Pulmonary arterial hypertension-related myopathy: An overview of current data and future perspectives

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Abstract Background and aim: Exercise intolerance is one of the key features of pulmonary arterial hypertension (PAH). The main determinants of exercise impairment include hypoxemia, reduced right ventricular output, perfusion/ventilation mismatch, and weakness of skeletal and breathing muscles. The aim of the current review is to describe the findings in the existing literature about respiratory and muscle dysfunction in PAH. Animal and clinical studies regarding both respiratory and peripheral skeletal muscles and the effect of exercise training on muscle function in PAH patients are analyzed.

Data synthesis: PAH myopathy is characterized by reduced skeletal muscle mass, reduced volitional and non-volitional contractility, reduced generated force, a fiber switch from type I to type II, increased protein degradation through ubiquitin–proteasome system (UPS) activation, reduced mitochondrial functioning, and impaired activation–contractility coupling. Increased inflammatory response, impaired anabolic signaling, hypoxemia, and abnormalities of mitochondrial function are involved in the pathophysiology of this process. Exercise training has been shown to improve exercise capacity, peak oxygen uptake, quality of life, and possibly clinical outcomes of PAH patients.

Conclusions: The skeletal muscles of PAH patients show a wide spectrum of cellular abnormalities that finally culminate in muscle atrophy and reduced contractility. Exercise training improves muscle function and bears a positive impact on the clinical outcomes of PAH patients.

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Introduction

The detrimental effects of increased catabolism on muscle homeostasis secondary to chronic illness often result in muscle wasting [1]. Under physiological circumstances, the skeletal muscle comprises almost 40–50% of body mass, and is responsible for up to 30% of resting oxygen consumption [2]. In this regard, it is important to stress that not only is muscle tissue merely a deputy to movements or contraction but it also plays a key role in metabolism as a reservoir of energetic substrates for the whole body.

Exercise impairment is a key feature of pulmonary arterial hypertension (PAH). It was traditionally attributed to low cardiac output or respiratory dysfunction. However, several studies highlighted a wide array of abnormalities of both skeletal [3–5] and respiratory muscles [6,7] in PAH
patients that may contribute to the occurrence of PAH-related exercise limitation. Muscle wasting and weakness in PAH present with the following features: a switch from “resistant” fiber I type to “fast” type II fiber, reduced muscle capillary density, lower aerobic enzyme activity, impaired mitochondrial biogenesis/function, and increased muscle protein degradation mediated by the ubiquitin–proteasome system (UPS), mitochondrial abnormalities, and altered excitation–contraction coupling [4,5]. The degree of muscle dysfunction correlates with exercise impairment of PAH patients [3–5] and can be improved by exercise training [8,9]. Exercise training has been shown to improve 6-min walking distance (6MWD), exercise capacity, quality of life (QoL), peak oxygen consumption, and possibly outcomes of PAH patients [10,11], and for this reason it is regarded as an important add-on to medical therapy.

The aim of the current review is to describe the findings in the existing literature about respiratory and muscle dysfunction in PAH. Animal and clinical studies regarding both respiratory and peripheral skeletal muscle and the effect of exercise training on muscle function in PAH patients are also reviewed. A review of the available literature until the end of April 2014 was performed in “PubMed” and “Web of Science” databases by two independent investigators (A.M.M and M.A.). In order to find relevant articles, we combined each of the following the keywords “skeletal muscle,” “respiratory muscle,” and “exercise training,” with “pulmonary arterial hypertension.”

Underlying mechanisms of PAH-related myopathy: lessons from animal studies

To date, there is no single unifying theory about the pathophysiological background of PAH muscular involvement. Inflammatory activation is believed to be primarily involved.

Pro-inflammatory cytokines have detrimental effects on striated muscle as they damage the function of contractile proteins [12] and stimulate their proteolysis [13]. Elevated levels of circulating pro-inflammatory mediators, such as interleukin (IL)-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, and IL-12p70 and tumor necrosis factor (TNF)-α, were found in both PAH animal models and patients [14,15] and were associated with poor outcome [15].

