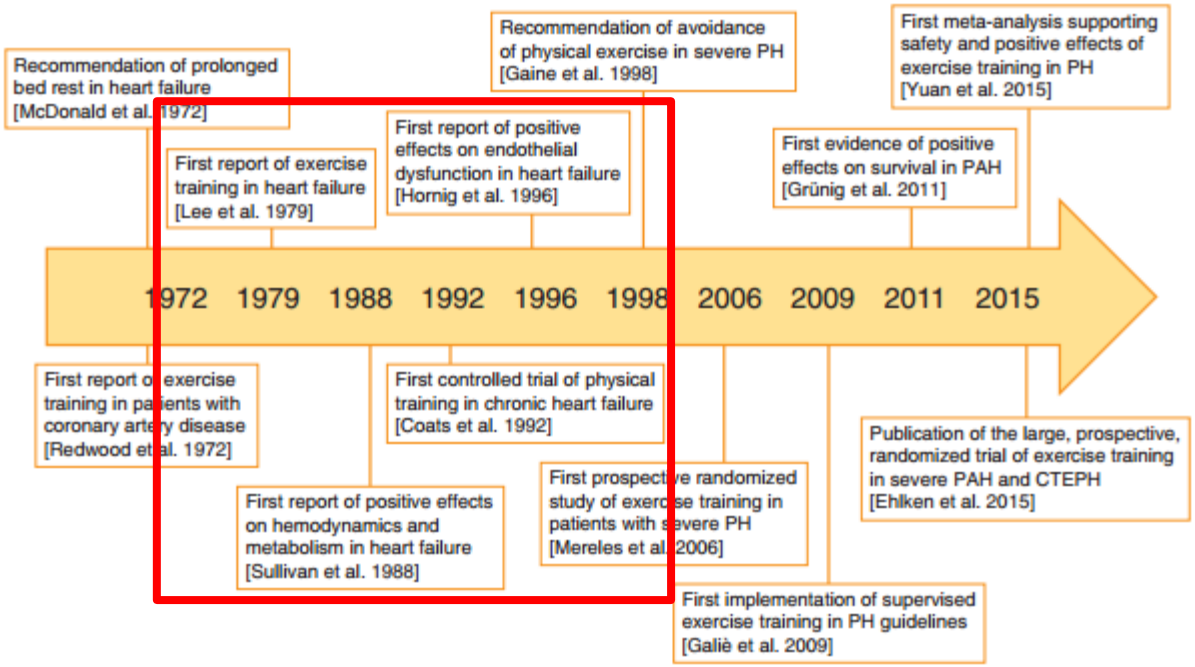


Effects of exercise training on pulmonary hemodynamics, functional capacity and inflammation in pulmonary hypertension

Manuel J. Richter[1,*], Jan Grimminger[1,2,*], Britta Krüger[3], Hossein A. Ghofrani[1,4,5], Frank C. Mooren[6], Henning Gall[1], Christian Pilat[6] and Karsten Krüger[6]



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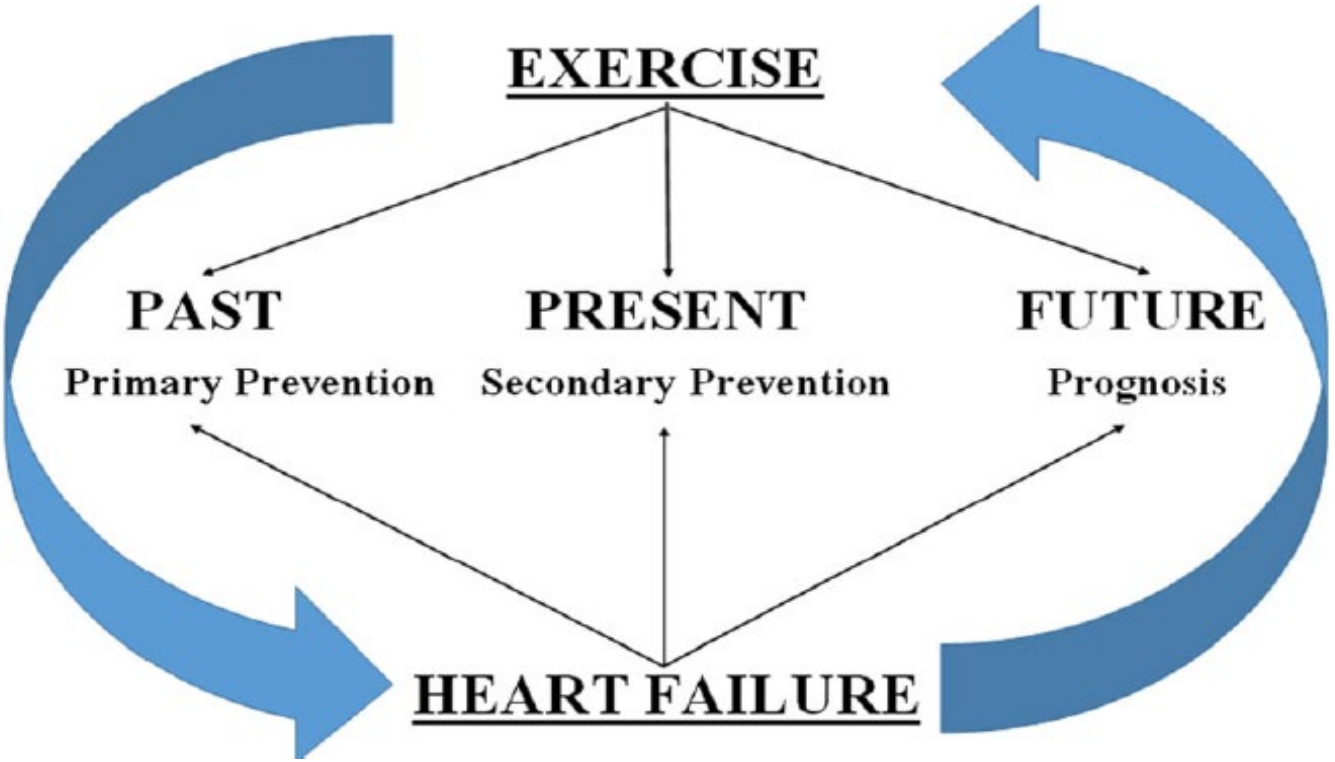
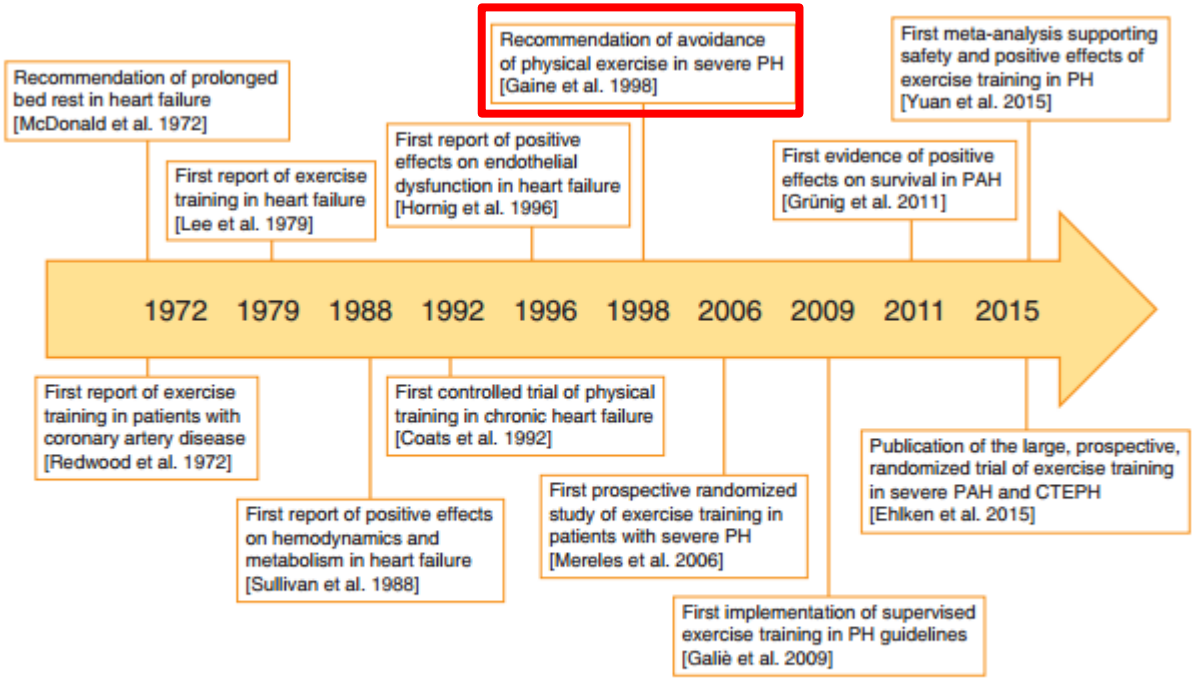
ESC HEART FAILURE
ESC Heart Failure (2017)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12225

REVIEW

Exercise and heart failure: an update

Gaia Cattadori[1*], Chiara Segurini[1], Anna Picozzi[1], Luigi Padeletti[1,2] and Claudio Anzà[1]





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Richter et al. Pulm Circ 2017; 7: 20-37

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.

