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Moving Forward Together: Exercise Physiology and Prescription Across the PH Lifespan

Program Description

The mission of *Advances in Pulmonary Hypertension* is to serve as the premiere forum for state-of-the-art information regarding diagnosis, pathophysiology, and treatment of pulmonary hypertension (PH). The 2018 Nice revision of the World Symposium on Pulmonary Hypertension (Simmonneu G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1). DOI:10.1183/13993003.01913-2018) serves as a guide to categories of PH addressed in *Advances in Pulmonary Hypertension*. While focusing on Group 1 PH (PAH: pulmonary arterial hypertension), the other categories (Group 2, PH due to left heart disease; Group 3, PH due to lung diseases and/or hypoxia; Group 4, PH due to pulmonary artery obstructions; Group 5, PH with unclear and/or multifactorial mechanisms) are also addressed. This mission is achieved by a combination of invited review articles, roundtable discussions with panels consisting of international experts in PH, and original contributions.

Objectives

- Provide up-to-date information regarding diagnosis, pathophysiology, and treatment of PH.
- Serve as a forum for presentation and discussion of important issues in the field, including new paradigms of disease understanding and investigational trial design.

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Advances in Pulmonary Hypertension is directed to cardiologists, pulmonologists, rheumatologists, pediatricians, internists, and other health care professionals involved in the treatment of patients with PH.

Advances in Pulmonary Hypertension: Official Journal of the Pulmonary Hypertension Association is a quarterly publication directed by an editorial board of renowned pulmonary hypertension (PH) experts with oversight by PHA's Scientific Leadership Council. The mission of *Advances in PH* is to assist physicians in their clinical decision-making by informing them of important trends affecting their practice and providing an analysis of the impact of new findings and current information in peer-reviewed publications. Each article is reviewed and approved by members of the Editorial Board.

While most articles are invited by the Editorial Board, the following submissions will be considered for publication:

- Reviews that summarize and synthesize peer-reviewed literature to date on relevant topics
- Letters to the Editor
- Clinical case studies

Submitted manuscripts are reviewed by the Editorial Board and other experts in the field. Acceptance of manuscripts is determined by factors such as quality, relevance, and perceived value to clinical decision-making.

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This issue marks my transition to editor-in-chief from my esteemed colleague, Dr Deborah J. Levine. Deb had the challenge of an extended editorship related to the pandemic and oversaw the successful transition of *Advances in Pulmonary Hypertension* to a fully online journal. I congratulate her on her tenure at *Advances* and further commend Deb for her continued, selfless dedication to our pulmonary arterial hypertension (PAH) community.

In my inaugural issue, Drs Layton and Avitabile tackle the critical impact of exercise on patients with pulmonary hypertension. It's hard to imagine that only 70 years ago recommending that a patient sit in a chair (rather than lying continually flat) within 1 week of a heart attack was considered medical heresy.[1] It would take almost another decade until early ambulation after such events was attempted.[2] The landmark Bethesda Conference nearly 20 years ago addressed competitive athletics for patients with cardiovascular disease. In this expert statement, the presence of concomitant pulmonary hypertension in patients with structural lesions was considered an absolute contraindication to participation in competitive athletics.[3] It's therefore not surprising that PAH treatment algorithms as recently as a decade ago discouraged routine exercise.[4] Exercise is a complex physiological event that impacts cardiovascular, pulmonary, and musculoskeletal systems. There are many forms of exercise (including aerobic, resistance, and inspiratory muscle training) and, of course, significant disease heterogeneity among the PAH patient population. This limits the "one size fits all" paradigm, as so elegantly reviewed in the roundtable discussion.

Medical providers are often challenged with providing an "exercise prescription" for patients. It's important to realize that exercise is generally very safe, except for the sickest (World Health Organization Class IV) PAH patients. I often find myself saying, "Start slow and build your way up…" In almost every case, walking is a good place for patients to start—many are unaware that smart phones contain GPS tracking, which can help them follow their activity. Getting patients to increase their daily steps is essential. Though challenges for financial coverage remain, a referral for cardiac or pulmonary rehabilitation provides better motivation and individualized attention. It's important to remind resistant insurance companies that supervised exercise training is now a Class I recommendation for patients receiving medical therapy for PAH.[5]

The wonderful reviews that follow remind us that exercise has numerous beneficial effects on skeletal muscle biology, lung mechanics, and cardiovascular function. And even more importantly, exercise has been consistently shown to improve quality of life in PAH patients. Despite these demonstrated benefits, in 2020 less than a quarter of the US population over 18 years of age met the 2018 physical activity guidelines for aerobic and muscle-strengthening activities.[6] The main costs for patients (particularly with walking) is simply time and personal effort. Like any healthy lifestyle change, reinforcement during routine office visits is essential for continued success. And now it's time to "move on" to this issue…

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This issue of *Advances in Pulmonary Hypertension* focuses on exercise and pulmonary hypertension (PH). Clinicians treating PH use exercise to determine a patient's degree of functional impairment, quantify the impact of PH therapy, and lessen the burden of the disease, leading to improved quality of life in patients with PH. Articles in this issue of *Advances in Pulmonary Hypertension* review the role of exercise in clinical disease management, present opportunities for future research, and motivate the integration of research findings into clinical care. We are grateful to the authors and roundtable collaborators for their terrific work. Readers will learn about the role of exercise training in PH with special considerations regarding skeletal muscle differences, inspiratory muscle weakness, and the added complications of sleep disordered breathing. Experts provide real-life insight into prescription of exercise in PH to improve overall wellness.

Dr. Simon Malenfant and coauthors summarize the unique landscape of abnormal skeletal muscle structure and dysfunction in contributing to exercise intolerance in the PAH population. These authors describe the microvascular and proinflammatory state of the muscle environment that lead to muscle dysfunction and ultimately exercise intolerance.

Dr. Ratwatte and colleagues summarize the benefits and limitations of exercise training, specifically inspiratory muscle training, in the PH population. The authors provide details of training and explore the broader implications of respiratory muscle training for the PH population. We believe our readers will find this summary of work helpful in deciding how to integrate exercise into their patients' care plan.

Drs. Mullin and Singh review the complex relationships among sleep-disordered breathing, exercise, and PH. The authors present several areas for further exploration as we consider how exercise may affect sleep-disordered breathing in the PH population.

Lastly, we conclude with a roundtable discussion with the experts on "Recommending Exercise in Pulmonary Hypertension: Adult and Pediatric Perspectives." Experts from across the globe provide their insight on how to use and recommend exercise training for their patients. This piece is particularly useful for translating the research into real work clinical practice.

We want to thank the contributing authors for their insightful reviews describing the role of exercise in the care of patients with PH.

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REGULAR ARTICLE

Sleep Disordered Breathing and Exercise in Pulmonary Hypertension

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Exercise intolerance is a common feature of many cardiopulmonary diseases including pulmonary hypertension (PH) and sleep disordered breathing (SDB), which includes obstructive sleep apnea and obesity hypoventilation syndrome. Physiologic abnormalities in both PH and SDB can drive exercise intolerance, and biological mechanisms overlap among the conditions including systemic inflammation, oxidative stress, metabolic dysfunction, and endothelial dysfunction. Despite this understanding, evidence establishing clear causal relationships among PH, SDB, and exercise intolerance is lacking. Data show that treatment of SDB may improve exercise capacity, and exercise training likely improves SDB, although these relationships specifically in PH remain understudied. In this manuscript, we summarize existing data of mechanisms and clinical observations in PH, SDB and exercise and identify gaps and opportunities for future investigation.

INTRODUCTION

Exercise intolerance is the hallmark of most cardiopulmonary diseases, including pulmonary hypertension (PH). In PH, subjective and objective assessments of exercise capacity are paramount in diagnosis, risk stratification, and therapeutic decision making. Sleep disordered breathing (SDB), including obstructive sleep apnea (OSA) and obesity hypoventilation syndrome (OHS), is associated with PH in a relationship that is likely bidirectional yet not completely understood. PH related to SDB is classified as Group 3 PH according to the most recent international consensus guidelines,[1] although the intersection among PH, SDB, and exercise likely involves Group 2 PH or PH due to left-heart disease and/or heart failure with preserved ejection fraction. Delineating PH subgroups is beyond the scope of this review but outlined in the most recent consensus guidelines.[1] There is a growing understanding that OSA and OHS are linked to physiologic abnormalities and limitations in exercise, even in those without apparent cardiopulmonary comorbidities.

Nocturnal hypoventilation and hypoxemia are the pathophysiologic basis for both OSA and OHS. PH is typically mild in isolated OSA,[2] although prolonged nocturnal hypoxemia is associated with worse hemodynamics in OSA when PH is suspected.[3] OSA severity is quantified by the Apnea-Hypopnea Index (AHI). The relationship between hypopneas, nocturnal hypoxia, and their systemic effects are reviewed separately.[4] Accordingly, in OHS, the risk for pulmonary vascular disease is much higher.[5,6] The prevalence of PH secondary to SDB remains unclear; however, OHS is common in the general population (0.4% of the general US population[7] and 17%–30% in high-risk individuals such as those with obesity and OSA[8]). When PH occurs as a complication of OHS, it is frequently quite severe and is associated with both right ventricular (RV) failure and poor long-term outcomes.[9] Given the growing obesity epidemic in the Western world, PH related to SDB is likely to become a more prevalent problem deserving of dedicated study.

Many overlapping mechanisms exist among SDB, PH, and exercise intolerance, including systemic inflammation, endothelial dysfunction, metabolic dysfunction, and cardiac impairment (Box). Despite this overlap, insights into causality among these conditions and the directionality of the relationships remains unclear. Much more work is needed to understand these relationships from epidemiologic associations to molecular mechanisms. In this review, we aim to discuss the current literature describing the relationships between SDB, PH, and exercise and identify gaps that are deserving of further study.

