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REVIEW

Acute and chronic exercise training in patients with Class II pulmonary hypertension: effects on haemodynamics and symptoms

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Abstract

More than half of heart failure (HF) patients have concomitant pulmonary hypertension, impacting symptoms and prognosis. The role of exercise in this category of patients is still unclear, probably because of the lack of a clear relationship between exercise and acute and chronic pulmonary artery pressure variations and related changes in symptoms. The limited evidence on this topic is contradictory and hardly comparable due to use of different exercise programmes and pulmonary artery pressure assessment techniques. This is further compounded by different functional and structural classes of HF making definite assessments and interpretations of exercise effect on outcomes difficult. Exercise training programmes were proven beneficial in HF patients; however, the lack of data about their pulmonary haemodynamic effects prevents clear indications on the best exercise types for patients presenting secondary pulmonary hypertension and different HF categories. Indeed, some data suggest that not all HF patients have similar responses to training, leading to either beneficial or detrimental effects, depending on the HF type. Future studies, involving modern technologies such as continuous pulmonary artery pressure monitoring implantable devices, may clarify the current gaps in this field, aiming at patient-tailored exercise training rehabilitation programmes, in order to improve clinical outcomes, quality of life, and hopefully prognosis.

Keywords Heart failure programmes; Pulmonary hypertension; Exercise; Implantable monitors

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Introduction

Pulmonary hypertension (PH) due to left-side heart failure (HF) (Class II according to last European guidelines[1]) is defined as a mean pulmonary artery pressure (PAP) $\geq$ 25 mmHg and a pulmonary artery wedge pressure (PAWP) $>$ 15 mmHg, measured by right heart catheterization (RHC).[1] Its prevalence among HF patients proportionally increases with the severity of functional impairment, peaking at 60% of patients presenting HF with reduced ejection fraction (HFrEF) and at 70% of those with HF with preserved ejection fraction (HFpEF).[1] Symptoms are insidious, and 70% of patients at the time of diagnosis are already in New York Heart Association (NYHA) functional Class II–III.[2]

The benefits [i.e. symptoms improvement, higher exercise tolerance, and better quality of life (QoL)] of exercise training in presence of any type PH are suggested by mostly uncontrolled clinical experiences and may be linked to several mechanisms, involving lungs, heart, circulating blood, and peripheral musculature.

A reduction in pulmonary arterial resistance has been described at a pulmonary level; an improvement of right ventricular (RV) systolic function following positive remodelling was reported at cardiac level; an increase of vasodilator molecules and a reduction of inflammatory cytokines were

observed at molecular level; and an improved strength of respiratory and peripheral muscles was described at the musculature level.[3]

This leads to multiple effects; among them, PAP changes are considered one of the most easily assessable and correlated to patients' symptoms.