ESC European Society of Cardiology

Cardiovascular Research (2017) **113**, 1499–1508
doi:10.1093/cvr/cvx156

SPOTLIGHT REVIEW

Exercise and the right ventricle: a potential Achilles' heel

Andre La Gerche[1,2,3]*, Dhrubo J. Rakhit[1,4], and Guido Claessen[2]

[1]Sports Cardiology and Cardiac Magnetic Resonance Imaging Lab, Baker Heart and Diabetes Institute, 75 Commercial Road, Melbourne, Victoria 3004, Australia; [2]Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium; [3]Cardiology Department, St Vincent's Hospital, Melbourne, Australia; and [4]Cardiovascular Imaging Department, Southampton University Hospital, Southampton, UK

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Canadian Journal of Cardiology 31 (2015) 502–508

Review

Is Exercise Good for the Right Ventricle? Concepts for Health and Disease

André La Gerche, MD, PhD,[a,b] and Guido Claessen, MD[b]

[a] *Baker IDI Heart and Diabetes Institute, Melbourne, Australia*

[b] *Department of Cardiovascular Medicine, University of Leuven, Leuven, Belgium*

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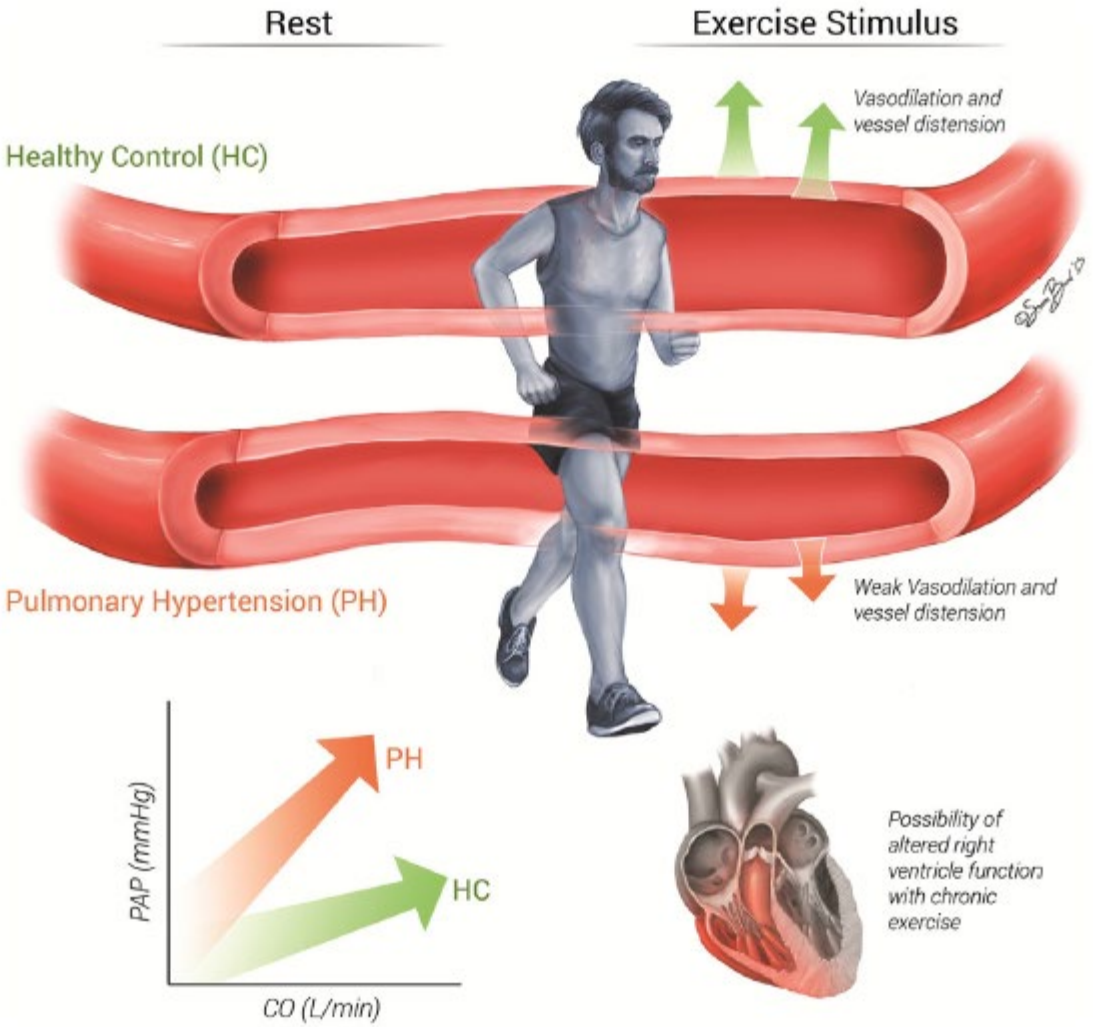
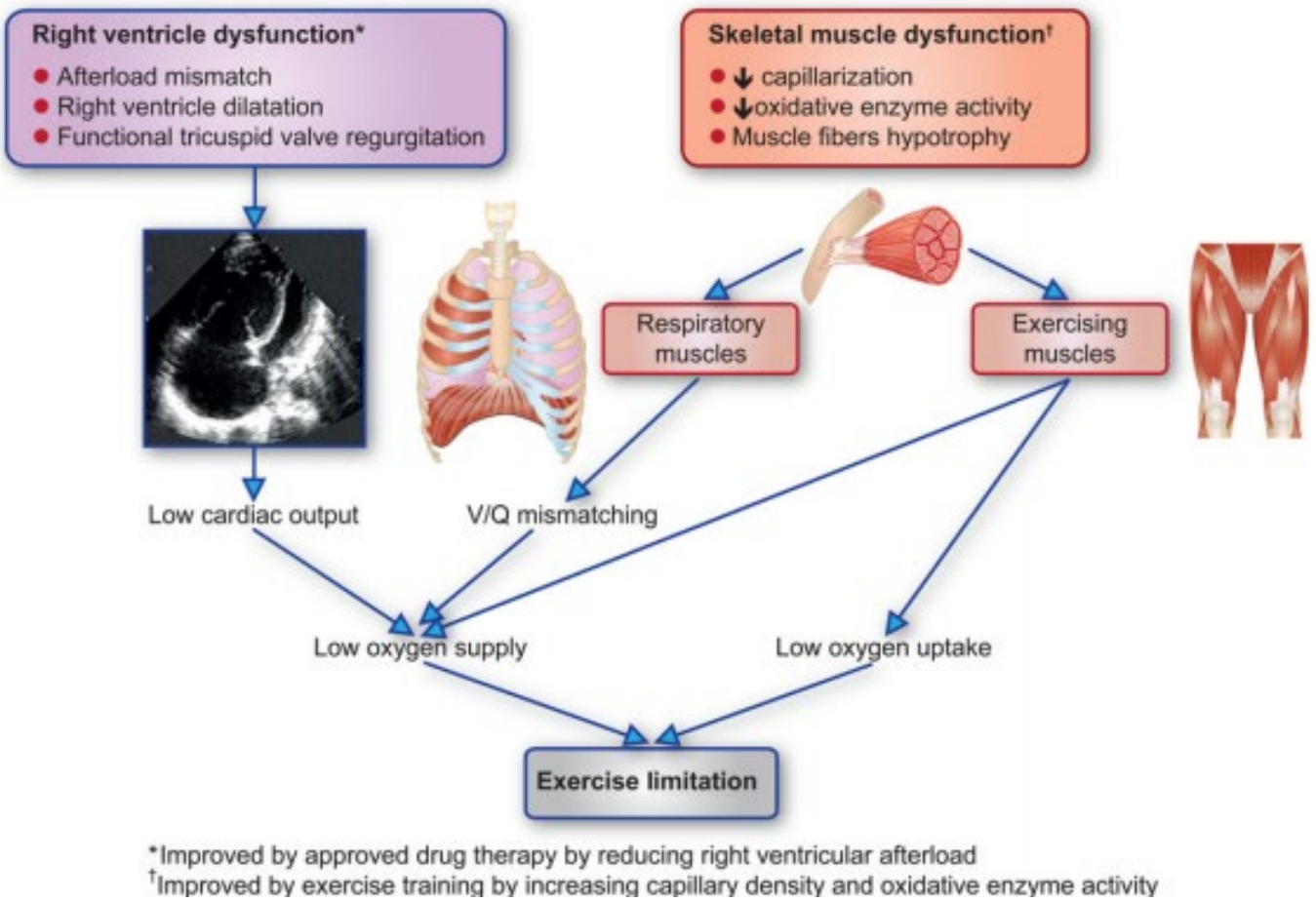


Fig 1 – Comparison between normal and abnormal pulmonary arterial vessel response to exercise: Implications for cardiac output with an acute exercise stimulus and right ventricular function with chronic exercise.