We will primarily discuss observations in adults. Although guidelines recommend screening echocardiograms for children with severe SDB[10] and treatment of concomitant SDB and PH has been demonstrated to improve exercise intolerance,[11] the prevalence of PH in the pediatric population is likely lower than commonly thought,[12] and more comprehensive study is needed. Mechanisms connecting these conditions in the pediatric population overlap with what is known in the adult population and are reviewed extensively elsewhere.[13]

MECHANISMS OF SDB AND EXERCISE INTOLERANCE IN PH

The primary pathophysiology of OSA is repetitive occlusion of the upper airway during sleep, which results in nocturnal

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Box. Shared themes of exercise intolerance in SDB and PH

Systemic inflammation
• Perivascular inflammation in PH
• Activation of HIFs
• Increased activity of NADPH oxidase and oxidative stress
• Thromboembolism in OSA due to oxidative stress
Endothelial dysfunction
• In part, instigated by chronic intermittent hypoxia
• Circulating endothelial progenitor cells may be part of the reparative vascular response to injury or a cancerlike tumorigenesis
• May correlate with leg fatigue during exercise
Skeletal muscle dysfunction
• Cellular metabolic dysfunction
• Diaphragmatic muscle proteolysis
• Respiratory muscle atrophy leads to ventilatory insufficiency
Mutual beneficial effects of exercise training and PAP therapy
• Exercise improves AHI and VO_2max
• PAP improves exercise performance with and without cardiopulmonary disease (including PH): VO_2max and heart rate recovery
• PAP improves pulmonary artery pressures

SDB = sleep disordered breathing; PH = pulmonary hypertension; HIF = hypoxia inducible factor; OSA = obstructive sleep apnea; PAP = positive airway pressure; AHI = apnea-hypopnea index.

hypoxemia and arousals.[14] OHS is characterized by obesity-related changes in the respiratory system, alterations in respiratory drive, and breathing abnormalities during sleep, all leading to chronic nocturnal hypoventilation.[15] Physiologic effects on pulmonary hemodynamics are consistently observed in patients with SDB. The increased intrapleural pressure seen during apneic episodes of SDB likely increases left atrial pressure and RV afterload.[16] Hypoxic episodes cause hypoxic vasoconstriction of the pulmonary vasculature, raising the pulmonary vascular resistance (PVR) and RV afterload, and activating hypoxia inducible factors (HIFs) that are responsible for downstream metabolic dysfunction, upregulation of VEGF, and activation of inflammatory and oxidative stress pathways (Figure 1). This culminates in endothelial dysfunction, a hallmark of all pulmonary vascular diseases that is clearly potentiated by SDB.[17]

Systemic inflammation and oxidative stress are shared mechanistic hallmarks of SDB and PH and likely contribute to exercise intolerance in both disorders.[18,19] In humans, chronic perivascular inflammation is linked to the loss of pulmonary vascular compliance and extracellular matrix remodeling and fibrosis in PH.[20,21] In preclinical PH models, HIFs and TNF-α mediate inflammation and potentiate oxidative stress via increased production of reactive oxygen species (ROS). Both mediators are hypothesized to regulate NADPH oxidases that are important sources of ROS, but human studies establishing the link among these processes are inconsistent, reinforcing the need for further mechanistic studies.[22–24]

Mice exposed to chronic intermittent hypoxia (simulating the nocturnal desaturations observed in SDB) developed PH associated with increased NADPH oxidase and increased activity of platelet-derived growth factor β and downstream protein kinase B.[25] Mice with inactive NADPH oxidase had a decrease in the development of PH and these molecular derangements, suggesting that NADPH oxidase may be a common mechanistic link between SDB and PH.[25] Several vasoactive mediators have been implicated in the overlapping pathogenesis of SDB and PH including serotonin, angiopoetin-1, endothelin-1, and nitric oxide. Stimulated by hypoxia, these mediators have a common effect in both SDB and PH by promoting pulmonary vascular remodeling and biventricular dysfunction.[26] Data suggesting that the oxidative stress generated by nocturnal hypoxia in OSA can predispose patients to venous thromboembolism but can be ameliorated by continuous positive airway pressure (CPAP) are encouraging[27]; however, these observations are confounded by concomitant obesity and advanced age, which are known risk factors for these processes. Unfortunately, human studies at manipulating these pathways in both SDB and PH have been disappointing and further work is needed.

Endothelial dysfunction is a critical common hallmark of both SDB and PH and likely inextricably tied to systemic inflammation and oxidative stress. Central to the pathobiology of both pulmonary vascular remodeling and risk of cardiovascular disease, endothelial dysfunction in both diseases is, in part, instigated by chronic intermittent hypoxia.[28,29] Circulating endothelial progenitor cells (EPCs) have long been hypothesized to play a role in both OSA and PH, either as part of the reparative vascular response to injury or instigating a cancerlike tumorigenesis. Studies in OSA have yielded conflicting results,[30,31] and although more encouraging data establish a role for EPCs in the pathobiology of PAH,[32,33] translation from preclinical studies to humans remains limited. Few studies link endothelial dysfunction in OSA with exercise and PH. Using a noninvasive device to approximate endothelial dysfunction, Jen et al.[34] were unable to detect a correlation between arterial stiffness after exercise and severity of OSA but did correlate vessel stiffness with leg fatigue and oxygen pulse (a marker of cardiac output). Studies using direct assessments of endothelial function related to exercise in OSA and PH remain lacking.

Significant gaps linking exercise intolerance to the many mechanisms that connect SDB and PH remain. Increasing our understanding of skeletal muscle dysfunction in these disorders will likely help to address this knowledge gap. Metabolic dysfunction is observed in the skeletal muscle of both patients with OSA and pulmonary arterial hypertension (PAH).[35,36] Although data recapitulating this dysfunction during exercise are limited, diaphragmatic dysfunction is a

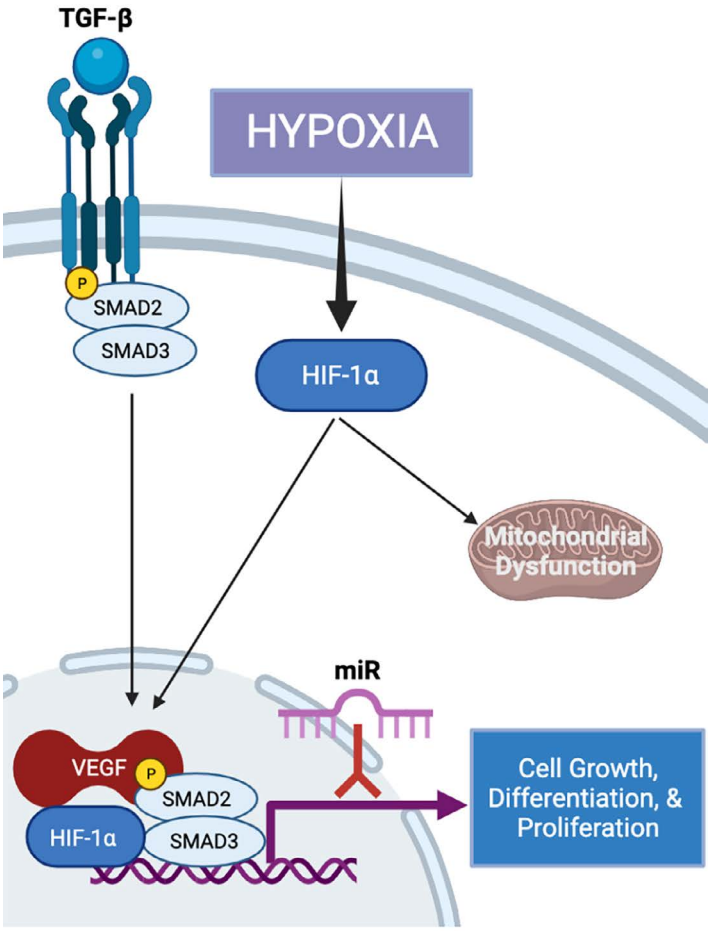

Figure 1: Shared molecular mechanisms of Group 3 pulmonary hypertension (PH) and sleep disordered breathing (SDB). TGF-β signaling and hypoxia inducible factor-1 alpha (HIF-1α) both activate VEGF expression which can lead to increased cell growth, differentiation, and proliferation. MicroRNAs (miRs) can regulate gene expression and prevent these downstream effects in pre-clinical models. HIF-1α is also theorized to play a significant role in mitochondrial dysfunction in both SDB and PH, though the exact mechanisms have yet to be clearly elucidated. Figure adapted from Singh et al. Circ. Res. 2021.[70]

likely contributor to exercise intolerance in both OSA and PAH. In PAH, reduced diaphragmatic muscle fiber cross-sectional area in experimental PH has been associated with increased proteolytic activity. These findings were recapitulated in human disease, suggesting that respiratory muscle atrophy is specifically implicated in the ventilatory inefficiency observed in PAH patients.[37] Abnormal cardiovascular responses to exercise in OSA are consistently observed in the forms of abnormal diastolic blood pressure response,[38] chronotropic incompetence,[39] heart rate recovery after exercise,[40,41] and left-ventricular dysfunction.[42–45] Systolic dysfunction of the RV is an inevitable consequence of persistent increases in afterload and may be the most pronounced in PAH patients with severe nocturnal hypoxemia and OSA.[46] As with Group 1 PAH, a sex-based differential response of the RV to afterload in all Group 3 PH with worsening RV function likely exists in males despite females having a significantly higher PVR.[47]

Though numerous physiologic and molecular mechanisms overlap between SDB and PH, their links to exercise intolerance remain unclear. Much more dedicated clinical and mechanistic study is needed.

EXERCISE IMPAIRMENT IN SDB AND PH

A growing body of evidence links SDB, particularly OSA, to exercise impairment. A recent meta-analysis demonstrated that, compared with healthy controls, subjects with OSA had decreased mean peak oxygen consumption (VO_2max),[48] a parameter considered an overall measure of health and one that is widely associated with mortality in health and disease. Although reduced VO_2max is not observed across all studies examining cardiopulmonary exercise testing in OSA,[49] other physiologic changes with exercise, including decreased peak heart rate and increased diastolic blood pressure, are consistently observed in patients with OSA.[48,50,51] Some of the physiologic abnormalities characteristic of pulmonary vascular disease, such as decreased ventilatory efficiency (VE/VCO_2) and reduced oxygen pulse,[52] have not been demonstrated in OSA.[48,50] Although the cardiopulmonary mechanisms of exercise impairment are different between PH and OSA, it is easy to postulate that these might combine to worsen exercise impairment where PH and OSA coexist. However, data examining the impact of OSA on exercise specifically in PH are more limited. In a heterogeneous PH population, those with OSA were older and had worse resting oxygenation that those without OSA, but no differences in any exercise parameters were found, including six-minute walk distance (6MWD), VO_2max, and VE/VCO_2.[53] Most other studies characterizing OSA in PH have less robust exercise data and have not consistently demonstrated that OSA reduces 6MWD in PH.[54–56]

With all these data, it is challenging to know if the association between OSA and exercise impairment is causal or if body mass index (BMI), comorbidities, and baseline levels of physical activity confound the relationship. In a large sleep cohort, increased reported amount of exercise was associated with a reduced degree of SDB, even after adjustment for age, sex, and body habitus.[57] In a recent study of 450 precapillary PH patients, those with OSA had a reduced 6MWD but were older, had more comorbidities (such as obesity, hypertension, diabetes, and coronary artery disease), were more likely to have left heart abnormalities on echocardiogram, and substantially more likely to have a diagnosis of atypical PAH.[55] However, the association between OSA and atypical PAH remained

even after adjustment for age, sex, and BMI. Further examination of the interplay between OSA, comorbidities, and exercise is needed, particularly given the increasing recognition of comorbidities and the atypical phenotype in PAH.

THERAPEUTIC INTERVENTIONS

Some, albeit limited, data examine the impact of exercise on SDB or the effects of treatment for SDB on exercise performance. Individual studies have demonstrated aerobic exercise can reduce the severity of OSA.[58,59] Pooled estimates from meta-analyses demonstrated regimented exercise improves AHI, VO_2max, and measures of daytime sleepiness and sleep quality with little[60] or no[61] change in BMI. The exercise regimens in these studies are typically aerobic exercise targeting anaerobic threshold, although one analysis found a combination of resistive and aerobic exercise resulted in greater improvement in the OSA severity.[61] Notably, these studies routinely exclude patients with significant cardiopulmonary disease, including PH.