TNF-α is a mediator that may lead to muscle protein degradation and skeletal muscle necrosis [16]. IL-1β and IL-6 [17] directly enhanced the activity of UPS inducing the proteolysis of muscle proteins [18]. UPS dysregulation has been recognized to be one of the underlying mechanisms of cardiovascular disease [18]. Increased UPS activity, indirectly measured as expression of E3 ligases, atrogin-1 (also called MAFbx-1) and muscle ring finger protein 1 (MURF-1), was found in diaphragm muscle fibers of rats with monocrotaline (MCT)-induced PH [19]. The same group also reported a possible role for sarcomeric dysfunction in the determinism of diaphragm weakness [20]. Both studies [19,20] led the authors to conclude that diaphragm weakness in PAH may be a specific local process, which is separate from peripheral skeletal muscle weakness and dysfunction [3–5].

Another possible mechanism underlying the muscle impairment in PAH may be the inhibition of hormonal/anabolic pathways, which in turn are essential in promoting protein synthesis and protecting muscular protein from degradation [21]. The most explored anabolic axis in PAH is insulin signaling. An increased prevalence of insulin resistance in PAH has been recently described [22,23] and predicted mortality in PAH patients [23]. Insulin acts mainly through the activation of the insulin receptor substrate (IRS)/phosphatidylinositol 3-kinase (PI3K)/Akt pathway with a wide spectrum of downstream results [24]. Its signaling is impaired by chronic inflammation [25]. In fact, TNF-α and IL-6 are likely to reduce insulin signaling through the inhibition of the IRS/PI3K/Akt pathway [26–29], also in muscle cells [24].

A reduced Akt activation and an increased atrogin-1 and MURF-1 activity were reported in muscle specimens of idiopathic pulmonary arterial hypertension (IPAH) patients [5]. One can speculate that impairment of the IRS/PI3K/Akt pathway and inflammatory activation are both linked with the activation of UPS in PAH contributing to muscle wasting. Interestingly, insulin signaling and other hormonal/anabolic pathways (testosterone, dehydroepiandrosterone, growth hormone/insulin-like growth factor 1) are also commonly downregulated in chronic heart failure (CHF) [30,31], and associated with impaired clinical condition and poor outcome [32]. Of note, preliminary studies showed that hormonal replacement therapy may improve surrogate prognostic markers in patients with CHF [33–36]. However, the prevalence and relevance of anabolic impairment in PAH are still unclear and need to be further assessed.

Chronic hypoxemia is also likely to be primarily involved in muscle dysfunction [37]. Skeletal muscle microcirculation of PAH patients appears to be impaired as shown by low O₂ saturation at the tissue level, measured by a near-infrared spectroscopy technique [38]. Moreover, abnormalities of the microvascular O₂ delivery-to-utilization rate, which in turn slow the rate of adaptation of aerobic metabolism, were found in woman with PAH [39]. Hypoxia has been described to promote the degradation of MyoD, a myogenic transcription factor of myoblast differentiation [40] and impaired skeletal muscle metabolism by activation of glycolysis and acid lactic fermentation [41]. Indeed, PAH patients show a so-called Warburg effect – a constitutive activation of the aforementioned aerobic/glycolytic switch – as testified by enhanced glucose uptake measured by positron emission tomography [42]. Quadriceps muscle biopsies of patients affected by IPAH World Health Organization (WHO) class II–III display higher phosphofructokinase (PFK)/3-hydroxyacyl-CoA-dehydrogenase (HADH) indicating a higher potential for anaerobic than aerobic metabolism [4].

Finally, abnormalities of mitochondrial function influence muscle mass and atrophy [43]. In MCT-treated rats,
abnormalities of mitochondrial biogenesis and respiration capacity have been documented in gastrocnemius muscle biopsies before right ventricular (RV) failure occurred [44]. Moreover, in the same animal models, a low mitochondrial adenosine diphosphate (ADP)-sensitivity and impaired mitochondrial respiratory function was found in a plantaris muscle specimen [45].