Arena R. et al. Prog Cardiovasc Dis 2016; 59: 87-94

Limitazione funzionale in PAH



Galiè N et al. Eur Heart J 2016; 37; 45-48

Review Article

Pulmonary Circulation

Effects of exercise training on pulmonary hemodynamics, functional capacity and inflammation in pulmonary hypertension

Manuel J. Richter[1,*], Jan Grimminger[1,2,*], Britta Krüger[3], Hossein A. Ghofrani[1,4,5], Frank C. Mooren[6], Henning Gall[1], Christian Pilat[6] and Karsten Krüger[6]

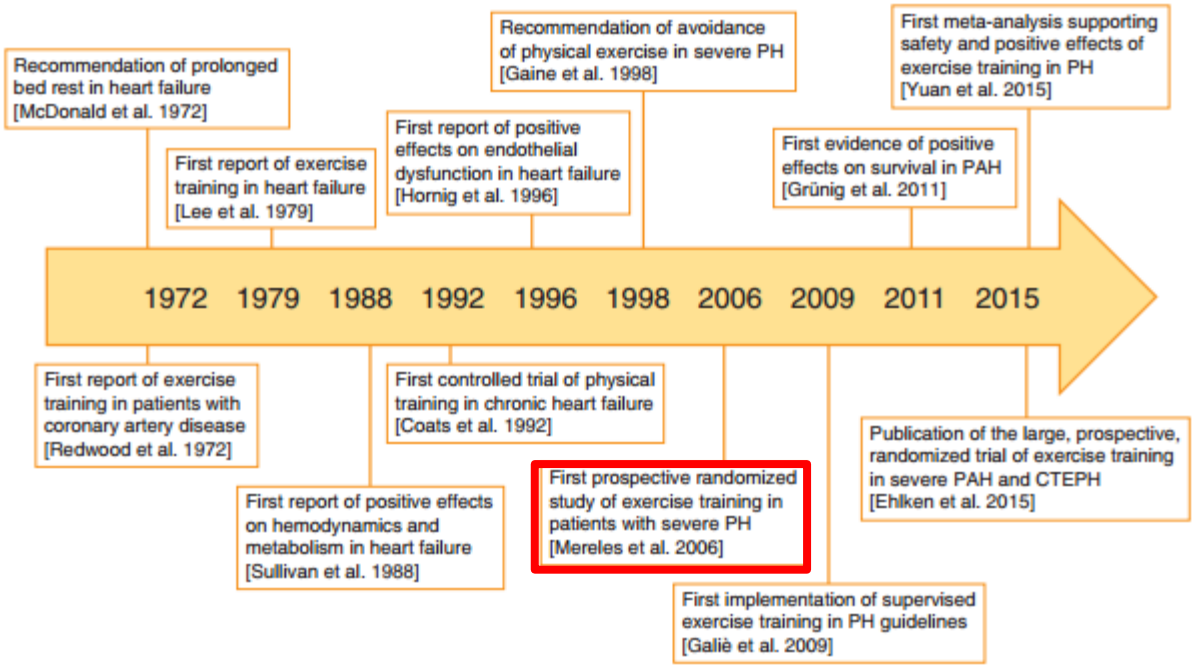


Fig. 1. Timeline of clinical evidence for exercise training in PH.
CTEPH,chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.

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

TABLE 1. Baseline Characteristics of the Patients

Characteristic	Control Group (n=15)	Primary Training Group (n=15)	*P*
Gender, M/F	5/10	5/10	...
Age, y	53±14	47±12	0.39
Height, cm	166±5	171±11	0.24
Weight, kg	78±18	75±13	0.91
WHO functional class	...	...	0.50
I	0	0	...
II	2	4	...
III	12	10	...
IV	1	1	...
Cause of pulmonary hypertension, n (%)	...	...	0.54
PAH	11 (73.3)	13 (86.6)	...
Chronic thromboembolic	4 (26.7)	2 (13.3)	...
Walking distance at 6 min, m	411±86	439±82	0.38
Cardiac catheterization			
Mean pulmonary artery pressure, mm Hg	49.6±12.3	49.5±17.6	0.98
Pulmonary vascular resistance, dyne · s · cm^{-5}	901.8±358.0	968.7±444.1	0.66
Cardiac index, L · min^{-1} · m^{-2}	2.1±0.5	2.3±0.5	0.61
Right atrial pressure, mm Hg	7±5	6±4	0.74

Values are mean±SD.

Gruppo MultiMedica

Mereles D et al. Circulation 2006; 114: 1482-9

Training cardio-respiratorio in PAH

Exercise Training Program

- 15 weeks (3 in-)

Interval bicycle training (1/2-1 minute)

- 10-25 minute
- 60-80% HR
- High limit: 120 bpm or SatO2 85%
- 7 d/week

Walking

- Mental training

Resistance training

- Dumbbell training with low weights (500-1000 g)

Respiratory training

- Streching, breathing techniques, yoga, strengthening of respiratory muscles

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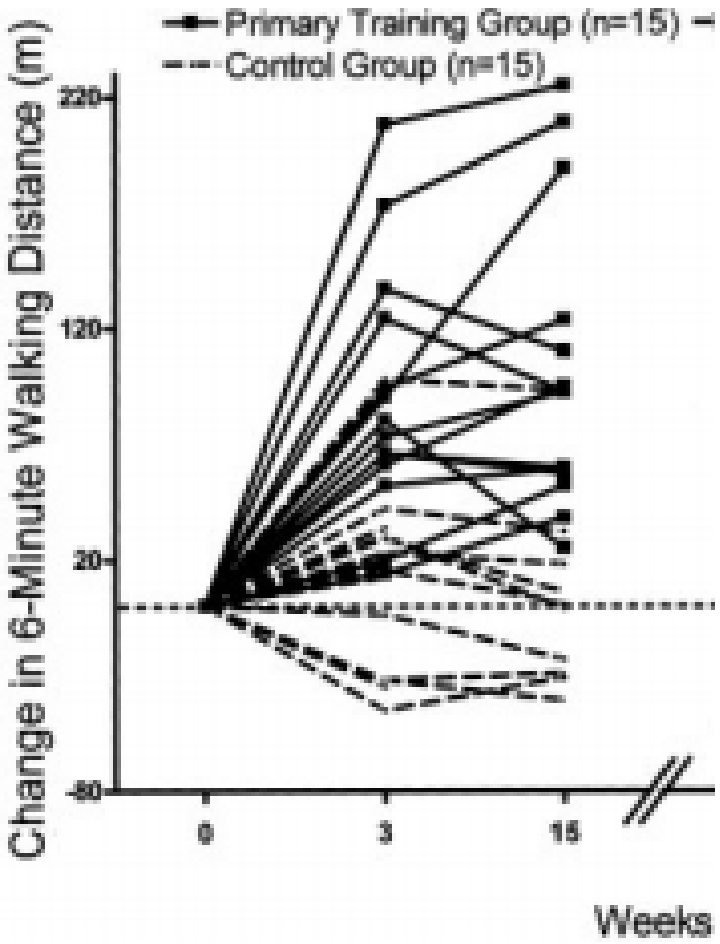
Mereles D et al. Circulation 2006; 114: 1482-9

Training cardio-respiratorio in PAH



Mereles D et al. Circulation 2006; 114: 1482-9

Training cardio-respiratorio in PAH

TABLE 3. Respiratory and Hemodynamic Variables at Baseline and After Intervention

	Control Group (n=15)			Primary Training Group (n=15)		
	Baseline	3 wk	15 wk	Baseline	3 wk	15 wk
$Workload_{max}$, W	64±22	60±24	67±20	70±17	85±26*†	90±25*†
Borg scale	15±2	15±1	16±1*	15±2	15±2	15±2
HR_{rest}, bpm	71±17	74±11	72±11	72±11	73±11	75±11
HR_{max}, bpm	108±19	107±22	110±20	118±16	125±15*†	132±17*†
VE_{max}, L · min	41.6±14.6	40.5±14.1	43.4±15.3	44.2±13.8	47.1±15.1	48.5±15.1
$\dot{V}O_{2\ peak}$, mL · min^{-1} · kg^{-1}	11.9±3.1	11.6±3.4	11.4±3.3	13.2±3.1	14.5±3.5*†	15.4±3.7*†
$\dot{V}O_{2\ \%\ predicted}$, %	46.3±10.7	45.9±14.6	49.8±12.7	51.6±16.3	56.5±18.0*	60.3±19.6*
Workload at AT, W	35±17	31±16	36±17	45±14	56±21*†	65±19*†
$\dot{V}O_2$ at AT, mL/min	640.7±187.4	613.4±206.6	610.4±200.4	736.6±210.3	802.3±229.8†	865.4±264.7*†
$Eqco_2$ at AT	42.4±11.3	50.7±10.8*	43.5±10.5	44.4±11.5	42.6±9.8†	42.9±10.4
Echocardiography						
$PASP_{rest}$, mm Hg	68±21	71±23	70±25	61±18	57±18†	54±18†
$PASP_{max\ exercise}$, mm Hg	98±28	104±29	102±30	89±17	84±23†	89±20
Cardiac $index_{rest}$, L · min^{-1} · m^{-2}	1.4±0.3	1.5±0.4	1.6±0.5	1.5±0.5	1.6±0.3	1.6±0.4
Cardiac $index_{max}$, L · min^{-1} · m^{-2}	1.9±0.7	1.8±0.7	1.9±0.7	2.3±0.6	2.3±0.7	2.5±1.1
RV $area_{rest}$, cm^2/m^2	16.2±5.8	16.0±4.3	13.3±4.7	13.0±3.9	14.2±4.3	12.2±3.8
RV $area_{max}$, cm^2/m^2	17.0±6	17.2±4.8	16.4±4.8	13.7±4.0	14.2±4.3	14.0±2.7
RA $area_{rest}$, cm^2/m^2	13.5±4.4	15.5±5.7	13.8±3.3	12.7±3.9	13.2±4.1	12.8±3.8
RA $area_{max}$, cm^2/m^2	15.3±4.8	15.0±5.9	14.7±3.9	13.9±4.5	14.8±4.3	12.3±3.3

$Workload_{max}$ indicates maximal workload; HR, heart rate; $Eqco_2$, respiratory equivalent of carbon dioxide at the anaerobic threshold (AT; $\dot{V}E/\dot{V}co_2$); $PASP_{rest}$, PASP at rest, $PASP_{max\ exercise}$, maximal PASP; RV, right ventricular; and RA, right atrial. Values are mean±SD. $P<0.05$ by Mann-Whitney rank sum test for the comparison between both groups and Wilcoxon signed rank test for the intergroup comparison.

*$P<0.05$ vs baseline.

†$P<0.05$, primary training group vs control group.