Emerging data show that treatment for SDB, particularly positive airway pressure, can improve exercise performance in patients both with and without cardiopulmonary disease and PH. Several small studies have shown that short-term CPAP improves exercise capacity in OSA without significant cardiopulmonary comorbidities.[62–64] Maeder et al.[65] found that effective longer-term CPAP use in otherwise healthy patients with newly diagnosed OSA improved VO_2max and heart rate reserve. Interestingly, the improvement in VO_2max was seen primarily in those with mild-moderate OSA, which may have been explained by increased effort during the cardiopulmonary exercise testing (CPET) compared with those with severe OSA. More recent work examined the effects of CPAP on exercise capacity in patients with cardiopulmonary comorbidities and PH. In moderate-severe OSA patients with some cardiovascular comorbidities (hypertension and ischemic heart disease), 8 weeks of CPAP improved VO_2max, minute ventilation, and peak oxygen pulse.[66] Sykes et al.[67] examined the effects of OSA and PH on exercise capacity in patients undergoing cardiac rehabilitation, indicated for significant cardiac disease, mostly heart failure with reduced ejection fraction and sequelae of coronary artery disease. Patients with OSA were more likely to have PH (defined by echocardiography), and while improvements in exercise capacity were not different between those with and without PH, patients with PH and OSA treated with CPAP had greater improvements in exercise capacity. Limited data also suggest that positive pressure therapy in patients with CPAP and PH can lower pulmonary artery pressures (as measured by echocardiography)[68,69]; however, more robust studies, including those using invasive hemodynamics, are required.

Although the current research is limited, effects of exercise on SDB are likely beneficial, and conversely, SDB treatment may improve exercise performance. The magnitude and longer-term clinical significance of these effects and in which patient populations they are the most impactful remain to be determined.

PRACTICAL CONSIDERATIONS FOR EXERCISE AND SDB IN PH

Screening for SDB is standard when evaluating a patient for PH and exercise intolerance[1]; based on epidemiologic evidence suggesting increased risk of severe disease, special attention should be given to patients with risk factors for OHS such as obesity, hypertension, and diabetes. In patients whom SDB is suspected, standard diagnostics including polysomnography are sufficient to detect the disease. Assessments of exercise capacity are typically performed by 6MWT in most PH centers. Although CPET is not uniformly used for the diagnosis and management of PH, it may be particularly helpful to assess cardiovascular and pulmonary responses to exercise when OSA and PH are clinically suspected. Some differences in CPET may be useful in differentiating between circulatory (Group 1 PAH) and ventilatory (Group 3 PH) limitations to exercise (Table 1). Guideline recommendations[1] and common clinical practice are to treat SDB in PH and refer PH patients for supervised rehabilitation programs. While these may be viewed as occurring in parallel, the mechanistic and clinical links between SDB and exercise would seem to suggest that these treatments might be synergistic in PH.

CONCLUSIONS

Exercise intolerance exists in both SDB and PH; however, the causality of these relationships, the mechanisms that underpin them, and the directions in which they occur remain understudied. Despite this, many of the pathophysiological mechanisms that drive SDB and PH clearly overlap, including systemic inflammation, oxidative stress, metabolic dysfunction, and endothelial dysfunction. Exercise intolerance occurs commonly in patients with SDB with or without PH, and both treatment of SDB and exercise training can improve clinical outcomes. The precise benefits, long-term therapeutic effects, and populations which find the most benefit have yet to be elucidated. Future work should focus on deep characterization of biological mechanisms that contribute to exercise intolerance

Table 1. Cardiopulmonary Exercise Test (CPET) Criteria That May Differentiate Group 1 PAH From Group 3 PH[a]

Criteria favoring Group 1 PAH	Criteria favoring Group 3 PH
Features of circulatory limitation to exercise: • Preserved breathing reserve • Reduced O_2 pulse • Low CO/VO_2 slope • Mixed venous oxygen saturation at lower limit • No change or decrease in $PaCO_2$ during exercise	Features of ventilatory limitation to exercise: • Reduced breathing reserve • Normal O_2 pulse • Normal CO/VO_2 slope • Mixed venous oxygen saturation above lower limit • Increase in $PaCO_2$ during exercise

Abbreviations: CPET = cardiopulmonary exercise test; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension.

[a]Adapted from Nathan et al. *Eur Respir J*. 2019;53(1):1801914.[2]

in SDB and PH and careful study of longitudinal relevant clinical outcomes in well-defined populations so treatment recommendations regarding exercise in these conditions can be made clear.

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REGULAR ARTICLE

Pulmonary Hypertension: Exercise Intolerance and the Benefits of Respiratory Muscle and Exercise Training

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Pulmonary hypertension is characterized by significant remodeling of the pulmonary vasculature, leading to raised pulmonary vascular resistance. Despite advances in medical therapy, decreased exercise tolerance remains a predominant symptom experienced by patients. Reduced exercise capacity has been shown to have implications on quality of life and prognosis. There is growing acknowledgment that the etiology of exercise tolerance is multifactorial with cardiac, respiratory, and skeletal muscle contributors. There has been a shift in management approach with exercise training now included as a Class 1 recommendation indication in recent guidelines. In this review, we summarize the literature on the pathophysiology of exercise intolerance in pulmonary hypertension and then describe the literature assessing the safety and efficacy of inspiratory muscle and exercise training in patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension.

Pulmonary hypertension (PH) is characterized by significant remodeling of the pulmonary vasculature, leading to raised pulmonary vascular resistance and eventually right heart failure.[1] It is defined hemodynamically as a mean pulmonary arterial pressure of ≥20 mmHg when measured invasively on right heart catheterization.[1] Despite numerous advances in medical therapy in treating group 1 pulmonary arterial hypertension (PAH) and chronic thromboembolic PH (CTEPH; group 4), decreased exercise tolerance remains a predominant symptom experienced by patients.[2-4] Reduced exercise capacity has been shown to have implications on quality of life (QoL), prognosis, and mortality[2].

Although traditionally the main drivers of reduced exercise tolerance in this population were thought to be cardiopulmonary factors such as increased afterload and ventriculoarterial uncoupling, there is growing acknowledgment that this is actually multifactorial with cardiac, respiratory, and skeletal muscle contributors.[2,5,6] Respiratory muscle dysfunction and weakness are 2 such factors that have been shown to correlate with exercise intolerance.[2,6,7]

Exercise training was previously discouraged in patients with PH due to

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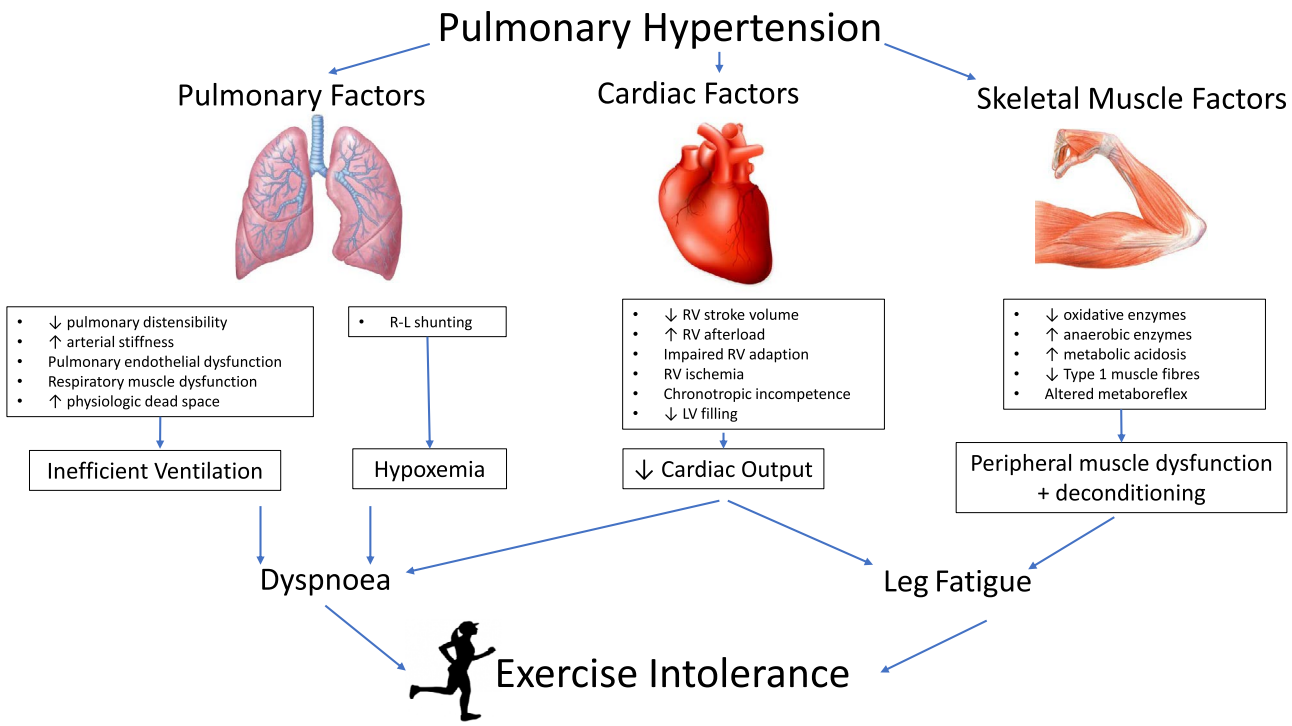

Figure 1: Multifactorial etiology of exercise intolerance in pulmonary hypertension. Abbreviations: L, left; LV, left ventricular; R, right; RV, right ventricular.

concerns about safety and potential worsening of cardiac function.[8] However, with increased understanding of the multifactorial nature of exercise intolerance, there has been a shift in management approach reflected by a Class 1 indication in international guidelines that emphasize the importance of supervised exercise training in PH cohorts in addition to optimal medical therapy.[1,9] It has been proposed that inspiratory muscle training (IMT) may ameliorate respiratory muscle weakness, while exercise training may improve skeletal muscle structure and function in PAH patients, thereby improving exercise capacity and QoL similar to heart failure and chronic obstructive pulmonary disease cohorts.[10-12]

In this review, we summarize the literature on exercise intolerance in PAH, with a particular focus on respiratory muscle weakness and inspiratory muscle and exercise training in these patients.

PATHOPHYSIOLOGY OF EXERCISE INTOLERANCE IN PH

Cardiac Factors

Right ventricular (RV) dysfunction is a major factor that limits exercise in patients with PH. In the early stages of disease, a progressive rise in the pulmonary vasculature load leads to increased RV afterload.[2] The RV adapts by becoming hypertrophied to maintain stroke volume at rest. During exercise, the RV may not be able to meet increased metabolic demands, leading to a subsequent decrease in stroke volume[13] (Figure 1).

As the disease progresses, RV maladaptation occurs in response to the chronic, pressure-overloaded state.[14] This results in RV dilatation, eccentric hypertrophy, and decreased systolic function. Associated cellular changes include a decrease in α-myosin heavy chain filaments and an increase in β-myosin heavy chain filaments.[15,16] Ventriculoarterial uncoupling is the physiologic consequence of RV maladaptation and occurs when the increase in RV contractility is inadequate to meet the demands of high afterload.[17-19] In PAH patients, RV-PA coupling is often preserved at rest, but a deterioration is noted during exercise.