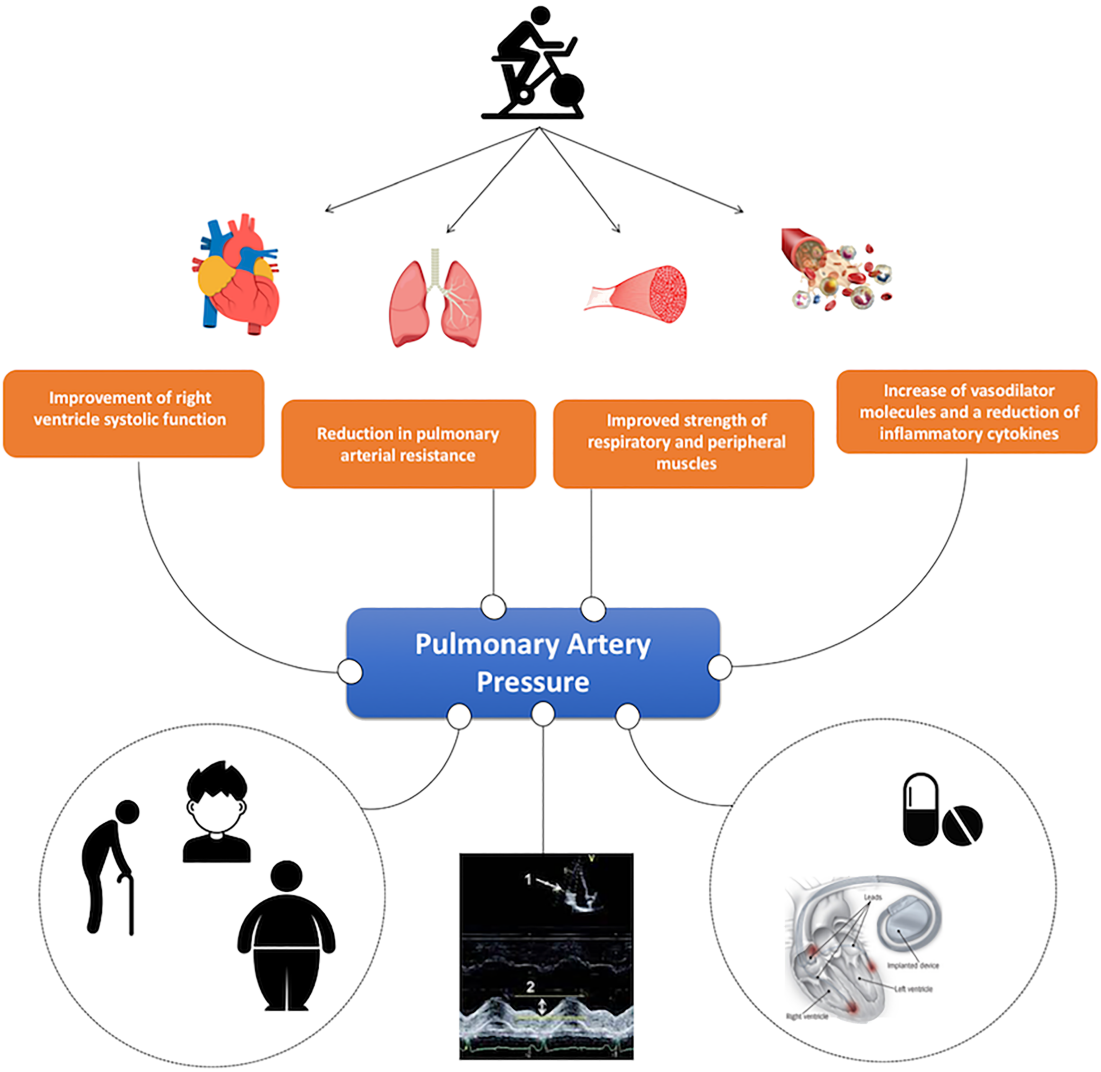
However, PAP measurement and its clinical association may be biased by various factors, which should be considered to properly interpret PAP changes during exercise and over time (*Figure 1*):

1 PAP proportionally increases with cardiac output during exercise; therefore, PAP measurement should be coupled with flow measurement.
2 PAP is affected by body position and this should be considered during measurement.
3 Baseline conditions (i.e. age categories, obesity, PH therapies, and cardiac resynchronization therapy[4]) influence PAP response to exercise and should be taken into account during investigations.

Physical activity was discouraged for long time in patients presenting with PH not because of left-side HF but because of the fear of acute RV decompensation and subsequent symptoms worsening.[5] This belief is currently changing in favour of strictly supervised and patient-tailored exercise training programmes. Supervised training has recently demonstrated to be safe in the acute setting, as well as potentially offering long-term benefits, as an add on to the medical therapy.[6–9]

Similar speculation are not available for patients with Class II PH, and exercise training has been recommended for HF

Figure 1 Interplay between exercise and patient's characteristics on pulmonary artery pressure variations.



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patients regardless the presence and severity of related PH (Class IIA),[10,11] without sufficient scientific evidence.

Also, due to the lack of concern for aforementioned aspects, evidence about exercise training for HF patients with PH seems still poor and inadequate to dictate clear indications.

The present review aims to synthetize the current knowledge and/or limitations regarding the acute and chronic effects of exercise on pulmonary haemodynamics in left-side HF patients with PH, particularly focusing on their association with symptoms, different types of HF, and different types of training protocols.

Acute exercise effects on pulmonary artery pressure and symptoms

Although first studies addressing the relationship between pulmonary haemodynamic and exercise-induced symptoms go back to decades ago, many uncertainties still exist nowadays (*Table 1*).