In conclusion, as depicted in Fig. 1, several mechanisms are likely to be involved in muscle wasting in PAH: increased inflammatory response, impaired insulin/anabolic signaling, hypoxemia, and abnormalities in mitochondrial function. This may lead to dysregulation of UPS with the resulting altered protein degradation/synthesis, MyoD degradation, and cellular aerobic/anaerobic shift.

Several issues in the determinism of PAH myopathy are still unsettled: (1) whether the wasting observed in peripheral and respiratory skeletal muscles is altered to a similar extent or if it is a part of two different pathophysiological processes; (2) which is the interplay of known determinants of PAH myopathy such as inflammation, anabolic deficiency, mitochondrial failure, etc.; and (3) whether there is a differential muscle involvement in PAH patients according to different patterns of PAH.

**Muscle dysfunction and wasting in PAH: human studies**

The aforementioned mechanisms (inflammatory activation, impaired insulin/anabolic signaling, hypoxemia, and abnormalities in mitochondrial function) finally culminate in a wide spectrum of cellular abnormalities of PAH muscles, which finally result in muscle atrophy and reduced contractility (see Fig. 1).

Indeed, PAH myopathy is characterized by reduced skeletal muscle mass, reduced volitional and non-volitional contractility, reduced generated force, a fiber switch from type I to type II, increased protein degradation through UPS activation, reduced mitochondrial functioning, and impaired activation–contractility coupling. Table 1 summarizes the main findings of all studies that evaluated both respiratory and peripheral skeletal muscle morphology, function, and molecular signaling.

**Respiratory muscle**

The first study investigating the muscle function of PAH patients was performed by Meyer and coworkers [6]. This study assessed IPAH patients WHO functional class II–IV and healthy controls. IPAH patients showed a significantly impaired function of the breathing muscles compared to the controls by reduced maximal inspiratory (PImax) and expiratory pressure (PEmax). The impaired inspiratory and expiratory pressures occurred independently from pulmonary hemodynamics, lung function at rest, diffusion capacity, blood gas analysis, exercise capacity, and 6MWD. The mouth occlusion pressure within the first second (P1s)/PImax ratio, an indirect measure of the central neural or respiratory drive, was significantly increased in IPAH females. This results led Naeije et al. to speculate that PAH patients breathe more but with a weaker respiratory muscle [46]. However, PImax and PEmax are indexes of volitional muscle function strength. Kabitz and colleagues found a reduced volitional and non-volitional strength of