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Mereles D et al. Circulation 2006; 114: 1482-9

Training cardio-respiratorio in PAH

Safety

Although patients included in the study had severe PH with right heart failure (5 patients had pericardial effusion at start of rehabilitation, 1 patient was under continuous intravenous prostacyclin, 1 was on a list for lung transplantation), no adverse effects or complications of low-

Mereles D et al. Circulation 2006; 114: 1482-9

Exercise training in pulmonary arterial hypertension

Laura Adelaide Dalla Vecchia, Maurizio Bussotti

Table 1 Baseline characteristics of studies exploring the effects of exercise training on patients with pulmonary arterial hypertension

Author	Year	Trained patients #, [F]	Control patients, [F]	PH classes	ET protocol	Duration and follow-up
Randomized control trial						
Ehlken *et al.*	2016	46 [26]	41 [21]	87 CTEPH	Bicycle, walking, dumbbell, RT, MT	3 weeks/in-hospital + 12 weeks/at home
Ley *et al.*	2013	10 [8]	10 [6]	16 PAH, 4 CTEPH	Bicycle, walking, dumbbell, RT	3 weeks/in-hospital
Mereles *et al.*	2006	15 [10]	15 [10]	24 PAH, 6 CTEPH	Bicycle, walking, dumbbell, RT, MT	3 weeks/in-hospital + 12 weeks/at home
Observational control studies						
Chan *et al.*	2013	10 [10]	13 [13]	PAH	Treadmill walking	10 weeks/outpatient rehabilitation clinic
Fox *et al.*	2011	11 [5]	11 [10]	20 PAH, 2 CTEPH	Bicycle, treadmill walking, step climbing, resistance, HT	12 weeks/outpatient rehabilitation clinic
Martinez-Quintana *et al.*	2010	4 [2]	4 [1]	CHD-PAH	Bicycle, resistance, educational lesson, HT	12 weeks/outpatient rehabilitation clinic
Weinstein *et al.*	2013	11 [11]	13 [13]	PAH	Treadmill walking	10 weeks/outpatient rehabilitation clinic
Becker-Grunig *et al.*	2013	20 [16]	–	–	Bicycle, dumbbell, RT, MT	3 weeks/in-hospital + 12 weeks/at home
Bussotti *et al.*	2016	15 [14]	–	PAH-CHD	Bicycle, dumbbell, RT, MT	4 weeks/outpatient rehabilitation clinic
De Man *et al.*	2009	19 [15]	–	IPAH	Bicycle, quadriceps strength, endurance	12 weeks/outpatient rehabilitation clinic
Grunig *et al.*	2012	21 [20]	–	–	Bicycle, dumbbell, RT, MT	3 weeks/in-hospital + 12 weeks/at home
Grunig *et al.*	2012	183 [126]	–	133 PAH, 31 CTEPH, 19 others	Bicycle, dumbbell, RT, MT	3 weeks/in-hospital + 12 weeks/at home
Grunig *et al.*	2011	58 [42]	–	47 PAH, 6 CTEPH, 1 COPD-PH, 2 ILD-PAH	Bicycle, dumbbell, RT, MT	3 weeks/in-hospital + 12 weeks/at home
Inagaki *et al.*	2014	8 [8]	–	8 CTEPH	Walking exercise, lower and upper-limb strength training, respiratory exercises	12 weeks/at home
Mainguy *et al.*	2010	5 [4]	–	IPAH	Bicycle, dumbbell, RT, MT	3 weeks/in-hospital + 12 weeks/at home
Nagel *et al.*	2012	35 [16]	–	CTEPH	Bicycle, dumbbell, RT, MT	3 weeks/in-hospital + 12 weeks/at home

#, number. F, females; PAH, pulmonary arterial hypertension; CHD, congenital heart disease; CTD, connective tissue disease; CTEPH, chronic thromboembolic pulmonary hypertension; ET, exercise training; IPAH, idiopathic PAH; HT, home training; MT, mental training; RT, respiratory training.

Dalla Vecchia and Bussotti. J Thorac Dis 2018; 10: 508-21

Cochrane Library

Cochrane Database of Systematic Reviews

Exercise-based rehabilitation programmes for pulmonary hypertension (Review)

Morris NR, Kermeen FD, Holland AE

Morris NR, Kermeen FD, Holland AE.
Exercise-based rehabilitation programmes for pulmonary hypertension.
Cochrane Database of Systematic Reviews 2017, Issue 1. Art. No.: CD011285.
DOI: 10.1002/14651858.CD011285.pub2.

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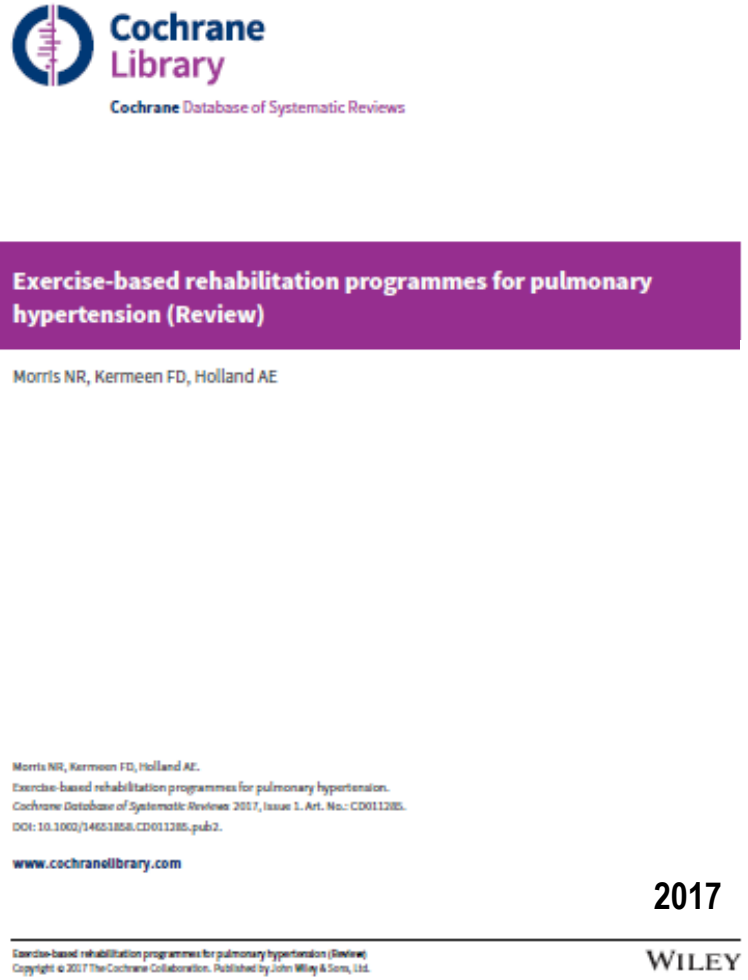
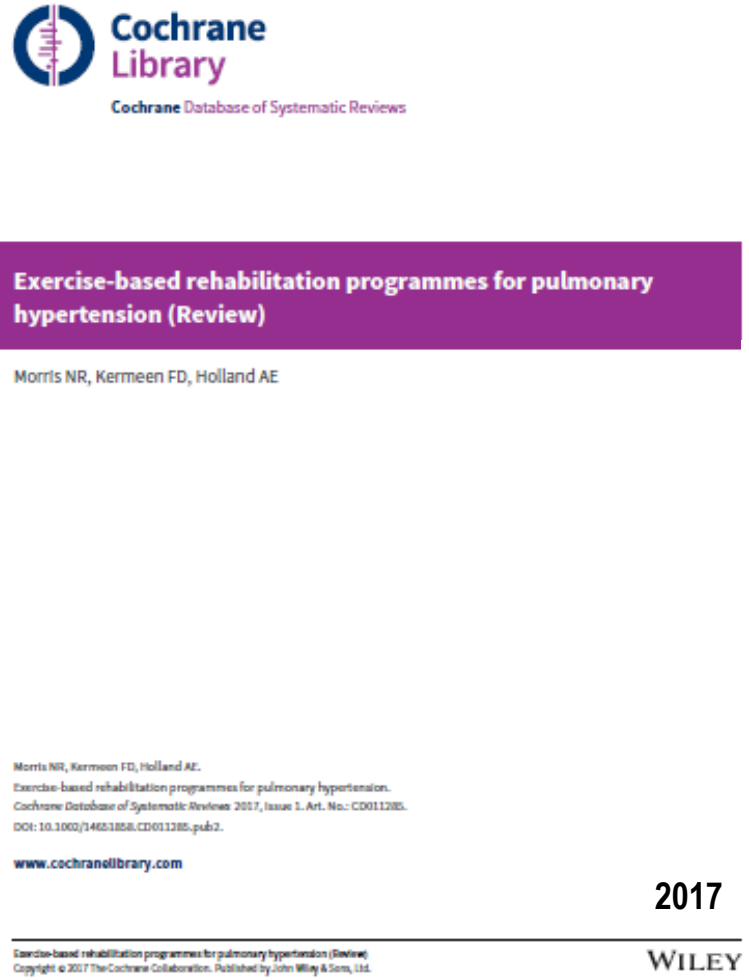
- The quality of evidence is low



- The quality of evidence is low
- Small number of studies



- The quality of evidence is low
- Small number of studies
- Not associated with any serious adverse events

Training cardio-respiratorio in PAH: sicurezza

Safety and efficacy of exercise training in various forms of pulmonary hypertension

Ekkehard Grünig*,+++, Mona Lichtblau*,+++, Nicola Ehlken*, Hossein A. Ghofrani#, Frank Reichenberger#, Gerd Staehler¶, Michael Halank+, Christine Fischer§, Hans-Jürgen Seyfarthƒ, Hans Klose**, Andreas Meyer##, Stephan Sorichter¶¶, Heinrike Wilkens++, Stephan Rosenkranz§§, Christian Opitzƒƒ, Hanno Leuchte***, Gabriele Karger###, Rudolf Speich¶¶¶ and Christian Nagel*

ABSTRACT: **The objective of this prospective study was to assess safety and efficacy of exercise training in a large cohort of patients with different forms and World Health Organization (WHO) functional classes of chronic pulmonary hypertension (PH).**

183 patients with PH (pulmonary arterial hypertension (PAH), chronic thromboembolic PH and PH due to respiratory or left heart diseases received exercise training in hospital for 3 weeks and continued at home. Adverse events have been monitored during the in-hospital training programme. Efficacy parameters were evaluated at baseline, and after 3 and 15 weeks.