In a prospective observational study, Gibbs *et al*. reported the association between PAP changes and symptoms in nine HF patients during maximal (treadmill and bicycle) and submaximal (walking up/downstairs and on a flat surface) exercise tests, thorough a 24 h invasive monitoring.[12] Baseline pressure measurements were taken in standing position. Maximal PAP was observed during treadmill (59.4 ± 26.1 mmHg), followed by bicycle, walking up/downstairs, and on a flat surface (54.9 ± 30.6, 52.5 ± 26.1, and 43.5 ± 23.9, respectively). Breathlessness was the principal symptom causing exercise limitation. Interestingly, the smallest PAP increases were associated with the mildest symptoms, although the contrary was not proven.

Authors hypothesized that breathlessness could be explained by an increase in pulmonary physiologic dead space, itself caused by ventilation-perfusion mismatch, only partially determined by PAP variations.

Similarly, Fink *et al*. toned down the role of PAP on exertional symptoms. While investigating the effect of PAWP lowering by vasodilators in 38 HF patients during maximal bicycle exercise, they found no relationship between acute PAWP variations and symptoms changes.[13]

More recently, several investigations offered opposite insights, claiming a role for exercise-induced PAP variations on symptoms onset.

Assessing PAP values at rest and during bicycle exercise by echocardiography (semi-supine position) in 46 HF patients, Tumminello *et al*. reported similar incidence of exertional dyspnoea in patients with and without moderate to severe PH at baseline (40% vs. 44%, P = non-significant). On the contrary, patients presenting systolic PAP $>$ 60 mmHg at peak exercise were more frequently limited by dyspnoea (70% vs. 27%, P = 0.0001).[14] A potential physio-pathological explanation of such an association lies in the overwhelming of the compensatory mechanisms in HF patients during exercise, leading to an acute rise in left atrial pressure transmitted to the pulmonary circulation, generating exercise-limiting dyspnoea and PAP increase.[18]

Another non-invasive study shed light on the hypothesized relationship between exercise-induced PAP increase and symptoms. Bandera *et al*.[15] investigated this association evaluating the functional capacity during cardiopulmonary testing in HF patients, expressed as the rate of VO_2 increase as related to work rate ($\Delta VO_2/\Delta WR$). The lack of a linear increase of such a ratio represents a common indicator of impaired functional capacity and reflects the exercise-induced exhaustion. One hundred thirty-six patients underwent exercise testing combined with exercise echocardiography. Of these, 36 presented a flattening of $\Delta VO_2/\Delta WR$, and exercise systolic PAP was found as independent predictor of this alteration (odds ratio = 1.06; confidence interval = 1.01–1.11; P = 0.01). Specifically, among this subgroup, exercise-induced systolic PAP was 61 ± 19 mmHg, compared with 51 ± 18 mmHg in those presenting a normal functional capacity ($P < 0.01$).

The link between exercise-induced PAP rise and symptoms was furthermore reinforced by a large prospective study, investigating 406 HF patients through an invasive haemodynamic assessment during maximum cardiopulmonary exercise testing.[16] Of these, 255 underwent testing for effort dyspnoea of uncertain aetiology. The investigators found that

Table 1 Available data of association between exercise-induced pulmonary artery pressure changes and symptoms in heart failure patients

Study	Sample size	Exercise	PAP assessment	Association between exertional symptoms and PAP changes
Gibbs *et al*.[12]	9	Treadmill, bicycle, walking up/downstairs, and on a flat surface	24 h RHC	Smallest PAP increases associated with mildest symptoms
Fink *et al*.[13]	38	Bicycle	RHC	No
Tumminello *et al*.[14]	46	Bicycle	Doppler	Yes
Bandera *et al*.[15]	136	Cardiopulmonary test	Doppler	Yes
Tolle *et al*.[16]	255	Cardiopulmonary test	RHC	Yes
Wright *et al*.[17]	38	Cyclo-ergometry	RHC	Yes

PAP, pulmonary artery pressure; RHC, right heart catheterization.

among them, exercise-induced PH (mean PAP greater than 30 mmHg at peak of exercise) was the most common cause.