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**Figure 1** Potential mechanisms involved in skeletal muscle atrophy and weakness in PAH. Muscle wasting in PAH is probably due to increased inflammatory response, impaired insulin/anabolic signaling, hypoxemia and abnormalities in mitochondrial function. This may lead to dysregulation of Ubiquitin–Proteasome system (UPS) with the resulting altered protein degradation/synthesis, MyoD degradation and cellular aerobic/anaerobic shift. The final result is a wide spectrum of cellular abnormalities of PAH skeletal muscles that finally culminates in muscle atrophy and reduced contractility.
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Type of muscle</th>
<th>Sample Size</th>
<th>Clinical setting</th>
<th>Measures of muscle morphology/function</th>
<th>Main findings</th>
<th>Biopsy</th>
<th>Biopsy findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meyer et al. (2005) [6]</td>
<td>Respiratory (Diaphragm)</td>
<td>37</td>
<td>IPAH WHO class II–IV versus Controls</td>
<td>$P_{\text{Imax}}, P_{\text{Emax}}$ (volitional twitch)</td>
<td>Reduction in both inspiratory than expiratory volitional twitch</td>
<td>Not performed</td>
<td>–</td>
</tr>
<tr>
<td>Bauer et al. (2007) [3]</td>
<td>Peripheral (Forearm)</td>
<td>24</td>
<td>IPAH WHO class II–III versus Controls</td>
<td>Isometric forearm muscle strength (handgrip)</td>
<td>Lower isometric forearm muscle strength. Direct correlation with 6MWD</td>
<td>Not performed</td>
<td>–</td>
</tr>
<tr>
<td>Kabitz et al. (2009) [7]</td>
<td>Respiratory (Diaphragm)</td>
<td>31</td>
<td>PAH (25) + CTEPH (6) versus Controls</td>
<td>$P_{\text{Imax}}, P_{\text{Emax}}$ (volitional twitch) $T_{\text{Wmo}}, T_{\text{Wdi}}$ (non-volitional twitch)</td>
<td>Reduction in volitional twitch. Marked reduction in non-volitional twitch</td>
<td>Not performed</td>
<td>–</td>
</tr>
<tr>
<td>Mainguy et al. (2010) [4]</td>
<td>Peripheral (Limb muscle/quadriceps)</td>
<td>10</td>
<td>IPAH WHO class II–III versus Controls</td>
<td>Limb-muscle CSA by CT scan; Quadriceps volitional (MVC) and non-volitional strength ($T_{\text{Wq}}$)</td>
<td>Trends in reduced CSA ($p = 0.15$) Reduced MVC and $T_{\text{Wq}}$ Quadriceps strength correlated with VO$_2$ max</td>
<td>Quadriceps specimens</td>
<td>Decreased type I fibers. Increased anaerobic metabolism. Both indexes correlated with VO$_2$ at AT. Reduced CSA in diaphragm, normal in quadriceps. Reduced contractility of diaphragm fibers Increased UPS activity Reduced mitochondrial fusion Impaired excitation/contraction coupling.</td>
</tr>
<tr>
<td>de Mann et al. (2011) [19]</td>
<td>Respiratory (Diaphragm) Peripheral (Quadriceps)</td>
<td>8</td>
<td>PH (4) + CTEPH (4) versus Controls</td>
<td>–</td>
<td>–</td>
<td>Diaphragm Quadriceps</td>
<td></td>
</tr>
<tr>
<td>Batt et al. (2013) [5]</td>
<td>Peripheral (Quadriceps/vastus lateralis)</td>
<td>12</td>
<td>PAH (12) WHO class II–III versus Controls</td>
<td>Quadriceps CSA by CT scan</td>
<td>lower CSA in PAH</td>
<td>Vastus lateralis</td>
<td></td>
</tr>
<tr>
<td>Dimopoulos et al. (2013) [38]</td>
<td>Peripheral (Thenar muscle)</td>
<td>8</td>
<td>PAH (six female/two male) versus Controls versus CHF</td>
<td>$\text{StO}_2$ by NIRS OCR, RHT after 3-min brachial artery occlusion</td>
<td>Lower $\text{StO}_2$ and higher RHT in PAH. Increase after 15 min O$_2$ 100%</td>
<td>Not performed</td>
<td>–</td>
</tr>
</tbody>
</table>

IPAH: idiopathic pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; CHF: chronic heart failure; $P_{\text{Imax}}$: maximal inspiratory pressure; $P_{\text{Emax}}$: maximal expiratory pressure; $T_{\text{Wmo}}$: twitch mouth pressure during bilateral anterior magnetic phrenic nerve stimulation; $T_{\text{Wdi}}$: transdiaphragmatic pressure during bilateral anterior magnetic phrenic nerve stimulation; $T_{\text{Wq}}$: potentiated twitched of the femoral nerve; NIRS: near-infrared spectroscopy; $\text{StO}_2$: tissue O$_2$ saturation; OCR: oxygen consumption rate; RHT: reactive hyperemia time; 6MWD: 6-min walking test distance; UPS: ubiquitin–proteasome system.
respiratory muscles [7] in patients with IPAH and chronic thromboembolic pulmonary hypertension (CTEPH) in comparison to healthy controls. Recently, the same group reported in a small cohort of PAH patients a beneficial effect of a combined exercise and respiratory training program on respiratory muscle strength (see paragraph 4) [9].

Diaphragm and quadriceps muscle biopsies of six PAH patients were analyzed by de Man et al. [19]. The cross-sectional area of diaphragm muscle fibers was found to be markedly reduced when compared with the control group, while the quadriceps fibers seemed to be protected. The force-generating capacity (expressed as maximal isometric force measured on a single fiber) of diaphragm fibers was reduced compared with controls.