Myocardial ischemia may also contribute; perfusion is dependent on the gradient between aortic root pressure and intramural pressure.[20] In PAH, an increase in systolic RV pressure leads to biphasic right coronary flow. This leads to decreased systolic function, which is most pronounced in exercise.[20] Furthermore, external compression of the left main coronary artery by dilated main pulmonary arteries has been shown to be a cause of angina and decreased exercise tolerance in PAH patients.[21]

Pulmonary Factors

Pulmonary vasculopathy is central to the pathophysiology of PH and contributes to exercise limitation. Endothelial dysfunction leads to vascular remodeling via vasoconstriction, cellular hyperplasia, and sclerosis.[2,22-24] During exercise, there is an increase in blood flow to the lungs, and the pulmonary vasculature must distend to accommodate this. These mechanisms are impaired in PAH due to a decrease in pulmonary vasculature distensibility; this causes an increase in mean pulmonary arterial pressure and RV afterload on exertion (Figure 1).[25]

In the absence of concomitant lung disease or obesity, most PAH patients have preserved gas exchange at rest. During exercise, however, arterial desaturation can occur from reduced mixed venous oxygen content from a widening of the systemic arterial-venous oxygen difference from a low cardiac output state.[2] Hyperventilation and ventilatory insufficiency also contribute to dyspnea

likely secondary to enhanced chemosensitivity and increased physiologic dead space from vascular obliteration.[26] Mechanical ventilatory limitations from dynamic hyperinflation and peripheral muscle dysfunction also contribute to dyspnea and exercise intolerance.[27]

Respiratory muscle dysfunction is now increasingly recognized as a key factor contributing to exercise limitation in PAH patients. Approximately 15% of cardiac output is directed to respiratory muscles during maximal exercise and thus may be affected by reduced blood flow in PAH and CTEPH.[28] PAH patients have been documented to have a >50% reduction in force-generating capacity and atrophy of the diaphragm.[29] This reduction in diaphragmatic strength likely contributes to exercise limitation and dyspnea. Furthermore, an association has been documented between peripheral muscle strength and maximal inspiratory pressure (MIP), suggesting that respiratory muscles may influence exercise intolerance.[30,31]

Weak respiratory muscle may impair the function of the respiratory muscle pump, which helps to increase RV stroke volume. In the setting of increased pulmonary vascular resistance, augmentation of the respiratory muscle pump may help enhance pulmonary blood flow.[2]

Skeletal Muscle Factors

Skeletal muscle abnormalities are now recognized as important factors contributing to reduced exercise capacity in PH.[5,31] Abnormalities include muscle atrophy, impaired oxygen extraction, reduced angiogenesis, and contractility.[5,31] These findings are similar to those observed in systemic myopathy seen in heart failure patients.[2,5] Unfortunately, while physical inactivity is known to lead to muscle atrophy and a myocyte fiber transition, PH patients often avoid physical activity to avoid precipitating symptoms, leading to an atrophy spiral (Figure 1).[2]

Skeletal muscle density correlates with exercise capacity and muscle strength. Diminished amounts of CD31+ cells, which promote revascularization, and miR-26, which is proangiogenic, are seen in the skeletal muscle of PAH patients.[32,33] Furthermore, low cardiac output leads to a hypoxic state during increased metabolic demand, which, combined with impaired skeletal oxygen extraction, leads to reduced exercise capacity. In addition, systemic inflammation, seen in chronic diseases, is known to have a catabolic effect on skeletal muscle and is seen in PAH.[34]

IMT

IMT is a feasible and well-tolerated physical therapy that aims to induce adaptive changes in respiratory muscle structures, thereby increasing inspiratory muscle strength and in turn reducing exercise intolerance.[35,36] Prior studies have objectively documented that MIP and maximal expiratory pressure are significantly lower in PAH patients, independent of ventilation efficiency or reduced pulmonary hemodynamics.[6,7] Respiratory muscle weakness has also been documented in the CTEPH population, with reduced diaphragmatic contractility noted within slow-contracting muscle fibers and reduced calcium sensitivity of fast-contracting fibers.[34] It is postulated that IMT may improve exercise capacity by increasing the strength, fatigue resistance, and endurance of diaphragm-based inspiratory muscles, thereby allowing patients to maintain higher ventilation volumes, increase gas exchange, and have a lesser sensation of dyspnoea.[15,35,37]

Broadly speaking, IMT is performed using a handheld device that applies resistance to inspiration.[38] Patients can participate in training at home or in a supervised setting. Training protocols include cycles of resistive breathing (either a certain number of repetitions or a certain amount of time) multiple times a week over a 6- to 10-week period. The feasibility and effectiveness of this training has been well established in chronic obstructive pulmonary disorder and heart failure populations, but the utility in PAH and CTEPH populations remains less clear.[10-12]

The literature on IMT in the PAH and CTEPH populations is limited to 6 small, randomized control trials (n = 10-31).[15,35,37,39-41] Table 1 summarizes these 6 studies; the interventional groups undertook IMT of varying resistance 3 to 7 times per week over a 6- to 10-week period. At baseline, respiratory muscle strength was reduced, with pooled data from a recent meta-analysis showing a mean MIP of 61 cmH_2O in included studies (normal MIP is ≥80 cmH_2O).[15,36,37] The MIP increased significantly in the intervention group of all studies, with pooled results showing a mean increase of 19 cmH_2O ($P < .001$) compared with control groups.[15,36,37,39] After intervention, the mean MIP reached normal thresholds, highlighting that IMT can potentially help PAH patients reach normal levels of resting respiratory muscle function.[36] Several studies reported a concomitant improvement in maximal expiratory pressure, suggesting that expiratory muscles also become retrained through forced ventilation.[15] However, this was not a consistent finding across studies.[35,37]

Prior studies have sought to determine whether these improvements in respiratory muscle strength translate into improved functional capacity and outcomes. Six-minute walking distance (6MWD) is generally accepted as a surrogate endpoint for long-term clinical outcomes in PAH patients.[42] Another recent meta-analysis reported the pooled data from 4 studies and reported a mean increase in 6MWD of 39 m compared with control groups.[43] This improvement, while likely clinically significant,[44,45] does not quite meet the reported threshold of 42 m, which has been associated with reduced incidence of clinical events.[46] Furthermore, meta-analytic studies show that the lower limit of the 95% confidence interval is less than 33 m, which is generally considered to be the lower limit of clinical significance for 6MWD.[43] These modest improvements in 6MWD suggest that IMT is an adjunct form of exercise training rather than a replacement for exercise training.

The attenuation of the inspiratory muscle metaboreflex through IMT is likely to explain functional improvement.[35] During exercise, sympathoexcitation leads to vasoconstriction and decreased vascular conductance. Blood is redirected from exercising muscles toward respiratory muscles to sustain ventilation and is further accentuated when the diaphragm fatigues.[28,47-49] Increased work of

Table 1. Summary of Studies Looking at Inspiratory Muscle Training in Pulmonary Hypertension Cohorts

Reference	Design	Participants		Intervention	Outcomes[a]
		Intervention	Control		
Saglam et al (2015)[15]	RCT	n = 14 Female: 78.6% Age: 46.8 ± 15.6 PH group: group 1 = 14 (100%) WHO FC I/II/III/IV = 0/7/7/0	n = 17 Female: 82.4% Age: 52.2 ± 8.8 PH group: group 1 = 17 (100%) WHO FC I/II/III/IV = 0/9/8/0	Intervention: IMT Resistance: 30% MIP Regimen: 30 min × 7 times/wk for 6 wks Location: home Monitoring: wkly MIP assessment Control: IMT, 10% of MIP	Dyspnea: mMRC dyspnea score ▲ Resp muscle strength: MIP ▲, MEP ▲ Pulm function: FEV1 ▲, FVC ◊, FEV1/FVC ◊ Functional capacity: 6MWD ▲ QoL: emotional reaction ▲, nil else
Laoutaris et al (2016)[39]	RCT (pilot study)	n = 5 Female: 80% Age: 48.6 ± 12.7 PH group: group 1 = 5 (100%) WHO FC I/II/III/IV = NR	n = 5 Female: 40% Age: 60.6 ± 12.4 PH group: group 1 = 2 (40%), group 4 = 3 (60%) WHO FC I/II/III/IV = NR	Intervention: IMT Resistance: 60% SMIP Regimen: 30 min × 3 times/wk for 10 wks Location: hospital Monitoring: NR Control: none	Resp muscle strength: MIP ▲ Functional capacity: 6MWD ▲ QoL: IMT group ▲, CG ◊
Tran et al (2020)[35]	RCT (pilot study)	n = 6 Female: 83.3% Age: 55 ± 17 PH group: group 1 = 5 (83.3%), group 4 = 1 (16.7%) WHO FC I/II/III/IV = 0/6/0/0	n = 6 Female: 83.3% Age: 66 ± 10 PH group: group 1 = 5 (83.3%), group 4 = 1 (16.7%) WHO FC I/II/III/IV = 0/5/1/0	Intervention: IMT Resistance: 30 to 40% of SMIP Regimen: 30 rep × 5 times/wk for 8 wks Location: home Monitoring: wkly MIP assessment Control: none	Resp muscle strength: PImax ▲, PEmax Pulm function: ◊ Functional capacity: 6MWD ▲ CPET: peak VO_2 ◊ NT-ProBNP: ◊
Aslan et al (2020)[37]	RCT	n = 15 Female: 86.7% Age: 47.2 ± 13.3 PH group: group 1 = 10 (66.7%), group 4 = 5 (33.3%) WHO FC I/II/III/IV = 7/5/3/0	n = 12 Female: 83.3% Age: 50.6 ± 16.9 PH group: group 1 = 10 (83.3%), group 4 = 2 (16.7%) WHO FC I/II/III/IV = 1/7/4/0	Intervention: IMT Resistance: 30% of MIP Regimen: 30 min BD × 5 times/wk for 8 wks Location: home Monitoring: wkly MIP assessment Control: IMT at 9 cmH_2O without change in threshold pressure	Resp muscle strength: MIP ▲, MEP ◊ Pulm function: ◊ Functional capacity: 6MWD ◊ QoL: ◊
Fontoura et al (2021)[40]	RCT (full paper not yet published)	n = 17 Female: 100% Age: 38.8 ± 6.8 PH group: group 1 = 16 (94.1%), group 4 = 1 (5.9%) WHO FC I/II/III/IV = 0/14/3/0	n = 14 Female: 100% Age: 41.5 ± 10.6 PH group: group 1 = 13 (92.9%), group 4 = 1 (7.1%) WHO FC I/II/III/IV = 0/8/6/0	Intervention: IMT Resistance: 50 to 60% of MIP Regimen: 30 rep × 2 BD × 7 times/wk for 8 wks Location: home Monitoring: wkly MIP assessment Control: IMT at 3 cmH_2O without change in threshold pressure	Resp muscle strength: MIP ▲, MEP ▲ Pulm function: ◊ Functional capacity: 6MWD ▲ QoL: IMT group ◊
Kahraman et al (2023)[41]	RCT	n = 12 Female: 91.7% Age: 49.2 ± 17.1 PH group: group 1 = 10 (83.3%), group 4 = 2 (16.7%) WHO FC I/II/III/IV = 0/9/3/0	n = 12 Female: 91.7% Age: 55.5 ± 19.2 PH group: group 1 = 11 (91.7%), group 4 = 1 (8.3%) WHO FC I/II/III/IV = 0/7/5/0	Intervention: IMT Resistance: 40 to 60% of MIP Regimen: 30 min × 7 times/wk for 8 wks Location: home/ supervised 1 time/wk Monitoring: wkly MIP assessment Control: none	Resp muscle strength: MIP ▲, MEP ◊ Pulm function: ◊ Functional capacity: 6MWD ▲ Blood pressure: brachial SBP ▲, central SBP ▲ Peripheral muscle strength: IMT grip $p = 0.16$, quadriceps $p = 0.01$; no significant difference in CG QoL: ▲

6MWD, 6-minute walking distance; BD, bi-daily; CG, control group; CPET, cardiopulmonary exercise test; FEV1, forced expiratory volume; FVC, forced vital capacity; IMT, inspiratory muscle training; MEP, mean expiratory pressure; MIP, mean inspiratory pressure; mMRC, modified medical research council; NR, not recorded; NT-proBNP, N-terminal pro B-type natriuretic peptide; PEmax, maximum expiratory pressure; PH, pulmonary hypertension; PImax, maximum inspiratory pressure; Pulm, pulmonary; QoL, quality of life; RCT, randomized control trial; Rep, repetition; Resp, respiratory; SBP, systolic blood pressure; SMIP, sm; WHO FC, World Health Organization Functional Class.