Similarly, a retrospective study by Wright *et al*., including 38 patients complaining exertional dyspnoea and underwent RHC during exercise testing, confirmed the occurrence of exercise-induced PH in most of them (24 out of 38).[17]

The inconsistency of available data shows an unclear understanding of exercise PAP variations and their association on exertional symptoms. Several limitations concur to this fact: inclusion of different patient phenotypes, lack of standardized methods of PAP assessment (i.e. technique and patient position), and multiple influencing factors not considered.

Studies assessing the acute effects of exercise on pulmonary haemodynamic and related symptoms in HF patients with PH are needed, to clarify when the risks exceed the benefits and therefore to select patients who better fit for training programmes.

Acute exercise effects on pulmonary artery pressure in different subtypes of heart failure patients

Different subtypes of HF patients [HFpEF, HF with mid-range ejection fraction (HFmrEF), and HFrEF] may present multiple responses to exercise. Maréchaux *et al*.,[19] investigating exercise-induced PH in patients with HFrEF, offered also interesting echocardiographic characteristics of this group. In the study, 85 patients [mean left ventricular (LV) ejection fraction 26 ± 8%] underwent symptom-limited exercise, on a semi-recumbent and tilting bicycle ergometer with a 20 W/3 min step protocol starting from 25 W. Exercise-induced changes in systolic PAP showed a highly individual variability, but overall systolic PAP increased from a baseline value of 27 ± 9 to 43 ± 18 mmHg at exercise peak ($P < 0.001$). Of note, in this category of patients, changes were unrelated to PAP at rest ($r = -0.08$, $P = 0.45$). In contrast, other echocardiographic parameters were found associated with exercise-induced PAP changes: (i) lower Δ-LV end-systolic volume at the exercise peak ($P = 0.029$), (ii) higher Δ-left atrium area at the exercise peak ($P = 0.007$), (iii) resting intra-LV asynchrony ($P = 0.042$), and (iv) resting higher tricuspid annular plane systolic excursion (TAPSE) ($P < 0.0001$). These findings are common characteristics of hearts with reduced ejection fraction and may directly explain the observed exercise-induced increase of PAP: a lower contractile reserve, represented by small Δ-LV end-systolic volume, leads to greater systolic PAP rise during exercise due to increased backward pressure; the reduced LV systolic phase efficiency produced by myocardial asynchronism lowers transmitral force closure especially during exercise and thereby exacerbates functional mitral regurgitation leading to systolic PAP increase; and lastly, the acute rise in left atrium size may derive from the impaired LV diastolic function, resulting in pulmonary congestion and thereby systolic PAP increase.

Further highlights within this category derive from a prospective study that aimed to investigate the pulmonary vascular resistance (PVR) patterns in relation to exercise in HFrEF.[20] Forty patients with mean PAP $\geq$ 25 mmHg, PAWP $>$ 15 mmHg, and cardiac index $<$ 2.5 L/min·m^2 were enrolled in this study. Patients underwent symptom-limited supine bicycle testing initially during continuous administration of sodium nitroprusside (SNP) and afterwards (after 1 day) during oral decongestive therapy (diuretics, renin–angiotensin system blockers, and hydralazine). The authors reported a dynamic exercise-induced PVR increase $>$3.5 Wood units in 19 patients (48%) under oral therapy vs. 5 (13%) under SNP. In 18 patients under oral therapy, PVR decreased during exercise. Most of the patients presenting a PVR increase had mixed PH (15/19), while only 4 had post-capillary PH. In addition, PVR increase was associated with a 33% decrease in RV stroke work index, partially attenuated by administration of SNP.

According to these data, HFrEF patients with mixed PH may not benefit from exercise training programmes, which might even worsen their haemodynamic status.