After 3 and 15 weeks, patients significantly improved the distance walked in 6 min (6MWD) compared to baseline, scores of quality of life, WHO functional class, peak oxygen consumption, oxygen pulse, heart rate and systolic pulmonary artery pressure at rest and maximal workload. The improvement in 6MWD was similar in patients with different PH forms and functional classes. Even in severely affected patients (WHO functional class IV), exercise training was highly effective. Adverse events, such as respiratory infections, syncope or presyncope, occurred in 13% of patients.

Exercise training in PH is an effective but not a completely harmless add-on therapy, even in severely diseased patients, and should be closely monitored.

Gruppo MultiMedica

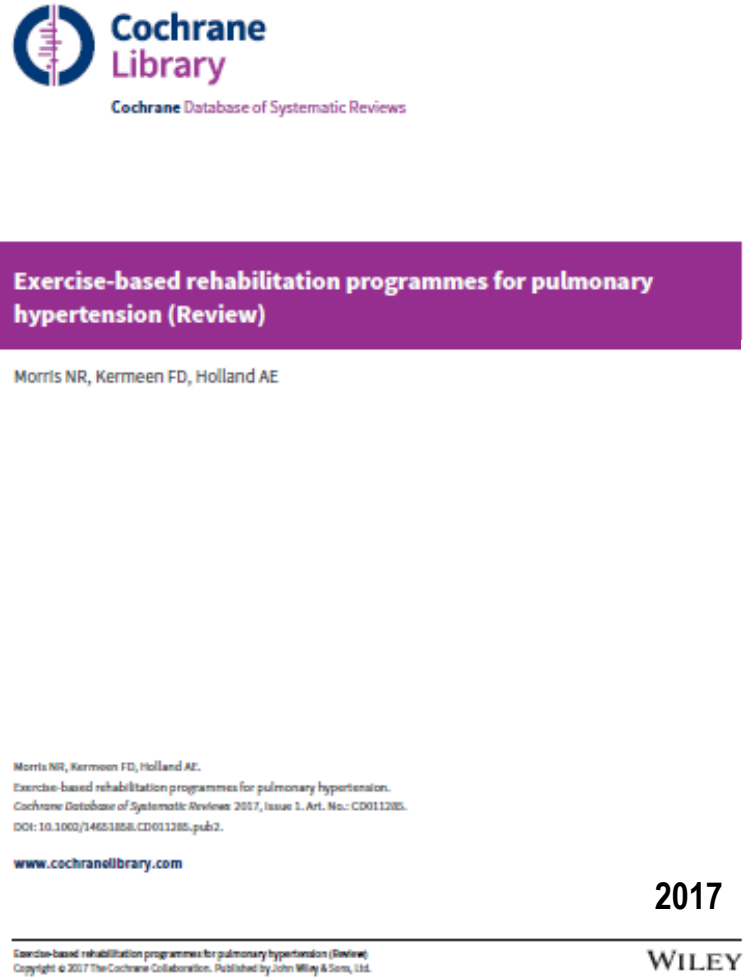
Grunig E. et al. Eur Respir J 2012; 40: 84-92

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

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



- The quality of evidence is low
- Small number of studies
- Not associated with any serious adverse events
- Relevant improvements in exercise capacity

Training cardio-respiratorio in PAH: capacità funzionale

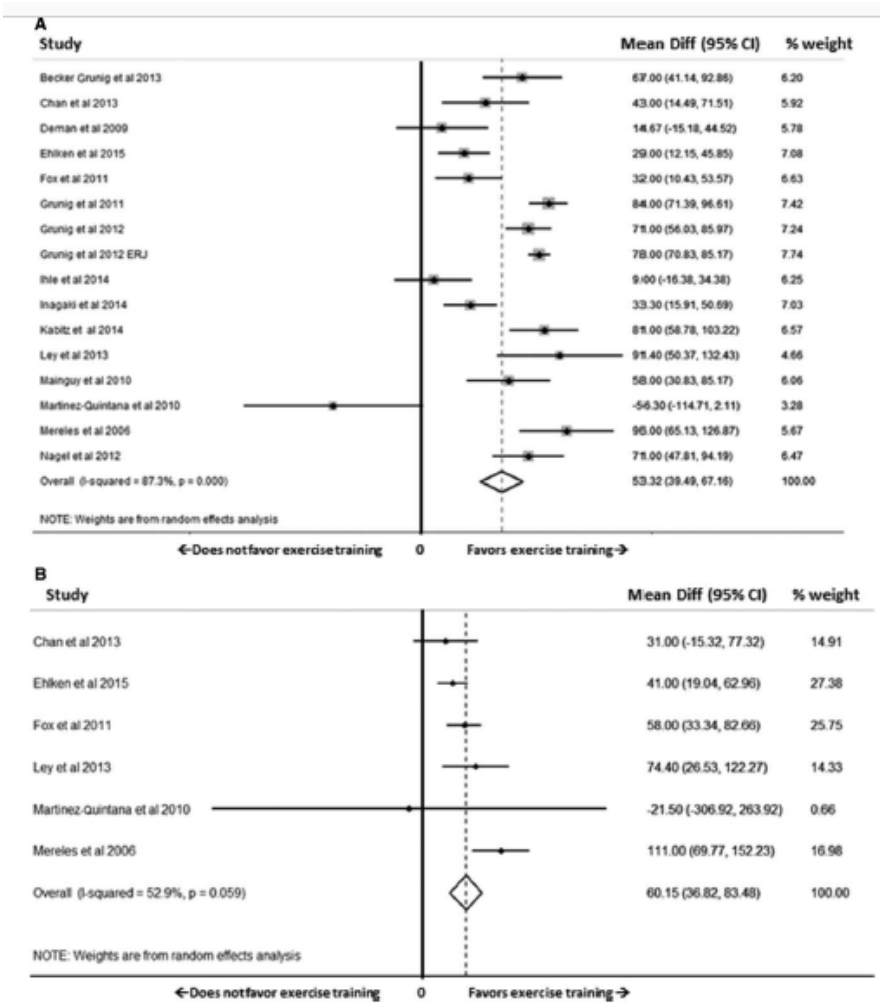


Figure 2. Forest plot showing effect of exercise training on 6-minute walk distance on pooled analysis of all included studies[14–29] (**A**) and parallel group trials with an intervention and control arm only[14,17,20,23,26,29] (n=6; **B**). CI indicates confidence interval.

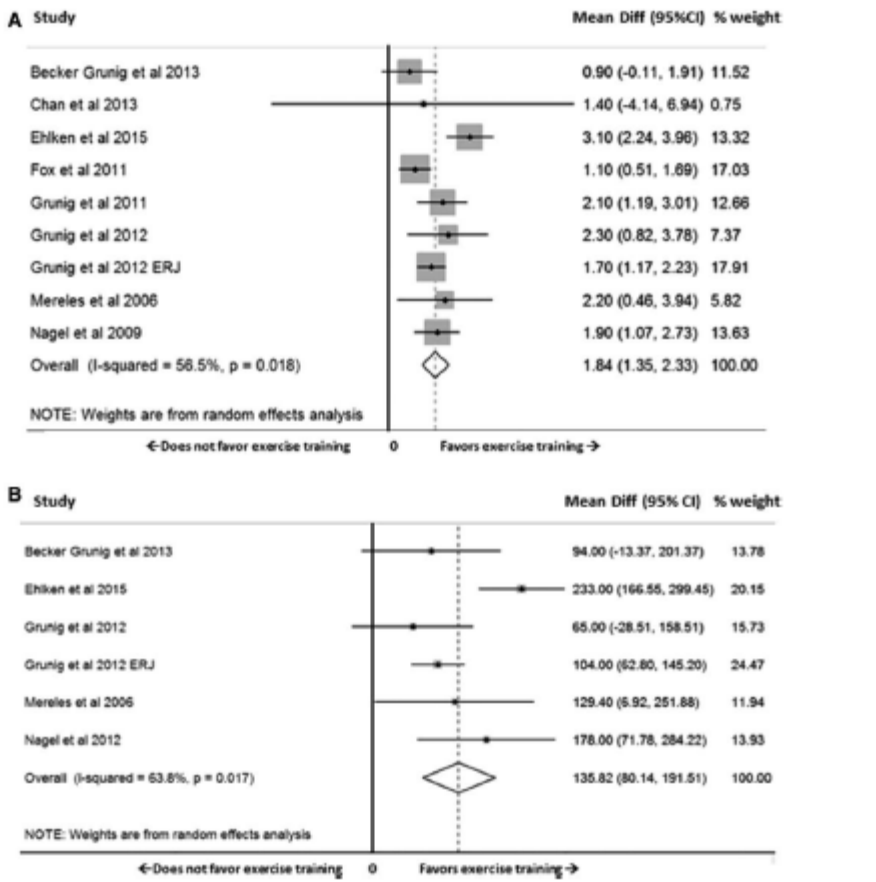


Figure 3. Forest plot showing effect of exercise training on peak relative oxygen uptake (mL/kg per minute; n=9, **A**)[14,17–20,27,29] and peak absolute oxygen uptake (mL/min) on pooled analysis of included studies (n=6, **B**).[14,19–21,27,29] CI indicates confidence interval.

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

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.