[a]The symbol ▲ indicates a significant result, and the symbol ◊ indicates a nonsignificant result.

Table 2. Summary of Studies Looking at Exercise Training in Pulmonary Hypertension Cohorts

Reference	Design	Participants		Intervention	Outcomes
		Intervention	Control		
Atef and Abdeen (2021)[56]	RCT	n = 14 Female: NR Age: 48 ± 7 PH group: group 1 = 14 (100%) WHO FC I/II/III/IV = NR	n = 15 Female: NR Age: 47 ± 8 PH group: group 1 = 15 (100%) WHO FC I/II/III/IV = NR	Intervention: exercise, aerobic bike Target: 60-80% target HR Regimen: 15-30 min × 3 times/wk for 12 wks Location: outpatient supervised Control: no exercise intervention, usual care	Exercise capacity: VO_2 max ▲ PASP ▲
Butāne (2021)[57]	RCT	n = 9 Female: 88.9% Age: 61.6 ± 18.5 PH group: NR WHO FC I/II/III/IV = 0/4/5/0	n = 7 Female: 100% Age: 68.3 ± 16.6 PH group: NR WHO FC I/II/III/IV = 1/2/5/0	Intervention: exercise, aerobic (walk/bike), resistance, respiratory, education Regimen: 2-40 min, aerobic 3 times/wk, resistance 2 times/wk, respiratory 5 times/wk for 12 wks Location: home-based with supervision Control: no exercise intervention, usual care	Exercise capacity: 6MWD ▲
Chan et al (2013)[58]	RCT	n = 10 Female: 100% Age: 53 ± 13 PH group: group 1 = 100% WHO FC I/II/III/IV = 1/4/4/1	n = 13 Female: 100% Age: 55.5 ± 8.5 PH group: group 1 = 100% WHO FC I/II/III/IV = 0/8/5/0	Intervention: exercise, aerobic (walk), education Target: 70-80% Regimen: 30-45 min × 2-3 times/wk for 10 wks Location: outpatient Control: education, usual care	Exercise capacity: 6MWD exercise group ▲ VO_2 max ▲ QoL ▲
Ehlken et al (2016)[53]	RCT	n = 46 Female: 56.5% Age: 55 ± 15 PH group: group 1 = 35 (76.1%), group 4 = 11 (23.9%) WHO FC I/II/III/IV = 0/8/36/0	n = 41 Female: 51.2% Age: 57 ± 15 PH group: group 1 = 26 (63.4%), group 4 = 15 (36.4%) WHO FC I/II/III/IV = 0/6/30/4	Intervention: exercise, aerobic, resistance, respiratory Target: 60-80% target HR Regimen: 10- to 25-min cycle, 60-min walk, 30 min resistance, 30 min respiratory × 3-5 times/wk for 15 wks Location: inpatient 3 wks, unsupervised outpatient 12 wks Control: no exercise intervention, usual care	Exercise capacity: 6MWD ▲ VO_2 max ▲ QoL ▲
Ertan et al (2022)[59]	RCT	n = 12 Female: 83.3% Age: 49.6 ± 9.9 PH group: group 1/ group 4 WHO FC I/II/III/IV = 0/10/2/0	n = 12 Female: 75% Age: 44.3 ± 9.4 PH group: group 1/ group 4 WHO FC I/II/III/IV = 0/9/3/0	Intervention: exercise-aerobic (walk) Regimen: 30-45 min × ≥3 times/wk for 8 wks Location: outpatient and home Control: no exercise intervention, usual care	Exercise capacity: 6MWD ◊ QoL ◊

(Continued)

Table 2. Summary of Studies Looking at Exercise Training in Pulmonary Hypertension Cohorts *(Continued)*

Ganderton et al (2013)[60]	RCT	n = 5 Female: 100% Age: 51, range 40-53 PH group: group 1 = 100% WHO FC I/II/III/IV = 0/3/2/0	n = 5 Female: 80% Age: 53, range 42-57 PH group: group 1 = 100% WHO FC I/II/III/IV = 0/3/2/0	Intervention: exercise (walk, cycle) Target: 60-70% of target HR Regimen: 60 min × 3 times/wk for 12 wks Location: outpatient supervised Control: no exercise intervention, usual care	Exercise capacity: 6MWD ▲ VO_2 max ▲ QoL ▲
González-Saiz et al (2017)[61]	RCT	n = 19 Female: 60% Age: 46 ± 11 PH group: group 1 = 17 (89.5%), group 4 = 2 (10.5%) WHO FC I/I-II/II-III/IV = 3/2/11/4/0	n = 16 Female: 60% Age: 45 ± 12 PH group: group 1 = 14 (87.5%), group 4 = 2 (12.5%) WHO FC I/I-II/II-III/IV = 6/2/10/0/2/0	Intervention: exercise, aerobic bike, resistance, respiratory Regimen: 20-40 min aerobic × 5 times/wk, resistance × 3 times/wk, respiratory BD × 6 times/wk for 8 wks Location: outpatient supervised Control: no exercise intervention, regular scheduled visits with clinicians	Exercise capacity: 6MWD ▲ VO_2 max ▲ QoL ▲
Grünig et al (2020)[54]	RCT	n = 58 Female: 58.8% Age: 52 ± 12 PH group: group 1 = 51 (87.9%), group IV = 7 (12.1%) WHO FC I/II/III/IV = 12/24/21/1	n = 58 Female: 77.6% Age: 55 ± 13 PH group: group 1 = 47 (81%), group 4 = 11 (19%) WHO FC I/II/III/IV = 0/34/24/0	Intervention: exercise (walk/cycle), respiratory Target: 40-60% HR Regimen: 10- to 25-min cycle, 60-min walk, 30 min resistance, 30 min resp 3-7 times/wk for 12 wks Location: inpatient 10-30 days, 12 wks home Control: no exercise intervention, usual care	Exercise capacity: 6MWD ▲ VO_2 max ▲ QoL ▲
Kagioglou et al (2021)[62]	RCT	n = 12 Female: 50% Age: 54.7 ± 15.6 PH group: group 1/ group 4 WHO FC I/II/III/IV = 0/10/2/0	n = 10 Female: 70% Age: 53.1 ± 12.1 PH group: group 1/ group 4 WHO FC I/II/III/IV = 0/10/0/0	Intervention: exercise, aerobic (walk, cycle) Target: 60-80% target HR Regimen: 45-60 min × 3 times/wk for 6 months Location: outpatient and home Control: no exercise intervention, usual care	Exercise capacity: 6MWD ▲ VO_2 max ▲ QoL ▲
Ley et al (2013)[63]	RCT	n = 10 Female: 80% Age: 47 ± 8 PH group: group 1 = 9 (90%), group 4 = 1 (10%) WHO FC I/II/III/IV = 0/3/7/0	n = 10 Female: 60% Age: 54 ± 14 PH group: group 1 = 7 (70%), group 4 = 3 (30%) WHO FC I/II/III/IV = 0/1/9/4	Intervention: exercise, aerobic, resistance, respiratory Target: 60-80% target HR Regimen: 10- to 25-min cycle, 60-min walk, 30 min respiratory × 5 times/wk for 3 wks Location: inpatient Control: no exercise intervention, usual care	Exercise capacity: 6MWD▲

(Continued)

Table 2. Summary of Studies Looking at Exercise Training in Pulmonary Hypertension Cohorts *(Continued)*

Mereles et al (2006)[64]	RCT	n = 15 Female: 66.7% Age: 47 ± 12 PH group: group 1 = 13 (86.7%)/group 4 = 2 (13.3%) WHO FC I/II/III/IV = 0/2/12/1	n = 15 Female: 66.7% Age: 53 ± 14 PH group: group 1 = 11 (73.3%)/group IV = 4 (26.7%) WHO FC I/II/III/IV = 0/4/10/1	Intervention: exercise, aerobic (walk/cycle), resistance, respiratory Target: 60-80% target HR Regimen: 10- to 25-min cycle, 60-min walk, 30 min resistance, 30 min respiratory × 5 times/wk for 15 wks Location: inpatient (3 wks) and outpatient (12 wks) Control: common rehabilitation	Exercise capacity: 6MWD ▲ QoL ▲
Rakhmawati et al (2020)[65]	RCT	n = 20 Female: 95% Age: 37.5 ± 8.8 PH group: group 1, ASD-PH = 100% WHO FC I/II/III/IV = 4/16/0/0	n = 18 Female: 88.9% Age: 35.5 ± 10.4 PH group: group 1, ASD-PH = 100% WHO FC I/II/III/IV = 4/14/0/0	Intervention: exercise (walk) Target: 60-70% of target HR Regimen: 30 min × 3 times/wk for 12 wks Location: outpatient Control: no information	Exercise capacity: 6MWD▲ QoL▲
Wilkinson et al (2007)[66]	RCT	n = 18 Female: NR Age: NR PH group: NR WHO FC I/II/III/IV = NR	n = 18 Female: NR Age NR PH group: NR WHO FC I/II/III/IV = NR	Intervention: exercise Regimen: 3 months Location: outpatient, 1 supervised, then unsupervised Control: no exercise intervention, usual care	Incremental shuttle walk Endurance shuttle walk
Wojciuk et al (2021)[67]	RCT	n = 16 Female: 43.7% Age: 48.9 ± 18.3 PH group: group 1 = 100% WHO FC I/II/III/IV = 0/8/8/0	n = 23 Female: 56.5% Age: 53.7 ± 12.8 PH group: group 1 = 100% WHO FC I/II/III/IV = 0/2/5/0	Intervention: exercise (interval) Target: 60-70% of target HR Regimen: 45-60 min × 5 times/wk for 24 wks Location: home based with supervision Control: no exercise intervention, usual care	Exercise capacity: 6MWD▲ QoL▲

[a]The symbol ▲ indicates a significant result, and the symbol ◊ indicates a nonsignificant result.