So far, the only study directly comparing exercise-induced PAPs changes between HFrEF and HFpEF patients was conducted by Obokata *et al*.[21] Eighty patients (HFpEF = 37 and HFrEF = 43) underwent echocardiography at rest and during 10 W of bicycle exercise. Exercise-induced PH was defined as an estimated systolic PAP of ≥50 mmHg at peak exercise. PAP was significantly increased during exercise in both HF phenotypes, but exercise-induced PH was more frequently observed in HFpEF compared with HFrEF (51% vs. 19%, $P = 0.004$). The authors also investigated other echocardiographic parameters aiming at describing potential different patho-physiologic mechanisms characteristic of the two HF phenotypes. In particular, they evaluated the ventricular–arterial coupling (the interaction of the heart and artery), as the ratio of Ea (effective arterial elastance) to Ees (end-systolic elastance), Ea/Ees. The Ea/Ees ratio decreased significantly (normal response) from rest to 10 W exercise only in HFrEF patients. HFpEF patients showed an attenuated per cent reduction in Ea/Ees compared with HFrEF (−6.4 [−12.8 to 10.2] % vs. −18.8 [−33.0 to −0.1] %, $P = 0.004$) because of a lower per cent increase in Ees (17.1 [−13.4 to 40.9] % vs. 32.4 [13.9 to 63.5] %, $P = 0.027$). In addition, the per cent change in systolic PAP during exercise was significantly associated with Ea/Ees ($r = 0.33$, $P = 0.047$) only in patients with HFpEF. These findings suggest an abnormal ventricular–arterial coupling response in patients with HFpEF, which could be explained

by an abnormal vasodilatation and limited contractility during exercise. Its correlation with more frequent development of exercise-induced PH might derive from elevation of LV filling pressure in HFpEF, but evidence is still lacking.

Whether these findings turned into a clinical worsening with exercise for HFpEF patients has not yet been investigated and remains unclear.

Does pulmonary hypertension impact heart failure prognosis?

Changes in pulmonary haemodynamic as well as secondary RV dysfunction have demonstrated major determinants of outcome in HF.

Kjaergaard *et al*.[22] investigated 388 patients with HFpEF or HFrEF, who were followed up to 5.5 years. Increased pulmonary pressure was associated with higher short-term and long-term mortality. Five-mmHg increase in RV systolic pressure was related with 9% increase in mortality. Another study including 701 HF patients[23] showed that those with combined pre-capillary and post-capillary PH had the worst long-term cardiac outcome. Gavazzi *et al*.[24] investigated 205 patients with HF, followed up for 2 years. RV ejection fraction was one of the independent predictors for both survival and event-free cardiac survival. Similarly, Ghio *et al*. found that PAP and RV ejection fraction were independent prognostic predictors in 377 HF patients with a median follow-up of 17 months.[25] Also, other echo-derived RV function measurements, such as TAPSE, were associated with clinical outcome in HFrEF and HFpEF populations.[26]

Chronic effects of exercise training for heart failure patients with pulmonary hypertension

Exercise training has been accepted as an important therapeutic method in HF patients due to its clinical benefits regarding exercise tolerance, QoL, and prognosis. Training programmes that have been investigated in HF include moderate-intensity aerobic exercise training, high-intensity aerobic interval exercise training, resistance exercise training, and inspiratory muscle training.[27] Summary of different exercise training programmes are shown in *Table 2*.

However, the majority of studies assessing the long-term effects of exercise training in HF patients did not report specific pulmonary haemodynamic data before and after the training programmes, making hard to draw conclusions on the positive or negative effects of exercise and its types in this subcategory of patients.

One of the largest RCTs (Efficacy and Safety of Exercise Training in Patients With Chronic Heart Failure: HF-ACTION trial)[28] compared aerobic training (walking, treadmill, or stationary cycling) vs. usual care in 2331 HF patients. The study showed that exercise training was associated with modest significant reductions for both all-cause mortality or hospitalization, and cardiovascular mortality or HF hospitalization. Unfortunately, the authors did not report information about the proportion of patients with concomitant PH, nor additional endpoint analysis were done with this aim.

Similarly, a comprehensive systematic review including 33 studies, and 4740 HF patients, reported a trend towards a reduction in mortality with exercise training after 1 year of follow-up, as well as the rate of HF-related hospitalization

Table 2 Summary of exercise training programmes in pulmonary arterial hypertension due to left-side heart failure (adapted from Ross Arena, *et al*., 'Exercise Training in Group 2 Pulmonary Hypertension: Which Intensity and What Modality', *Progress in Cardiovascular Diseases*)

Exercise training type	General prescription types	Training mode
Aerobic: Moderate intensity	3–7 days/week 30–60 min/day (accumulated or continuous) 50–85% of maximal aerobic capacity	Walking/treadmill Lower extremity ergometer Elliptical Combination of above
Resistance: Moderate intensity	2–3 days/week 1 set 10–15 repetitions per set 8–10 exercises; preferably multi-joint (e.g. bench press and hip sled) Alternate upper and lower body exercise	Cable weight systems Free weights Bands
Inspiratory muscle	1–2 times/day 15–30 min per session 3–7 days/per week ≥30% of maximal inspiratory pressure	Handheld, threshold load trainer

and improved QoL.[11] Still, the potential impact of concomitant PH was neither disclosed nor investigated.

