Skeletal muscle dysfunction in pulmonary arterial hypertension

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1. WHAT IS PULMONARY ARTERIAL HYPERTENSION (PAH)?

Pulmonary hypertension (PH) is defined as a mean pulmonary arterial pressure >20 mmHg at rest and is classified into five clinical groups[1,2] (**Table 1**). Pulmonary arterial hypertension (PAH; group 1) is a form of precapillary PH defined by a pulmonary arterial wedge pressure ≤15 mmHg and pulmonary vascular resistance >2 Wood units[1,2]. PAH primarily affects the small pulmonary arteries, where sustained vasoconstriction and vascular remodeling increase pulmonary vascular resistance and eventually lead to right ventricular dysfunction or failure[3].

Table 1. Clinical classification of pulmonary hypertension

Group 1	**Pulmonary arterial hypertension (PAH)** • Idiopathic • Heritable • Associated with drugs and toxins • Associated with connective tissue disease, HIV infection, portal hypertension, congenital heart disease or schistosomiasis • PAH with features of venous/capillary involvement
Group 2	**PH associated with left heart disease** • Heart failure • Valvular heart disease
Group 3	**PH associated with lung diseases and/or hypoxia** • COPD and/or emphysema • Interstitial lung disease • Other parenchymal or restrictive lung diseases • Hypoxia without lung disease (e.g., high altitude)
Group 4	**PH associated with pulmonary artery obstructions** • Chronic thromboembolic PH • Other pulmonary artery obstructions
Group 5	**PH with unclear and/or multifactorial mechanisms** • Hematological, systemic or metabolic disorders • Chronic renal failure

Adapted from Kovacs et al.[1] PH: pulmonary hypertension; PAH: pulmonary arterial hypertension; COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus.

2. SKELETAL MUSCLE DYSFUNCTION IN PAH: WHY SHOULD WE CARE?

Exercise intolerance and dyspnea are common symptoms of PAH[4]. These symptoms are not solely explained by pulmonary hemodynamic impairment but rather reflect interacting mechanisms, including a limited cardiac output response, excessive ventilatory demand and skeletal muscle dysfunction[4,5] (**Figure 1A**).

In PAH, skeletal muscles show structural and functional changes, such as reduced capillary density, impaired microcirculatory perfusion[6,7], a shift toward faster-fatiguing fibers[8,9] and reduced energy production capacity[10] (**Figure 1B**). Reduced skeletal muscle capillarity has been associated with impaired muscle oxygenation during exercise, even in the absence of differences in cardiac output responses between patients with PAH and healthy controls[7].