6MWD, 6-minute walking distance; ASD-PH, atrial septal defect - pulmonary hypertension; CG, control group; HR, heart rate; NR, not recorded; PH, pulmonary hypertension; QoL, quality of life; RCT, randomized control trial; SBP, systolic blood pressure; WHO FC, World Health Organization Functional Class.

breathing therefore increases the cardiac output required to maintain ventilation. In PAH, this is particularly significant as cardiac output is often limited; thus, the redirection of blood flow comes at the expense of premature exercise muscle fatigue.[35] Increased ventilatory load and weak respiratory muscle capacity augment neural respiratory drive, while the recruitment of accessory respiratory muscles to facilitate ventilation during diaphragmatic fatigue provides further sensory feedback to the central nervous system.[48,50] These further compound the sensation of breathlessness. Increasing inspiratory muscle strength through IMT increases the ventilatory load needed for the onset of the metaboreflex and may thus improve exercise capacity.[35]

Interestingly, despite objective improvements in respiratory muscle strength and functional capacity, only Saglam et al[15] reported significant improvements in forced expiratory volume in the first second, with no other studies reporting significant improvements in lung function as measured by spirometry.[15,35,37,39-41] This was reflected in the pooled data reported in both recent meta-analyses.[36,43] The sensation of dyspnea during daily activities was only reported in 2 studies (modifiec medical research council scale). Pooled analysis showed a small but significant decrease of 0.5 points in the IMT group compared with the control group.[15,40] QoL scores were assessed in 4 studies; pooled analysis of 3 studies showed no significant difference in emotional or physical measures of QOL.[15,37,40] One of the remaining studies showed that the IMT group had significant improvements in

physical QoL measures ($P = .002$) and some subcomponents of emotional QoL but had no significant differences between intervention and control groups.[39] Safety of IMT has been reported in 2 studies, with Aslan et al reporting no adverse outcomes and Saglam et al having 1 patient self-report wrist pain.[15,37] Compliance to IMT training programs was reported as ≥98% in the 3 studies that reported on completion rates.[15,35,37]

Exercise Training

Exercise training has been shown to be a feasible, safe, and efficacious treatment for PH patients.[51] It has been reported to improve skeletal muscle function by increasing capillarization and changing muscle fiber type.[29] Exercise training also influences the pulmonary vasculature through regulating pulmonary vascular remodeling and has recently been shown to improve pulmonary hemodynamics, with reductions in mean pulmonary arterial pressure noted on right heart catheterization following exercise-based rehabilitation.[52-54] It is important to note, however, that to achieve hemodynamic improvements, high volumes of exercise per patient (>220 hours) was needed, with a recent study unable to replicate this at lower levels.[55]

Exercise training in this setting refers to a combination of aerobic and low-load resistance exercise training. Aerobic exercise involves activation of large skeletal muscle groups through walking or cycling for 20 to 40 minutes. Resistance training may also be used with upper and/or lower body muscle groups targeted through repetitions of set exercises. However, evidence on the safety and efficacy of isolated resistance training in PH remains limited. Exercise training is often supervised and can occur in an inpatient, outpatient, or remote setting. Sessions are generally 2 to 3 times per week over a minimum of 4 weeks.[51]

A recent Cochrane review analyzed data from 14 parallel grouped randomized control trials (n = 10-129) that looked at the impact of exercise rehabilitation on outcomes in patients with PH.[51] Included studies enrolled 571 patients with PAH or CTEPH who were stable on medical therapy. All exercise training programs were similar to standardized recommended cardiac and pulmonary rehabilitation programs. Programs were primarily aerobic, although some included additional resistance training components. Table 2 summarizes the studies and their outcomes.[53,54,56-67]

Exercise capacity was the key outcome assessed across studies. A pooled analysis of 11 studies showed a mean difference in 6MWD of 49 m following exercise training when comparing the intervention and control groups,[53,54,57-65] which exceeds both the minimal threshold for clinical significance and the threshold for reduced clinical events. Cardiopulmonary exercise testing was also assessed in 7 studies and showed a significant increase in peak oxygen uptake (VO_2 max), the gold standard measure of cardiopulmonary fitness, following intervention when comparing the exercise groups with the control groups (mean difference of 2.1 mL/kg/min, 95% confidence interval of 1.57-2.57).[53,54,58,60-62,64] A significant increase in peak power between groups was also noted. There was a large amount of heterogeneity between studies, and it remains unclear if these variations were due to disease severity, location of program (inpatient versus outpatient), or study population.[51]

Aerobic exercise training in athletes has been shown to lead to an increase in skeletal muscle capillarization with elevated capillary density and capillary-to-fiber ratio.[68,69] This leads to enhanced transport and extraction of oxygen from skeletal muscles causing increased aerobic activity. In chronic heart failure patients, exercise training has been shown to reverse skeletal muscle atrophy, improve ventilatory efficacy, and attenuate endothelial dysfunction.[70-72] These mechanisms are also likely to play a role in increasing exercise capacity in PH patients.[51] Further research is needed to determine if there are PH-specific mechanisms.

No increased risk of serious adverse events were seen in a recent metanalysis when comparing exercise programs to usual care.[51] Only 5 serious adverse events were reported across 11 studies (439 patients).[51] Grünig et al reported 3 events in the exercise group (stroke, generalized edema, and decompensated diabetes), whereas Ganderton et al reported that 1 patient experienced presyncope during 1 training session.[54,60]

Exercise training programs have also been shown to significantly improve physical and emotional indicators of QoL in PH patients undergoing training compared with controls using both general and PH-specific QoL scores.[56-58,65-67] This emphasizes the holistic approach adopted in such rehabilitation programs, which enables patients to not only improve in objective measures of functional capacity but also extend their individual spectrum of daily activity.[51] Future studies should investigate the optimal type, intensity, and volume of exercise required to improve physiological measures and clinical outcomes. Major PH treatment centers are often located within major cities; thus, access to face-to-face exercise programs may be limited for patients who face geographic or socioeconomic barriers. More recently, entirely remote exercise programs have been evaluated and have been shown to be effective, suggesting that this may be suitable for stable patients as a more scalable intervention.[73]

CONCLUSIONS

Exercise intolerance is a predominant symptom in patients with both PAH and CTEPH, with complex pathophysiology. IMT and exercise training target different pathophysiologic pathways and can feasibly be used as an adjunct to standard medical therapy. Both exercise training programs and IMT have been shown to lead to significant objective improvements in functional capacity, although increases with the former are more marked. Exercise training also consistently improves QoL indicators and should be incorporated into standard care models for stable patients.

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REGULAR ARTICLE

Skeletal Muscle Structural and Functional Impairments as Important Peripheral Exercise Intolerance Determinants in Pulmonary Arterial Hypertension

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Reduced exercise tolerance stands as the foremost symptom, profoundly impacting the lives of those grappling with pulmonary arterial hypertension (PAH). This decline stems from both pulmonary and cardiac irregularities. Nonetheless, there is a burgeoning recognition that dysfunction within peripheral skeletal muscles (SKMs) significantly contributes to compromised exercise capacity. Consequently, the morphological and functional impairments of SKMs, coupled with microvascular loss, proinflammatory states, and oxidative disorders, play substantial roles in limiting exercise capacity in PAH. Regrettably, these facets have only undergone partial scrutiny. Thus, this review aims to spotlight the current body of literature concerning SKM dysfunctions in PAH and pinpoint knowledge gaps warranting further exploration to deepen our comprehension of SKM dysfunction and exercise intolerance in PAH.

INTRODUCTION

Pulmonary hypertension (PH) is a complex, multisystem disease divided into 5 heterogenous groups according to its clinical presentation, pathological findings, underlying diseases, and management characteristics.[1] Each group is characterized by distinct pathological features and has been heterogeneously studied. Exercise physiology has been primarily studied in group 1 (pulmonary arterial hypertension; PAH) and to a lesser extent in group 4 (chronic thromboembolic PH). Although the mechanisms underlying exercise intolerance in heart failure with reduced or preserved ejection fraction and chronic obstructive pulmonary disease (COPD) have been extensively explored, this phenomenon remains significantly understudied in the context of PH arising from left heart disease (group 2 PH) and PH attributable to lung diseases (group 3 PH).[2]

Group 1 PH or PAH is an orphan disease with an incidence and a prevalence of 6 and 48 to 55 cases/million adults, respectively. Although PAH was initially described to preferentially affect young females, recent data from US and European registries suggest that the epidemiology of PAH is changing, resulting in a more equal distribution between sexes. Patients are also more likely to suffer from various comorbidities, including cardiovascular and respiratory disorders.[3]

The early cardinal symptom of PAH is dyspnea with a progressively more rapid time to exhaustion inversely related to physical intensity, drastically limiting daily life activities. Late symptoms may include palpitations, postexercise syncope, hemoptysis, and weight gain due to fluid retention, which most commonly reflects concomitant right ventricle (RV) dysfunction. However, cardiac and pulmonary functions are not the sole determinants of exercise

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capacity. Although advancements in treatment over the past decade have notably enhanced patient survival, current therapies only partially alleviate symptoms such as dyspnea and exercise intolerance.[4] This observation underscores the need for a deeper understanding of the complex peripheral pathophysiological mechanisms underlying exercise intolerance in PAH. Such insights are crucial for developing strategies that more effectively tackle exercise intolerance and enhance the quality of life for patients. The present review summarizes the current knowledge regarding skeletal muscle (SKM) dysfunction and aims to highlight gaps in knowledge that need to be filled for a better understanding of exercise intolerance in PAH, complementing previous reviews about the complex central and peripheral pathological mechanisms regulating exercise intolerance in PAH.[5]

STRUCTURAL AND CONTRACTILE ALTERATIONS IN PAH SKELETAL MUSCLES

SKM contraction is generated by the formation of a strong actin-myosin cross-bridge that drives the thin actin filament toward the center of the sarcomere after neurostimulation, generating power and force. SKM consists of 2 basic fibers: the slow-contractile oxidative type I fiber and the fast-contractile type II fiber. The latter fiber type is divided into fast-contractile oxidative type IIa and fast-contractile glycolytic type IIx. Over the past 15 years, numerous studies have consistently documented alterations in mechanical properties and fiber type dysfunction across various SKMs in patients with PAH.

Respiratory Skeletal Muscles

Patients with PAH demonstrate a significant reduction in generating maximal inspiratory and expiratory pressures[6-8] due in part to atrophied and hypocontractile diaphragm muscle fibers.[8-10] These abnormalities correlate with in vivo reduction in inspiratory muscle contractility[11] and to a lesser extent with exercise capacity.[12] A recent study using a female rat model of PH induced by monocrotaline (MCT) revealed altered regional blood flow distribution. This alteration notably limited the blood supply to the diaphragm, further contributing to impaired contractility.[13] Whether the same phenomenon occurs in human PH remains to be investigated. These pathophysiological mechanisms observed in humans and animal models illustrate the various potential contributors to respiratory muscle dysfunction and their potential impact on exercise intolerance (Figure 1). Several small randomized controlled trials have demonstrated that respiratory muscle rehabilitation has the potential to improve respiratory muscle strength and to a limited extent, exercise capacity, functional daily life activities, and quality of life in PAH.[14,15] Nonetheless, more studies are needed to confirm these findings.