A recent study including 42 patients with HFpEF suggested that sub-maximal exercises of short duration may improve pulmonary vascular haemodynamic both at rest and during repeat exercise. The exercise used in the study consisted in supine cycle ergometry, conducted at 60 rotations per minute at a 20 W workload for 5 min. Mean PAP at rest were reduced from 32 to 28 mmHg ($P < 0.001$). Also during following exercises, PAWP increase was markedly attenuated compared with the first exercise.[29]

Given the little evidence on the long-term impact of different exercise training in HF patients with PH, some input may derive from studies involving other PH classes.

Tran *et al*.[30] investigated the effects of a specific exercise type (inspiratory muscle training) in PH patients. A total of 12 patients were enrolled and randomized to training or control group. The training group performed two cycles of 30 breaths at 30–40% of their maximal static inspiratory pressure 5 days a week for 8 weeks. By 8 weeks, patients of training group had significantly improved 6 min walk distance, while the pVO_2 was similar between groups. Ehlken *et al*.[31] investigated the impact of aerobic exercise associated with respiratory training at 4–7 days/week. A total of 87 patients were followed up to 15 weeks. Peak VO_2/kg and haemodynamic parameters were improved in the training group.

Besides the clinical evidence, another study[32] compared the high-intensity interval training with continuous exercise training programmes in mild PH rats. The continuous training group showed better haemodynamic and ameliorated RV hypertrophy.

Nevertheless, we should be aware of the physio-pathological differences between PH categories that prevent to generalize these results to HF patients.

These findings may help researchers to promote dedicated studies focused on Class II PH patients, aiming at answering the questions: is exercise training safe and effective for HF patients presenting abnormal PAP? What level of training programmes are beneficial in the presence of PH?

Considering that most of HF patients present with PH, and previous studies revealed exercise training as effective and safe on long term, we might expect benefits also in the pulmonary haemodynamics of these patients. However, at a first sight, more cautious programmes (i.e. short duration but constant, moderate-intensity aerobic exercises; respiratory muscles training) might represent better solutions for this category of patients.

Although physical training represents a very attractive treatment modality in this field, we must bear in mind that cannot replace the pharmacological approach, which remains the essential component of HF and secondary PH treatment. Also, it is worth to mention that in the subgroup of Class II PH, the use of therapies specifically designed for primary PH treatment (i.e. prostanoids, endothelin receptor antagonists, or phosphodiesterase type 5 inhibitors) is not supported by enough scientific evidence and should be not considered as first-line option. In contrast, the core treatment addressing PH due to left-side HF includes improvement of HF global management, with particular attention to the optimization of volume status. Some patients may also benefit from aspecific vasodilators, such as nitrates and hydralazine, but evidence is still limited.[1] The addition of physical rehabilitation programmes should be considered on the top of an optimized medical treatment first.

Limitations and future perspectives

Many studies agree on the beneficial effects of rehabilitation training programmes for patients suffering from HF, aiming to improve symptoms and their QoL. However, the lack of proper methodology and dedicated studies focusing on different exercise types and HF categories in presence of PH still prevents the routine implementation of such programmes in the clinical practice.

Current knowledge is based on a wide mix of patients, who were on different therapies, and mostly evaluated during a single exercise test, preventing to draw any conclusion.

Future researchers should pose attention to the multiple factors potentially affecting PAP that may nullify their investigations. Understanding the relationship between exercise and symptoms cannot be limited, in fact, to the mere PAP measurements. Precise evaluation of other symptoms determinants is mandatory to have a comprehensive physio-pathological picture. For instance, a proper assessment of RV function is crucial to investigate the RV–pulmonary arterial coupling that might be better related to symptoms than the only PAP. In addition, the correct stratification of patients according to their demographic, pathological characteristics, and therapies is essential to provide right solutions.