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

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

Review Article

Pulmonary Circulation

Effects of exercise training on pulmonary hemodynamics, functional capacity and inflammation in pulmonary hypertension

Manuel J. Richter[1,*], Jan Grimminger[1,2,*], Britta Krüger[3], Hossein A. Ghofrani[1,4,5], Frank C. Mooren[6], Henning Gall[1], Christian Pilat[6] and Karsten Krüger[6]

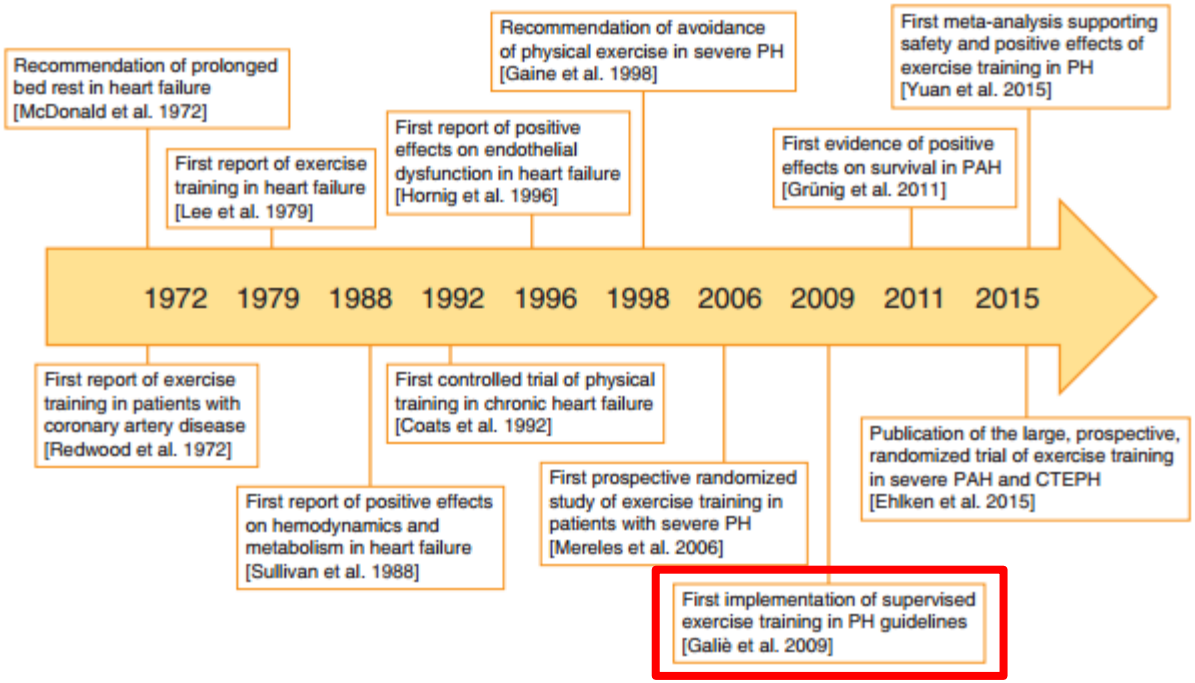

Fig. 1. Timeline of clinical evidence for exercise training in PH.
CTEPH,chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.

Training cardio-respiratorio in PAH: Guidelines 2015

Table of Contents

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CME **2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension**

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	

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IJCA-26901; No of Pages 7

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General measures and supportive therapy for pulmonary arterial hypertension: Updated recommendations from the Cologne Consensus Conference 2018

Ekkehard Grünig [a,*], Nicola Benjamin [a], Ulrich Krüger [b], Harald Kaemmerer [c], Satenik Harutyunova [a], Karen M. Olsson [d], Silvia Ulrich [e], Felix Gerhardt [f], Claus Neurohr [g], Armin Sablotzki [h], Michael Halank [i], Alberto M. Marra [a,m], Hans-Joachim Kabitz [j], Günther Thimm [k], Klaus-Günther Fliegel [k], Hans Klose [l]

Avoid pregnancy
I C

Influenza and pneumococcal immunisation
according to STIKO
I C

Psychological counselling
Frequent depression, anxiety disorders
I C

Supervised exercise training
IIa B to I A

Supplemental oxygen (during air travel and at altitudes >1500 metres above sea level)
IIa C

Regional anaesthesia
should be preferred over general anaesthesia whenever possible
IIa C

Comments: *Since the publication of the ESC/ERS guidelines, another randomised controlled trial [10] and several meta-analyses have been published [11–13] that confirm the positive effect of training in PH. Therefore, the evidence level should be upgraded from IIa B to I A, with the caveat that the involvement of a PH expert centre should be considered mandatory (Table 1).*

Training cardio-respiratorio in PAH e CTEPH

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]

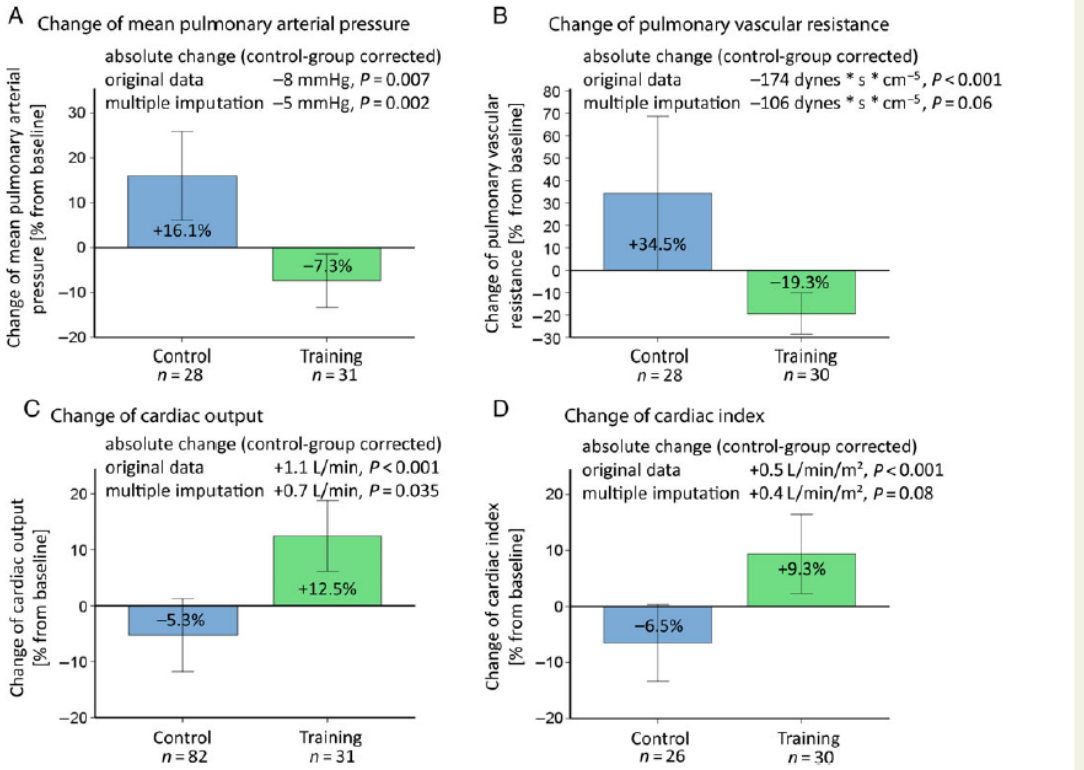


Figure 3 Secondary endpoints: haemodynamic function. Results from RHC for mean pulmonary arterial pressure (*A*), pulmonary vascular resistance (*B*), cardiac output (*C*) and cardiac index (*D*) at rest. The graphs depict the change of each parameter in per cent from baseline to 15 weeks after exercise training/no training. The mean changes of the training group, compared with baseline and control, as absolute values are given at the top of each graph with corresponding *P*-values of the ANCOVA for original data and multiple imputations. The bars are representing two times standard error.