**Peripheral skeletal muscle**

A 30% reduction in forearm muscle strength, assessed using a hand dynamometer, was found in IPAH patients by Bauer and coworkers [3]. In the same study, a direct linear correlation between muscle strength and 6MWD was reported [3]. Moreover, the forearm muscle strength directly correlated with maximal inspiratory and expiratory pressures, leading to the speculation that weakness of skeletal muscle is paralleled by inspiratory and expiratory muscle dysfunction.

Mainguy et al. found a trend in reduction of the limb muscle cross-sectional area assessed by computed tomographic (CT) scan and a reduction of volitional and non-volitional contraction of quadriceps [4]. The same group also analyzed a skeletal muscle specimen of quadriceps finding a lower proportion of type I fibers (and a higher PFK/HADH enzyme ratio). This pattern is compatible with a relatively higher potential for anaerobic than for aerobic metabolism (see paragraph 2), as well as lower muscle strength [4]. Among IPAH patients, quadriceps strength positively correlates with exercise capacity (VO₂ max). Furthermore, the oxygen uptake at the aerobic threshold correlates with oxidative enzyme expression, such as citrate synthase, and with the capillary/type I fiber ratio [4]. An exploratory analysis of data suggested a negative correlation between disease duration and type I fiber [4].

Butt et al. found a smaller cross-sectional area of the quadriceps measured by CT scan, a reduced number of type I fibers, and increased concentration of type II fibers [47]. This study provided interesting insights regarding molecular mechanisms underlying muscle dysfunction. PAH patients showed lower levels of phosphorylated (activated) Akt and forkhead box protein O and increased levels of atrogen-1 and MURF-1 [47]. This pattern was consistent with a reduction of Akt activity and consequently activation of UPS. Moreover, reduced levels of mitofusin-1 and mitofusin-2 were found, indicating a damaged mitochondrial fusion process while mitochondrial biogenesis seemed to be unaffected [47]. Interestingly, in the same study, the muscle activation–contraction coupling was evaluated.

An increased phosphorylation of ryanodine receptor 1 was found in muscle specimens of PAH, which in turn induces sequestration of Ca²⁺ into the sarcoplasmic reticulum, leading to reduced muscle contraction [47].

**Exercise training in PAH**

Exercise training reverses some of the skeletal muscle abnormalities, such as mitochondrial respiratory capacity [48]. Although exercise training was thought harmful in patients with severe pulmonary hypertension for a long time, now it is recognized as a valuable integrative approach to improve exercise capacity and QoL in both WHO class II and III [49]. Positive results with exercise training in CHF encouraged exercise-based rehabilitation programs in patients with various forms of PAH.

Some supportive evidence also came from preclinical studies. Training in pulmonary hypertensive rats (chronic hypoxia exposure model) did not affect pulmonary vaso-reactivity alterations [50], but exercise training markedly increased exercise endurance and capillary density in stable MCT-induced PH rats [51]. Moreover, another research group showed positive structural and functional modifications on the right ventricle and the pulmonary artery in the same rat model [52].

The first randomized clinical trial was published in 2006 by Mereles et al. [11]. In this study, 30 patients with PAH and CTEPH were randomized into two groups: the control group received a common rehabilitation program based on nutrition, counseling, physical therapy without exercise, and respiratory training for 3 weeks. The training group received a special exercise program consisting of interval bicycle ergometer training with a low workload (20–60 W) for 10–25 min/day. Exercise was administered and supervised 7 days per week and the intensity was individually adjusted according to subjective physical exertion and safety measures (peak heart rate < 120 bpm, oxygen saturation >90%). Moreover, patients were invited to walk for 60 min, to train single muscle groups with low weights for 30 min and to perform respiratory exercise for an additional 30 min, for at least 5 days a week. At discharge, patients were asked to continue at home bicycle exercise training, respiratory exercise, and dumbbell training for 12 additional weeks, and agreed to be monitored by phone interviews every 2 weeks. This comprehensive exercise program resulted in an improvement of 6MWD after 3 weeks (+85 ± 56 m) and a further improvement to 96 ± 61 m after 15 weeks (p < 0.0001 versus controls and versus baseline). Consistently, oxygen uptake at peak exercise and at anaerobic threshold increased over time, along with physical and mental QoL scores.