Taking into account such needs, the PAP role in such a context deserves dedicated diagnostic techniques, able to catch its continuous variations, before, during, and after any physical activity (*Table 3*).

With this regard, interesting technologies have been recently developed. In 2014, the CardioMEMS™ HF System (Abbott, USA) was approved in the USA for its usage in HF patients. The device is a wireless and battery-less pressure sensor, percutaneously implanted distally in the left pulmonary artery, allowing a continuous monitoring of the PAP changes. The system has been proven through clinical trial

Table 3 Conventional vs. new monitoring technique for pulmonary artery pressure

Techniques	Advantages	Limitations
Conventional		
Chest X-ray	Less invasive Reproducible Information about potential lung-related causes of PH	No precise measurements of PAP No during exercise Radiations Only indirect signs of PH Not useful at early stages or normal PAP
Electrocardiogram (RV alterations)	Non-invasive Reproducible	No precise measurements of PAP Only indirect sign of PH Not useful at early stages or normal PAP
Echocardiogram	Non-invasive Both at rest and during exercise RV and LV size and function	Inter-operator and intra-operator variability Dependent on images quality Indirect PAP measurements Not feasible during all exercise types Only instantaneous PAP values
Cardiopulmonary test	Non-invasive Simultaneous assessment of cardiac (ECG/echocardiogram) and pulmonary function RV and LV size and function	Not feasible during all exercise types Patient compliance required
Right heart catheterization	Direct and precise PAP assessment Measurements of all right-side pressures (RA, RV, PAP, PAWP) Additional testing allowed (i.e. cardiac output) Drug tests allowed Both at rest and during exercise	Invasive Not feasible during all exercise types Only instantaneous PAP values
New		
Implantable PAP sensor	Accurate PAP measurements (= RHC) Continuous monitoring PAP assessment at rest, during any exercise type, and daily activities Immediate measurements reading Telemedicine Battery-less Association of vital signs monitoring	Invasive implantation procedure Ongoing studies PAP values only Costs

LV, left ventricular; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; RA, right atrium; RHC, right heart catheterization; RV, right ventricular.

to reduce HF hospitalizations and mortality, as well as improve QoL for HFrEF and HFpEF patients.[33,34]

Similarly, in 2019, Endotronix (USA) has started the SIRONA II Trial (NCT04012944), aiming to obtain the CE mark for the Cordella Pulmonary Artery Pressure Sensor. The Cordella device implements a similar technology to the CardioMEMS system. However, it offers different advantages for the patients: it has a handheld reader, allowing the patients not to lay down during the sensor reading; and it can be used along the pressure sensor, so that physicians can monitor, in addition to PAP, the systemic blood pressure and heart rate. The initial experience of the Cordella device has been recently described in the SIRONA first-in-human study. The technique, incorporating comprehensive vital signs and PAP monitoring, enabled safe and accurate monitoring of HF status.[35] Moreover, it allowed precise PAP measurements, comparable with those obtained with RHC (primary efficacy endpoint of a mean PAP met in all patients with a cohort difference of 2.7 mmHg; Cordella Sensor 22.5 ± 11.8 mmHg, Swan–Ganz catheter 25.2 ± 8.5 mmHg).

These extraordinary technologic advances are offering a unique opportunity to overcome some of the limitations encountered during previous studies.

Therewith, the long-term monitoring of exercise-induced PAP changes may also help to guide therapy and to assess its effect over time.[4]

Conclusions

Continuous monitoring of PAP, both at rest and during exercise, could clarify the immediate and long-term haemodynamic changes, and related symptoms or clinical benefits, deriving from different types of exercises in different subtypes of patients.

These data, combined with other essential pathophysiological factors, might help to identify patient-tailored exercise training rehabilitation programmes, in order to improve clinical outcomes, QoL, and hopefully prognosis.

Conflict of interest

W. Wijns reports institutional research grants from Terumo, MiCell, and MicroPort; honoraria from MicroPort; and be-

ing a medical advisor of Rede Optimus Research and co-founder of Argonauts, an innovation accelerator. P. W. Serruys reports personal fees from Biosensors, MiCell Technologies, Sino Medical Sciences Technology, Philips/Volcano, Xeltis, and HeartFlow, outside the submitted work. The other authors have no conflicts of interest to declare.

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