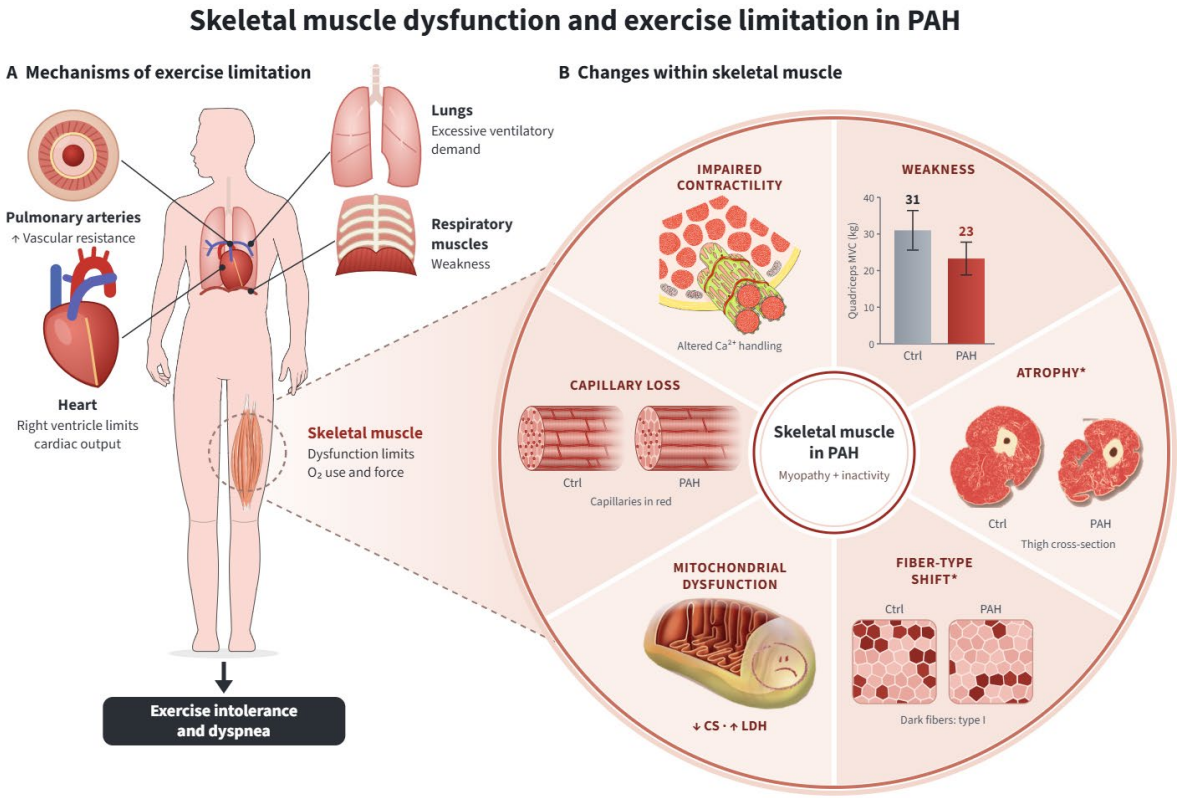


Figure 1. Skeletal muscle dysfunction and exercise limitation in PAH. (A) Central and peripheral mechanisms that contribute to exercise intolerance and dyspnea[4,5]. (B) Skeletal muscle changes reported in PAH[6–10]. Bars show mean ± SD quadriceps MVC, and capillaries are drawn in proportion to capillary density (201 vs 304/mm²), in patients with PAH (n = 10) and healthy sedentary controls matched for age, sex, weight and height (n = 10); both $P \leq 0.01$[7]. *Not consistent across studies. Mitochondrion and thigh cross-section illustrations adapted from Maltais F, Decramer M, Casaburi R, et al. An official American Thoracic Society/European Respiratory Society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2014;189(9):e15-e62, with permission of the American Thoracic Society. Body, quadriceps and muscle-fiber illustrations adapted from Servier Medical Art (smart.servier.com), licensed under CC BY 4.0. CS, citrate synthase; LDH, lactate dehydrogenase; MVC, maximal voluntary contraction; O_2, oxygen; PAH, pulmonary arterial hypertension; SD, standard deviation.

3. WHAT HAPPENS TO SKELETAL MUSCLE IN PAH?

Patients with PAH show reduced handgrip and quadriceps strength as well as reduced quadriceps endurance compared with healthy controls[6–8,11,12]. Human studies reported lower lean mass, smaller muscle-fiber cross-sectional area, a shift from slow (Type I, oxidative) to fast (Type II, glycolytic) fibers, and impaired force generation. Physical inactivity likely contributes to these impairments[13]. However, impaired skeletal muscle angiogenic signaling, including reduced miR-126 expression[6], and reduced force-generating capacity of individual muscle fibers, independent of fiber size[14], suggest the presence of a PAH-associated skeletal muscle phenotype. Capillary rarefaction and reduced cardiac output may further limit oxygen delivery to skeletal muscles by impairing diffusive and convective oxygen transport, respectively. These findings point to the involvement of multiple cellular and microvascular mechanisms, although it remains uncertain whether these alterations are specific to PAH[4,15].

4. CAN REHABILITATION REVERSE SKELETAL MUSCLE DYSFUNCTION?

A Cochrane review of 14 randomized controlled trials (574 participants, mostly with PAH) showed that supervised exercise-based rehabilitation in medically stable patients with PAH improved functional capacity (mean improvement of 48 m in 6-minute walk distance [6MWD]) and quality of life without

increasing the risk of adverse events[16]. However, only a few small studies have assessed changes in skeletal muscle function and structure[17],[18].

Twelve weeks of interval cycling and quadriceps resistance training increased quadriceps strength and endurance by 13% and 34%, respectively, along with increased muscle capillarity and oxidative enzyme activity[17]. Another program that included upper- and lower-limb strengthening exercises and walking reduced the proportion of fast-fatigable (type IIx) muscle fibers and improved 6MWD, without changing muscle strength[18].

5. COULD PAH-SPECIFIC TREATMENTS AFFECT SKELETAL MUSCLE FUNCTION?

PAH-specific therapies may improve skeletal muscle exercise performance through indirect mechanisms, including increased oxygen delivery. Preclinical studies also suggested that dual ET_A/ET_B blockade may increase quadriceps perfusion and microvascular density in rodent models of PH[19] . In a recent study, 24 weeks of sotatercept treatment was associated with improved isolated quadriceps exercise performance and increased peripheral oxygen utilization, alongside improved oxygen delivery during exercise[20]. Although these findings suggest that improved peripheral oxygen transport contributes to the functional benefits of sotatercept, direct effects on skeletal muscle through modulation of activin and myostatin signaling are also biologically plausible. Whether such direct effects contribute to improvements in skeletal muscle function in patients with PAH remains to be determined.

6. WHAT DO WE STILL NEED TO KNOW?

Several knowledge gaps remain. Evidence on skeletal muscle dysfunction in PAH remains limited compared with that in chronic obstructive pulmonary disease (COPD)[21]. Most evidence comes from small studies[15], particularly those investigating the effects of exercise-based rehabilitation, highlighting the need for larger studies to better characterize improvements in skeletal muscle function and associated morphological adaptations.

Although current evidence suggests the presence of a PAH-associated skeletal muscle phenotype, the underlying mechanisms are not completely understood. The extent to which skeletal muscle abnormalities result from PAH-related pathophysiological mechanisms, physical inactivity or their interaction remains uncertain. Moreover, how skeletal muscle characteristics interact with central cardiovascular and ventilatory limitations to determine exercise capacity and responses to exercise training remains unclear. Finally, the direct effect of PAH-specific therapies beyond increased oxygen delivery remains largely unknown.

7. WHAT DOES THIS MEAN FOR PULMONARY REHABILITATION?

Although exercise-based rehabilitation improves functional exercise capacity, the extent to which these benefits are mediated by skeletal muscle adaptations remains unclear. Evidence from small studies suggests that exercise training can improve muscle strength, endurance, capillarity and oxidative capacity[17],[18]. However, further studies are needed to identify patients most suitable for rehabilitation, to better characterize the effects of different training modalities on skeletal muscle function and structure and to determine how these adaptations interact with central cardiovascular and ventilatory limitations to influence exercise capacity. A better understanding of these mechanisms may help optimize exercise training strategies for patients with PAH.

8. FINAL MESSAGE

Skeletal muscle dysfunction is an important contributor to exercise intolerance in PAH and a relevant target for pulmonary rehabilitation. Although exercise-based rehabilitation can improve functional capacity and skeletal muscle function, a better understanding of the underlying mechanisms and adaptations to training is needed to optimize rehabilitation strategies and improve patient outcomes.

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