This exercise program was repeated in further non-randomized trials enrolling PH patients with different etiologies and disease severity [10,53–56]. All these studies consistently confirmed the beneficial effects of rehabilitation program in terms of walking distance, oxygen consumption, and QoL assessment (see Table 2). Moreover, similar positive results were confirmed also by studies that employed different training approaches, such as a less intensive training program [57], treadmill walking.
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Sample</th>
<th>Clinical setting</th>
<th>Type of exercise</th>
<th>Training duration</th>
<th>Safety information</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mereles et al. (2006) [11]</td>
<td>30</td>
<td>IPAH (73%); CTEPH (27%) WHO II–IV</td>
<td>Bicycle ergometer + respiratory muscle training</td>
<td>3 weeks, institution based + 15 weeks, home based</td>
<td>No major adverse events. Two short episodes (%) of dizziness</td>
<td>Improved 6MWD and QoL</td>
</tr>
<tr>
<td>de Man et al. (2009) [57]</td>
<td>19</td>
<td>IPAH WHO II–II</td>
<td>Cycling and quadriceps training</td>
<td>12 weeks, institution based</td>
<td>No adverse events related to training exercise</td>
<td>Improved 6MWD</td>
</tr>
<tr>
<td>Shoemaker et al. (2009) [69]</td>
<td>2</td>
<td>IPAH and APAH</td>
<td>Bicycle ergometer</td>
<td>6 weeks, institution based</td>
<td>No adverse events related to training exercise</td>
<td>No improvement in 6MWD, QoL, handgrip, leg strength</td>
</tr>
<tr>
<td>Martinez-Quintana et al. (2010) [70]</td>
<td>22</td>
<td>PAH associated with CHD WHO II–III</td>
<td>Bicycle ergometer and resisted exercise</td>
<td>12 weeks, institution based</td>
<td>No adverse events related to training exercise</td>
<td>Improved 6MWD</td>
</tr>
<tr>
<td>Mainguy et al. (2010) [71]</td>
<td>5</td>
<td>IPAH WHO II–III</td>
<td>Bicycle ergometer and resisted exercise + stair-climbing</td>
<td>12 weeks, institution based</td>
<td>No adverse events related to training exercise</td>
<td>Improved 6MWD</td>
</tr>
<tr>
<td>Fox et al. (2011) [60]</td>
<td>21</td>
<td>APAH (36%), WHO II–IV</td>
<td>Aerobic and resistance training (bicycle ergometer) + respiratory muscle training</td>
<td>3 weeks, institution based + 15 weeks, home based</td>
<td>No major adverse events. Two short episodes (%) of dizzines immediately after training</td>
<td>Improved 6MWD, VO2 peak and QoL</td>
</tr>
<tr>
<td>Grünig et al. (2012) [56]</td>
<td>183</td>
<td>IPAH (45%), APAH (25%), other PAH (30%) WHO I–IV</td>
<td>Aerobic and resistance training (bicycle ergometer) + respiratory muscle training</td>
<td>3 weeks, institution based + 15 weeks, home based</td>
<td>Out of 25 patients (13.6%) who experienced adverse events, few related to exercise training; pre-syncope (n = 1), SV-T (2)</td>
<td>Improved 6MWD, VO2 peak and QoL</td>
</tr>
<tr>
<td>Nagel et al. (2012) [55]</td>
<td>35</td>
<td>CTEPH WHO II–III</td>
<td>Aerobic and resistance training (bicycle ergometer) + respiratory muscle training</td>
<td>3 weeks, institution based + 15 weeks, home-based</td>
<td>One case of syncope; one case of herpes zoster probably related to exercise training</td>
<td>Improved 6MWD, VO2 peak and QoL</td>
</tr>
<tr>
<td>Grünig et al. (2012) [53]</td>
<td>21</td>
<td>APAH WHO II–IV</td>
<td>Aerobic and resistance training (bicycle ergometer) + respiratory muscle training</td>
<td>3 weeks, institution based + 15 weeks, home-based</td>
<td>No adverse events related to training exercise</td>
<td>Improved 6MWD, VO2 peak and QoL</td>
</tr>
<tr>
<td>Weinstein et al. (2013) [59]</td>
<td>24</td>
<td>APAH (75%), IPAH (25%), WHO I–IV</td>
<td>Treadmill walking (30–45 min per session)</td>
<td>10 weeks, institution based</td>
<td>Not reported</td>
<td>Improved 6MWD and QoL</td>
</tr>
<tr>
<td>Chan et al. (2013) [58]</td>
<td>23</td>
<td>APAH (74%), IPAH (22%), other PAH (4%) WHO I–IV</td>
<td>Treadmill walking (30–45 min per session)</td>
<td>10 weeks, institution based</td>
<td>No adverse events related to training exercise</td>
<td>Improved 6MWD and QoL</td>
</tr>
<tr>
<td>Becker-Grünig et al. (2013) [54]</td>
<td>20</td>
<td>PAH associated with CHD WHO II–III</td>
<td>Bicycle ergometer + respiratory muscle training</td>
<td>3 weeks, institution based + 15 weeks, home based</td>
<td>No adverse events related to training exercise</td>
<td>Improved 6MWD, VO2 peak, and QoL</td>
</tr>
</tbody>
</table>
Training [58,59], or a mixed training strategy [60] (see Table 2). Interestingly, exercise training may lead to reduced health-care costs (657 €/patient within a period of 2 years) as reported recently by Ehlken et al. [61].