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

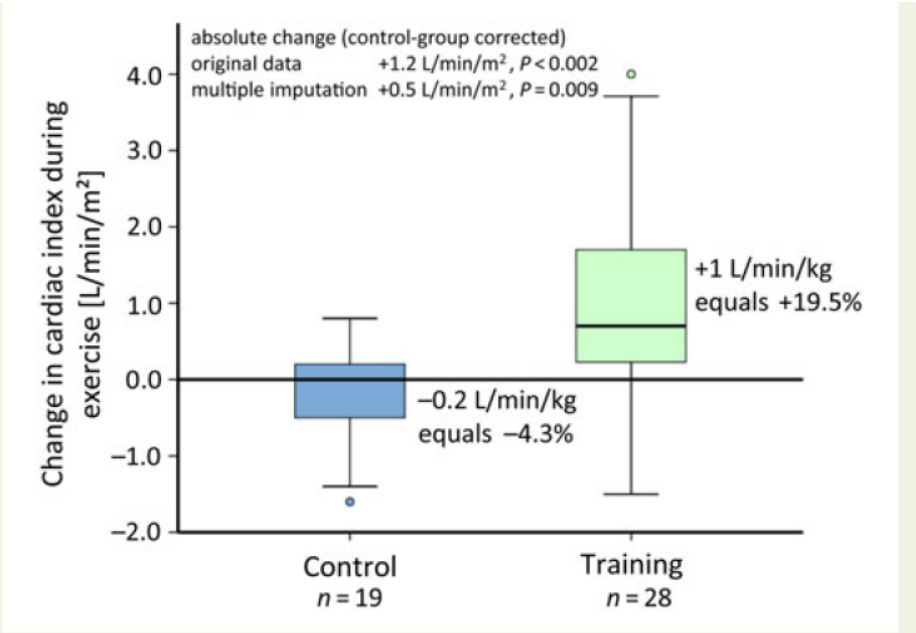
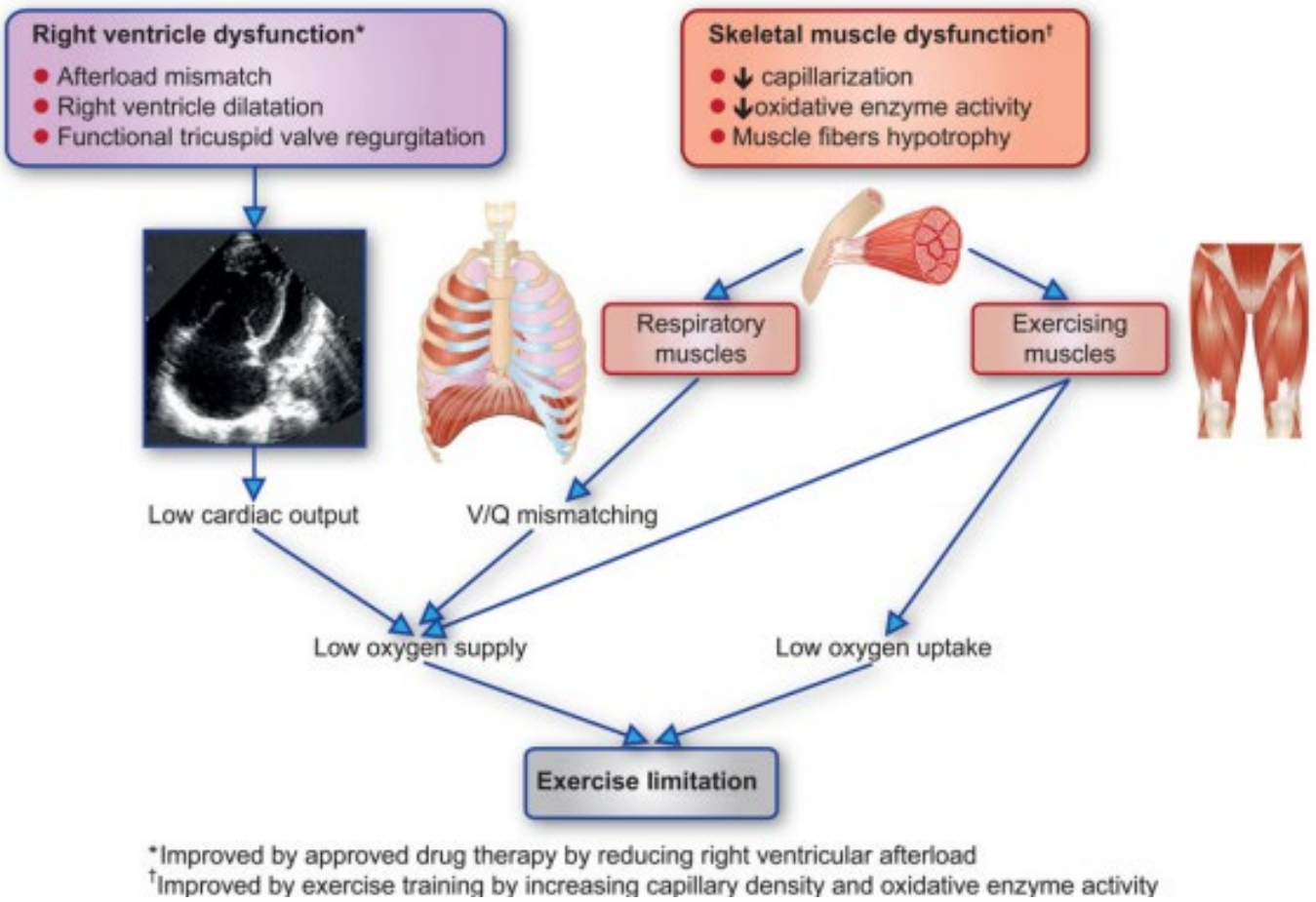


Figure 4 Haemodynamics during exercise. The distribution of absolute changes in CI during exercise ($P < 0.001$) is shown by a boxplot for each group. The training group improved CI by 19.5%, whereas the control group had a decrease of 4.3%. *P*-values are given for the ANCOVA for original data and multiple imputations.

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

Effetti del Training in PAH



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Galiè N et al. Eur Heart J 2016; 37; 45-48

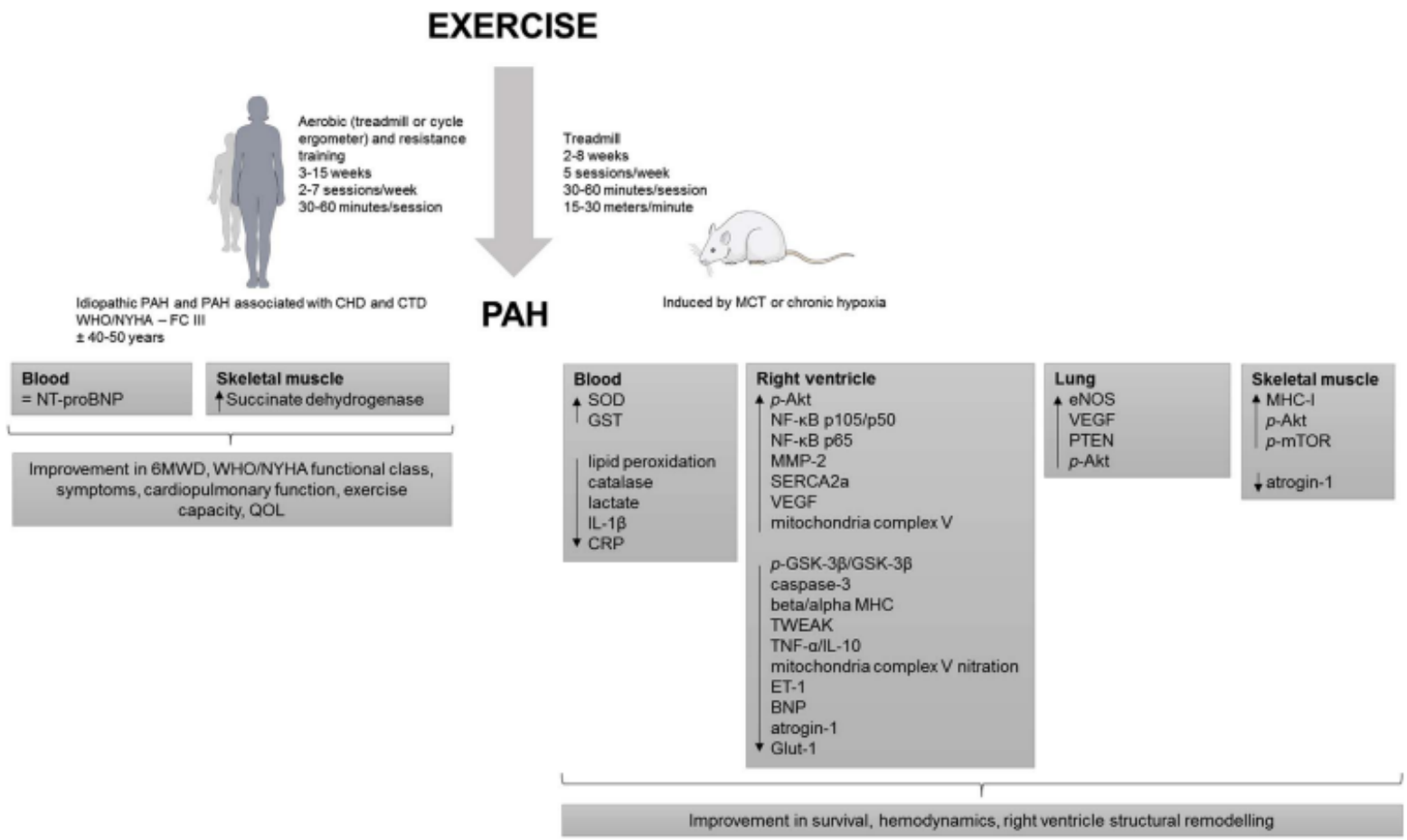

Fig. 2. Molecular changes underlying exercise training effects in pulmonary arterial hypertension patients and in experimental pulmonary hypertension. Figure made with Servier Medical Art. Legend: ↑, increase; ↓, decrease; = , no change; 6MWD, 6-min walk distance; CHD, congenital heart disease; CRP; C-reactive protein; CTD, connective tissue disease; eNOS, endothelial nitric oxide synthase; ET-1, endothelin-1; GSK-3β, glycogen synthase kinase-3β; GST, glutathione S-transferase; IL, interleukin; MCT, monocrotaline; MHC, myosin heavy chain; MMP-2, matrix metalloproteinase-2; mTOR, mammalian target of rapamycin; NT-proBNP, N-terminal-pro brain natriuretic peptide; NYHA – FC, New York Heart Association functional class; PAH, pulmonary arterial hypertension; *p*-GSK-3β, phosphorylated GSK-3β; PTEN, phosphatase and tensin homolog; QOL, quality of life; SERCA2a, sarco(endo)plasmic reticulum calcium-ATPase; SOD, superoxide dismutase; TNF-α, tumor necrosis factor-α; TWEAK, TNF-related weak inducer of apoptosis; VEGF, vascular endothelial growth factor; WHO – FC, World Health Organization functional class.