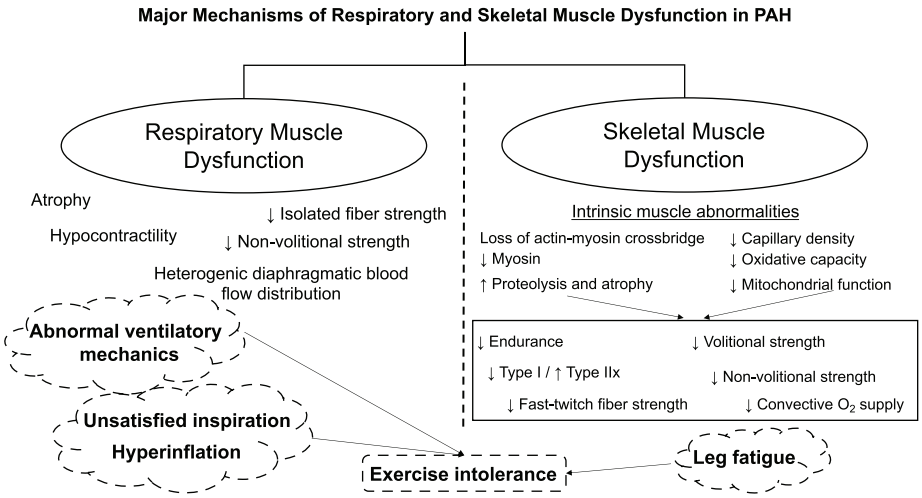

Figure 1: Pathophysiology and mechanisms of respiratory and peripheral skeletal muscle dysfunction in pulmonary hypertension. Volitional and nonvolitional strength correspond to voluntary and nonvoluntary skeletal muscle strength. Abbreviation: PAH, pulmonary arterial hypertension.

Peripheral Skeletal Muscles

Sarcopenia is defined as low appendicular SKM mass index, low grip strength, and slow gait speed. Sarcopenia is a common complication of heart failure with reduced ejection fraction and heart failure with preserved ejection fraction[16] as well as COPD[17] but was only recently recognized in PH. Indeed, a recent retrospective study has demonstrated its presence in up to 14% and 58% of patients with PAH and chronic thromboembolic PH, respectively, and was associated with a lower mean 6-min walk distance.[18] However, several limitations preclude a broader interpretation of those results. First, no self-reported or measured step count or anorexia of aging was considered to better assess daily life and age-related declines in physical activity. Second, sarcopenia was defined using the Asian Working Group for Sarcopenia, which is well validated but not necessarily applicable to North American and European populations. Nonetheless, this study further suggests that exercise intolerance is due to complex interactions between organ systems, including SKM and sarcopenia.

Our group established in 2010 that, compared with healthy controls, patients with PAH exhibit significant morphological and functional changes in the quadriceps. These changes include a reduced proportion of type I muscle fibers and decreased quadriceps strength, both of which were found to correlate with maximal exercise capacity.[19] Over the years, a significant shift in SKM fiber type from type I to type IIx has been described in most studies involving human biopsies[19-21] and experimental PH models,[22] although it remains inconsistent in the current literature.[23,24] This shift may contribute, in part, to reduced quadricep muscle strength[19,24] and endurance,[23,25] both correlating with lower exercise capacity in patients.

At the molecular level, quadriceps strength loss was further characterized by Manders et al, who reported a lower maximal force-generating capacity from isolated permeabilized fast-twitch fibers when normalized to their cross-sectional

area, which correlated with a decreased active stiffness in fast-twitch fibers.[26] Another contributor to strength loss is SKM atrophy. Batt et al characterized it and suggested 2 main pathways. First, they reported enhanced proteolysis through overactivation of the ubiquitin-proteasome system, supported by higher levels of atrogin-1 and muscle RING-finger protein-1 in the quadriceps of patients.[20] Second, they suggest that SKM atrophy may also come from mitochondrial dysfunction. As such, mitofusin-1 and mitofusin-2, mitochondrial membrane proteins, essential for the development of mitochondrial networks and redistribution of mitochondrial content,[27] were both significantly decreased in patients.[20] Therefore, loss of force-generating capacity in fast-twitch fibers and active SKM atrophy contribute to quadriceps strength loss (Figure 1).[22]

Current guidelines for PAH advocate for engaging in physical activities and enrolling in supervised rehabilitation programs.[1] These recommendations aim to ameliorate SKM dysfunction and exercise intolerance, highlighting the importance of these interventions in managing PAH effectively. Indeed, the literature extensively demonstrates that SKM readaptation has beneficial effects on exercise capacity and a modest improvement in quality of life in stable patients on optimal treatment.[28-30] A single-center nonrandomized trial including 19 patients with PAH showed improved endurance capacity, a shift of the anaerobic threshold to a higher level, increased quadricep strength and endurance, and increased quadricep type I fiber and capillarization after a 12-week supervised training program.[31] Since that time, no subsequent studies have assessed the effects of exercise on SKM function in PAH, particularly within the framework of contemporary treatment approaches.

UNDERLYING ETIOLOGY OF SKM DYSFUNCTION IN PAH

Convective and Diffusive O_2 Transport to Peripheral SKM

In PAH, studies examining SKM blood flow and its effect on O_2 transport are scarce. Convective O_2 transport, driven by the heart's pumping, delivers O_2 via the bloodstream, as described by the Fick principle. Meanwhile, diffusive O_2 transport, governed by Fick's Law, involves the passive movement of O_2 from higher to lower concentration areas across membranes. Alterations in these 2 mechanisms in PAH can significantly impact O_2 delivery and use in SKM.

In patients with PAH, only a lower convective O_2 transport has been demonstrated during exercise, as illustrated by a lower O_2 systemic extraction. This phenomenon resulted from a lower cardiac output,[32] while exercising muscles were able to extract O_2 similar to healthy controls.[33] Our group confirmed these results by demonstrating a decreased O_2 SKM saturation and systemic extraction during submaximal supine exercise.[24] We also documented that impaired O_2 SKM saturation was related to a lower total capillary density without a decreased capillary-to-fiber ratio.[24] We subsequently demonstrated that capillary density loss was related, at least in part, to an angiogenic defect secondary to a lower expression of microRNA-126 (miR-126).[23] Interestingly, the same pathophysiological mechanism was linked to capillary density rarefaction specifically in the RV samples of patients with PAH, contributing to RV failure,[34] as no loss of expression was identified in respiratory muscles. This loss of expression was associated with the methylation-dependent downregulation of miR-126 in the RV of patients.[34] Whether the same mechanism is responsible for the lower expression of miR-126 in the SKM of patients remains to be determined.

However, the diffusive portion of O_2 transport has not been demonstrated in humans using integrative physiology as it was for convective O_2 transport. Only recently have a few animal studies been conducted, but they only allow indirect interpretation regarding Fick's Law. As such, using the MCT model, Schulze et al[35] addressed both the convective and diffusive components of O_2 transport and demonstrated a reduced convective and diffusive O_2 transport, illustrated by lower SKM O_2 blood flow related to reduced red blood cell flux and velocity and increased nonflowing capillaries within the active muscles, indicating a potential heterogeneous distribution of functional and dysfunctional capillaries in this animal model. Such heterogeneity might explain the unchanged level of whole-muscle O_2 extraction reported by Schulze et al, as reduced red blood cell velocity and flux allow more time for O_2 extraction, counterbalancing dysfunctional capillaries. In accordance with decreased Fick principle,[35] the same group also demonstrated a compromised dynamic matching of SKM O_2 delivery to utilization after the initiation of exercise, indicating a slow VO_2 kinetic response to exercise in the same animal model.[36]

By contrast, Long et al[37] observed a diminished SKM blood flow and lower SKM O_2 extraction during moderate exercise in a slightly distinct preclinical protocol of MCT rats. This was notably associated with higher exercise-induced blood lactate levels and RV dysfunction. However, they did not find a correlation between blood flow and capillary ratio or function, suggesting that the limitation in blood flow might be more attributable to metabolic disturbances rather than structural abnormalities in the capillaries. This study suggests an impairment in convective O_2 transport, while diffusive O_2 transport remains unaffected in PAH. The discrepancies between these studies may be related to differences in animal models and the protocols used between studies. Moreover, because MCT-induced PH is associated with multisystem toxicity,[38,39] including the vascular system, these results should be interpreted with caution, as no replication in human studies has been performed. Finally, it is important to note that both the human and animal studies have relied solely on indirect measurements of O_2 transport. Until direct assessments in patients with PAH of both convective and diffusive O_2 transport are conducted, inconsistencies across studies are likely to persist, precluding a definitive conclusion.

SKM Mitochondrial Function

From a metabolic perspective, SKM tissue in PAH patients demonstrates notable downregulation of critical proteins pivotal to various metabolic pathways.[21] These include components of the

electron transport chain (complexes I and III), the ATP synthase complex, enzymes of the citric acid cycle, pathways involved in mitochondrial metabolism, the ADP/ATP translocase, and those governing fatty acid metabolism. Further bioinformatic analysis confirmed significant downregulation of proteins involved in biological function related to oxidative metabolism and mitochondrial integrity, whereas electron microscopy and enzymatic activity showed abnormal mitochondrial structure and density.[21] Although impaired mitochondrial function is expected to largely contribute to impaired oxidative metabolism and SKM endurance, its specific impact on muscle function and exercise capacity as well as its relationship with disease severity remain to be explored.

SKM Ergoreflex Contribution to Exercise Intolerance

The role of the SKM metaboreflex/ergoreflex system in exercise intolerance in PAH, mediated by group III and IV nerve fibers, has recently been explored. Because this system regulates blood flow to SKM and ventilation during exercise based on metabolic demand and muscle work, its dysfunction in PAH may impede proper blood flow adjustment to working muscles and respiratory modulation.[5] Briefly, this system consists of contraction-induced mechanical and chemical stimuli that activate thinly myelinated (group III) and unmyelinated (group IV) afferent nerve fibers projecting via the dorsal horn of the spinal cord to various sites within the central nervous system to inhibit the central motor drive, leading to exercise termination.[40] This system prevents profound SKM fatigue and is one of the central controls of ventilatory and circulatory responses to exercise.[41] Its overactivation was associated with an abnormal exercise ventilatory response in heart failure with reduced ejection fraction,[42] while its inhibition via spinal anesthesia in COPD resulted in a reduced ventilatory response to exercise and a longer cycling endurance capacity.[43] This system was recently investigated in PAH by Plunkett et al, demonstrating that increased activity in the SKM metaboreflex/ergoreflex system was associated with an increased ventilatory drive and perceived dyspnea using a posthandgrip exercise cuff occlusion to trap exercise metabolites,[44] therefore filling an important knowledge gap in PAH exercise pathophysiology. However, one of the main limitations of this study is its lack of group III/IV central inhibition to better confirm its role in the increased ventilatory response to exercise, reducing by the same occasion potential confounding factors like patients' exercise deconditioning or increased dyspnea secondary to cuff pain after handgrip exercise.