The overall positive effects of training are most likely due to the attenuation of endothelial dysfunction [62], reduction of the inflammatory activation [63], and improvement in gas exchange [11].

In this scenario, muscle dysfunction attenuation is one of the key mechanisms of the beneficial effect of exercise training in PAH. This might be gathered by a recent pilot study of Kabitz and colleagues [9] performed on seven patients with IPAH and associated pulmonary arterial hypertension (APAH) who underwent a combined exercise and respiratory training program and where both volitional and non-volitional respiratory muscle functions were assessed at baseline and after 3 and 15 weeks. The authors reported a significant improvement of twitch mouth pressure during bilateral anterior magnetic phrenic nerve stimulation (p = 0.0037), the sniff nasal inspiratory pressure measured at the level of the nose (p = 0.025) and PEmax (p = 0.021) after exercise and respiratory training leading to the conclusion that respiratory muscle strength is likely to be improved by exercise and respiratory training in PAH patients [9].

Virtually in all studies, different training schemes had positive results on both subjective well-being and objective parameters of physical activity in the short term. However, even if some studies reported good survival rates over a follow-up period of up to 3 years (97–100% at 1 year, 94–100% at 2 years, and 80–86% at 3 years) [10,53,55,61], to date, no study was designed to assess whether the exercise training gave patients a measurable survival advantage.

### Conclusion and future perspectives

Exercise impairment is a key feature of PAH [64]. It limits daily activity and lowers the QoL of PAH patients. Similar to the observations in CHF, exercise capacity (ergospirometric measurements and walk distances) is better related to prognosis than hemodynamic function [65,66].

Traditionally, exercise intolerance was attributed to reduced RV output and consequent perfusion/ventilation mismatch. However, similar to the observations made in CHF [67] and chronic obstructive pulmonary disease [67,68], skeletal muscle weakness contributes to the development of exercise impairment in PAH. This phenomenon is probably due to increased inflammatory response, impaired anabolic signaling, hypoxemia, and abnormalities in mitochondrial function. The skeletal muscle of PAH patients displays a wide spectrum of cellular abnormalities that finally culminates in muscle atrophy and reduced contractility. Exercise training improves muscle function and bears a positive impact on the clinical outcomes of PAH patients. However, several issues are still unsettled concerning muscle dysfunction in PAH: (1) a systematic evaluation of the underlying mechanisms of PAH myopathy and their interplay, (2) a better definition
of muscle dysfunction in different types of PAH, which in turn have different pathophysiological backgrounds (i.e., inflammation in connective tissue disease-associated PAH and hypoxemia in PAH-associated congenital heart disease), (3) a better understanding of the additional value of muscle biopsy in the clinical management of PAH patients, and (4) implementation of clinical trials to test whether muscle may represent a target organ of specific PAH therapy.

References