Nogueira-Ferreira R eta al. Respiratory Medicine 2018; 134; 70-78

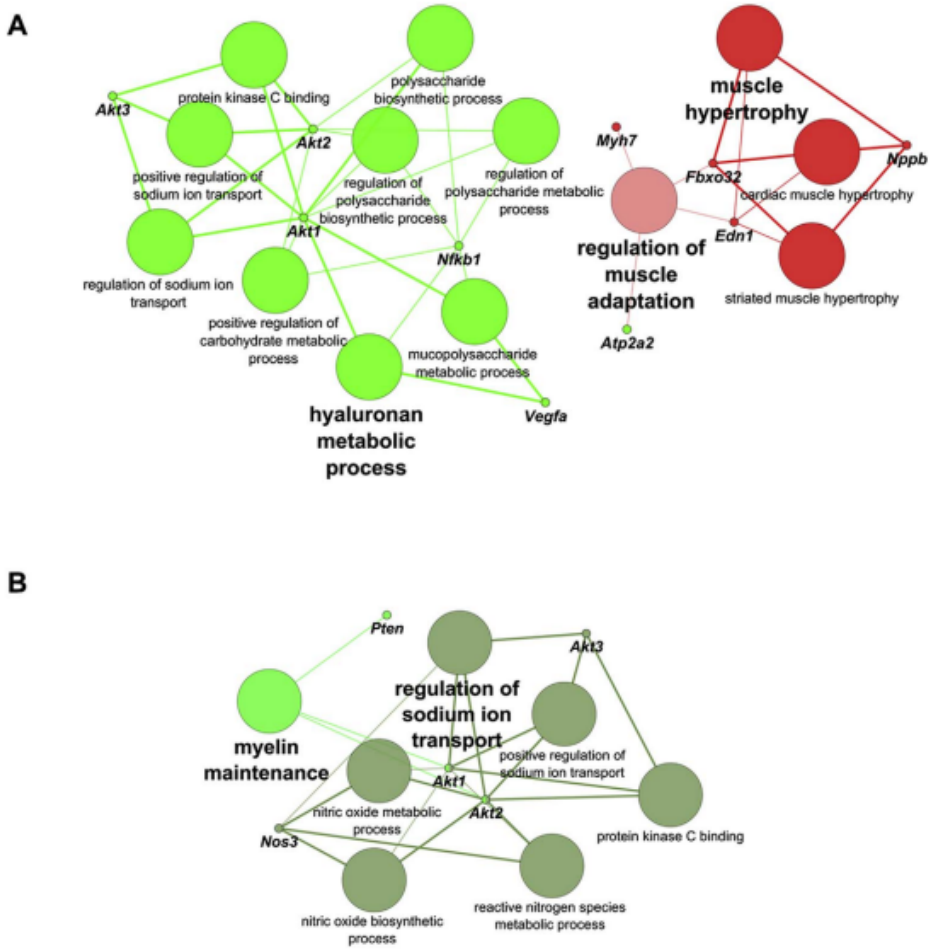

Fig. 1. Protein-protein interaction analysis considering the proteins described as up- and down-regulated in heart (A) and lungs (B) of rats with pulmonary hypertension submitted to exercise training. Green nodes represent the over-represented biological processes and red nodes refer to the ones under-represented. Release date: March 1, 2017. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

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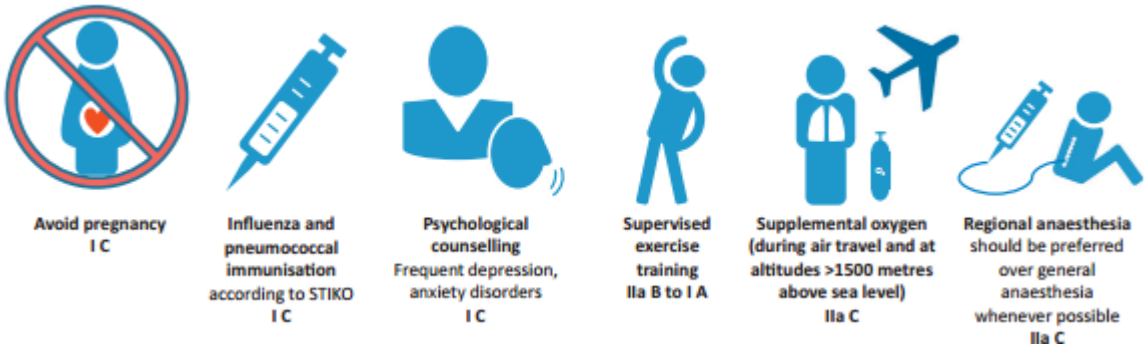

Avoid pregnancy
I C

Influenza and pneumococcal immunisation
according to STIKO
I C

Psychological counselling
Frequent depression, anxiety disorders
I C

Supervised exercise training
IIa B to I A

Supplemental oxygen (during air travel and at altitudes >1500 metres above sea level)
IIa C

Regional anaesthesia
should be preferred over general anaesthesia whenever possible
IIa C

Therefore, the evidence level should be upgraded from IIa B to I A, with the caveat that the involvement of a PH expert centre should be considered mandatory (Table 1).

Training cardio-respiratorio in PAH

Preliminary visit
- stable status (at least 2 months)
- optimal PAH therapy

Echocardiography at rest and ex
Contractile Reserve (Vdx)

Cardiopulmonary exercise test
- PeakVO2
- AT

Swiss Med WKLY 2017; 147:w14462

Training cardio-respiratorio in PAH

REVIEW
PULMONARY ARTERIAL HYPERTENSION

The role of cardiopulmonary exercise tests in pulmonary arterial hypertension

Stefania Farina[1], Michele Correale[2], Noemi Bruno[1,3], Stefania Paolillo[4], Elisabetta Salvioni[1], Roberto Badagliacca[5] and Piergiuseppe Agostoni[1,6], on behalf of the "Right and Left Heart Failure Study Group" of the Italian Society of Cardiology

Affiliations: [1]Centro Cardiologico Monzino, IRCCS, Milan, Italy. [2]Dept of Cardiology, University of Foggia, Foggia, Italy. [3]AOR S.Carlo, Dipartimento Cardiovascolare, Potenza, Italy. [4]IRCCS SDN, Istituto di ricerca diagnostica e nucleare, Naples, Italy. [5]Dipartimento di Scienze Cardiovascolari, Respiratorie, Nefrologiche, Anestesiologiche e Geriatriche, "La Sapienza" University of Rome, Rome, Italy. [6]Dept of Clinical Sciences and Community Health (Cardiovascular Section), University of Milan, Milan, Italy.

Correspondence: Piergiuseppe Agostoni, Dept of Cardiovascular Sciences, Centro Cardiologico Monzino, IRCCS, via Parea 4, Milan 20138, Italy. E-mail: piergiuseppe.agostoni@ccfm.it

@ERSpublications
CPET provides valuable information on diagnosis, prognosis and therapy in PAH but it should be performed by experts http://ow.ly/q5O230j6hta

Cite this article as: Farina S, Correale M, Bruno N, *et al.* The role of cardiopulmonary exercise tests in pulmonary arterial hypertension. *Eur Respir Rev* 2018; 27: 170134 [https://doi.org/10.1183/16000617.0134-2017].

Training cardio-respiratorio in PAH

Table 2: Safety precautions and adverse effects of exercise training in pulmonary arterial hypertension (PAH).

Safety precautions	
Inclusion of stable patients on optimised PAH targeted therapy and without signs of heart congestion after a thorough assessment in an expert centre	
Intensively supervised start of the exercise programme, if possible in an in-hospital setting	
Continuously supervised exercise training by experts	
Avoidance of exhausting exercise (low workload ; training range between 40 and 80% of peak exercise capacity)	< 120 bpm
Adequate oxygen supplementation; avoidance of deep desaturation	> 85-90%
Dumbbell training of single muscle groups with low weights	
Potential adverse effects to be considered and immediately treated	rari
Respiratory infections	
Presyncope, syncope, dizziness, hypotension	
Arrhythmias	
Haemoptysis	

Swiss Med WKLY 2017; 147:w14462

Training cardio-respiratorio in PAH

Exercise Training Program

- 15 weeks (3 in-)

Interval bicycle training (1/2-1 minute)

- 10-25 minute
- 60-80% HR
- High limit: 120 bpm or SatO2 85%
- 7 d/week

Walking

- Mental training

Resistance training

- Dumbbell training with low weights (500-1000 g)

Respiratory training

- Streching, breathing techniques, yoga, strengthening of respiratory muscles

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Mereles D et al. Circulation 2006; 114: 1482-9

Training cardio-respiratorio in PAH

Exercise Training Program

- 4 weeks out

Aerobic Training (bike or treadmill)

- 30 minutes
- AT (start at 50%)
- High limit: 70% HR max or SatO2 90% or Borg 5
- 5 d/week

Resistance training

- Dumbbell training with low weights (500-1000 g)

Respiratory training

- Inspiratory muscle training, slow breathing sessions

Muscle relaxation

Psychological Intervention Sessions

Bussotti et al. Cardiovasc Hematol Disord Drug Targets 2017; 17: 3-10

Training cardio-respiratorio in PAH

International Journal of Cardiology 259 (2018) 178–182

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Physiological insights of exercise hyperventilation in arterial and chronic thromboembolic pulmonary hypertension☆

Stefania Farina [a,1], Noemi Bruno [a,1], Cecilia Agalbato [a], Mauro Contini [a], Roberto Cassandro [c], Davide Elia [c], Sergio Harari [c], Piergiuseppe Agostoni [a,b,*]

[a] Cardiology Department, Centro Cardiologico Monzino IRCCS, Milan, Italy
[b] Department of Clinical Sciences and Community Health, Cardiovascular Section University of Milan, Milan, Italy
[c] Unit of Pneumology and Respiratory Semi - Intensive Care Unit, Respiratory Pathophysiology and Pulmonary Hemodynamics Service, San Giuseppe Hospital, Multimedica IRCCS, Milan, Italy

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 already on combination therapy. However, t is highly subject to a "learning effect", eve training regimen, and the 6-min walk trials have typically been much greater th subsequent double-blind trials [4]. Furth 50 m or more have been observed in pla 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 hold a PH Special Olympics.

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…grazie per l’attenzione.