Additional Mechanisms Involved in PAH Pathophysiology Likely to Impact SKM Function

An increase in systemic proinflammatory cytokines has been proposed as an important mechanism leading to myopathy, exercise intolerance, and adverse prognosis observed in heart failure and cancer.[45,46] Interestingly, increased circulating levels of the interleukins (ILs) IL-1β, IL-2, IL-4, IL-6, IL-8, and IL-10 and tumor necrosis factor-α have been repeatedly reported in PAH.[47,48] Although likely contributing to impaired SKM function and sarcopenia, their role in peripheral myopathy remains to be established in PAH.[39,42]

Similarly, hypoxemia and subsequent oxidative stress/mitochondrial reactive oxygen species (ROS) accumulation have also been related to myopathy. Although mitochondrial handling of ROS remains one of the most critical environmental factors for life, its accumulation and mismanagement are thought to be a common determinant in the loss of both SKM quality and quantity.[49,50] SKM capacity and ability to handle ROS is compromised with aging but also in chronic diseases like COPD[51] and heart failure,[52] contributing to advancing sarcopenia in those ailments. However, its implication in SKM dysfunction in PAH remains an important mechanism to investigate, especially as SKM mitochondrial dysfunction has been described.

SUGGESTIONS FOR FUTURE RESEARCH

Despite several advances in the characterization of SKM function in PAH, important questions remain, similar to those in other chronic cardiopulmonary diseases. For example, we do not know what proportion of SKM dysfunction is attributable to years of prediagnostic inactivity and specific forms of myopathy in PAH or in specific PAH phenotypes. To better characterize this concept, there are some suggestions for future studies designed to improve our understanding of the development of SKM dysfunction in PAH, in line with current guidelines in other chronic cardiopulmonary diseases.[53]

1. The investigation of molecular SKM dysfunction is a key issue to understand the pathological process and to develop specific strategies to target it.
2. Matched controls and patients with a similar level of physical activity are of paramount importance when considering the presence of disuse versus myopathy.
3. Studies should be done with accepted quadriceps muscle strength assessments and normative values to allow better comparisons between studies.
4. Longitudinal studies investigating changes in SKM over time will be important to understand when pathological processes begin and how they evolve with the disease progression.
5. Whether SKM dysfunction can be either completely or partially normalized with exercise training should be a part of large, multicenter randomized clinical trials studying the effect of exercise training on cardiopulmonary function.
6. Clinical trials are also warranted to evaluate the impact of treatment specifically targeting SKM dysfunction on exercise capacity, quality of life, and survival.

CONCLUSION

In summary, pathophysiological abnormalities within SKM compromise its ability to effectively generate power and force. These abnormalities stem from intrinsic alterations in muscle architecture and the loss of capillaries, leading to compromised convective

O_2 transport, but without a definitive answer regarding its diffusive capacity. Additionally, SKM in PAH exhibits metabolic and oxidative irregularities. Although current treatments have extended patient lifespans, many still grapple with significantly diminished quality of life. Despite the demonstrated effectiveness of pulmonary rehabilitation over the years, there remains a pressing need for ongoing efforts to thoroughly characterize SKM function in PAH. This pursuit is essential for identifying new treatment avenues and determining the most suitable patient selection criteria and exercise regimens in the context of PAH.

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PH ROUNDTABLE

Recommending Exercise in Pulmonary Hypertension: Adult and Pediatric Perspectives

Catherine Avitabile, MD, Children's Hospital of Philadelphia; Nicola Benjamin, Dr. sc. hum, MSc. med, Universitätsklinikum Heidelberg; Erika S. Berman Rosenzweig, MD, Columbia University Medical Center; Karen Chia, MBBS, FAFRM (RACP), PhD, Sydney University Medical School; Prof. Dr. med. Ekkehard Grünig, Universitätsklinikum Heidelberg; and Aimee M. Layton, PhD, Columbia University Medical Center.

Catherine Avitabile and Aimee Layton asked questions of their colleagues from around the world on their experiences with exercise recommendations in PH patients of varying ages. They discussed patients' and their families' views on physical activity, benefits and risks of engaging in exercise, and resources for both health care providers and patients.

Avitabile/Layton: Do you find most of your patients exercise regularly or are physically active when you talk to them about their daily routines?

Chia: Most are quite sedentary.

Benjamin/Grünig: Patients with pulmonary hypertension are often very active or used to be very active before the onset of severe symptoms and their initial diagnosis. This changes with the recommendation to avoid physical exertion and an uncertainty how much exercise can be performed without causing harm and worsening the disease. Consequently, patients with pulmonary hypertension are often highly motivated to regain physical activity in their daily life.

Berman Rosenzweig: I find that this is quite variable between patients. Many patients are highly motivated to exercise once they feel up to it. I believe, in addition to helping their overall physical fitness, there is an important sense of empowerment that can't be quantified but I see all the time. Being able to exercise and know that you are contributing to your wellness in PH can make a real difference for patients. For those that are not feeling well enough to exercise, we still try to encourage them to participate in cardiopulmonary rehab to try to enable reconditioning.

Avitabile/Layton: How do patients/families react to a discussion around physical activity?

Chia: People are very open to it once they've had some discussion/education on benefits and safety. The main concerns are whether exercise is safe for them.

Benjamin/Grünig: Patients who plan to enter a rehabilitation program often seem to have been waiting for specialized training and an answer to the question which exercises can be done safely. They are keen to be active again and motivated to learn techniques to improve their exercise capacity. Patients' families are usually supportive and very much appreciated, when the exercise capacity improves and daily activities are enabled, e.g., going for a walk together. The prospect of this improvement is motivating for both patients and families.

Berman Rosenzweig: Patients and families often have many questions about physical activities and the dos and don'ts. This is one of my favorite conversations because one of the many goals of treatment is to enable patients to be able to resume their usual activities which includes exercise. There are precautions of course, for example, no heavy weightlifting, but we review these in our conversations together.

Avitabile/Layton: What do you perceive as the benefits of routine physical activity or planned regular exercise in your patients?

Chia: There are many, such as increased exercise capacity and therefore functional capacity, peripheral physiological adaptations (increased capillaries in muscle, increased muscle strength), and possibly central adaptations. It can also contribute to increased quality of life and engagement/agency.

Benjamin/Grünig: In our studies, we have already shown that a specialized exercise training program can improve exercise capacity, with improvement of 6-minute walking distance and peak oxygen consumption, quality of life, symptoms, and possibly right heart function. In addition, patients learn which exercises they can do to support their well-being and to be active again. In our program, patients also learn to avoid overexertion, which is key to safe exercising in PH. Whether this also has an impact on the clinical course and stability of the disease still needs to be investigated.

Berman Rosenzweig: There are many benefits to exercise, both physical and emotional. Patients often don't realize how deconditioned they've become when they weren't feeling well even before they were diagnosed. They often self-limit due to their breathing limitations, and this leads to physical deconditioning. So there is a real benefit, once feeling well, to reestablishing regular exercise. Muscle reconditioning is important, but being in better shape overall is less taxing on their heart and lungs when they exert themselves.

Avitabile/Layton: Are there specific guidelines you follow when recommending planned exercise to your patients?

Chia: No specific guidelines—more general safety recommendations (e.g., Borg RPE, symptoms to watch out for). Anything more strenuous than gentle walking I would usually recommend starting exercise in a supervised manner, e.g., cardiac or pulmonary rehab program.

Benjamin/Grünig: We do not recommend patients perform exercise training on their own. Patients often tend to overexert themselves. Therefore, exercise training should be taught in a supervised setting and consecutively transferred to the patients' daily routine. Our exercise training program was specifically developed for patients with pulmonary hypertension. In contrast to other training programs, we use a low-dose training intensity. However, it has also been shown in professional athletes that modern exercise programs are mainly focused on lower intensity training which is highly effective if it is individually adjusted. A key characteristic of our program is also a close supervision and adaptation of the exercises to the individual patient. This is enhanced by assessment of heart rate, oxygen saturation, subjective estimation of exertion, and information on right ventricular function throughout different stages of workload during an entrance examination.

Berman Rosenzweig: We work very closely with our exercise physiologists or with local cardiopulmonary rehab programs to establish guidance for our patients. Again, each patient is different and will have different constraints so the exercise guidance must be individualized.

Avitabile/Layton: What resources do you access when making these recommendations?

Chia: For patients, we use plain language guides, like those on PH Websites about exercise and PH. For myself, I access evidence-based research articles.

Benjamin/Grünig: The specialized training in Heidelberg is started as an inpatient rehabilitation for 3 weeks in cooperation with the rehabilitation clinic Koenigstuhl. At the beginning and at the end of the in-hospital phase, a detailed examination gives insight into the patient's exercise capacity, individual goals, and challenges. After continuation of the program at home for 3 months, a follow-up examination is offered to the patients to have feedback on the training effects and to discuss training adaptation.

Avitabile/Layton: What barriers do you face when recommending increased physical activity or planned exercise in your patients?

Chia: Personal factors such as fear/anxiety, breathlessness, lack of time, and lack of support/motivation. There are also logistical factors like access to appropriately supervised exercise, cost, or weather.

Benjamin/Grünig: In Germany, the health insurance companies mostly cover the costs for a rehabilitation program. However, it is not always easy to receive cost coverage for the specialized PH program, as this is more individualized and has higher costs. Insurance companies are often also attached to certain rehabilitation clinics, which makes it harder to receive cost coverage for a specific clinic and program.

Due to the inherent risks of exercise training in patients with right heart failure and to avoid worsening of the disease or an ineffective training, we recommend patients to take part in a specialized program rather than a general program to enhance physical activity. The specialized program in Heidelberg was specifically developed for patients with pulmonary hypertension and was continuously scientifically evaluated. Learning the right exercises and techniques is key to safe and successful training in these patients and should not be initiated in a general recommendation to be more active. If the exercise training is too intense, it can lead to disease worsening and increasing right heart failure.

Berman Rosenzweig: Patients can be apprehensive. In these cases, I do think it's important to work with rehab programs that can help monitor during initial trials of exercise and give tangible parameters (oxygen saturation and heart rate, for example) so patients can self-regulate when comfortable exercising on their own.

Avitabile/Layton: What type of research do you feel would be impactful in this area?

Chia: I think it's clear that exercise improves exercise capacity and QOL in patients with PH. I would love to see more studies about possible central benefits (e.g., effect of exercise on SV, CO, mPAP, etc.). However, these studies are invasive and difficult to recruit.

Benjamin/Grünig: We are still in need of more research in this area, though the impact of exercise in pulmonary hypertension has already been investigated in numerous studies. Especially the impact on the long-term outcome, time to clinical worsening and survival, right heart function and the mechanisms of action have still to be investigated. Furthermore, there is a lack of data on the optimal training methods and setting in these patients, and of course, training effects on different types of pulmonary hypertension as well as stages of severity should be focused on in future research.

Berman Rosenzweig: I believe we are just on the early cusp of integrating wearable technology into our day-to-day practices. Measures such as sedentary time can be so informative about the day-to-day activities or limitations our patients face. Heart rate trends and other measures in real time can also tell a much richer story about the real daily activities our patients can achieve and help us to tailor treatment. I would really love to see more actigraphy studies integrated into clinical trials for PH.

Advances in
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