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.

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

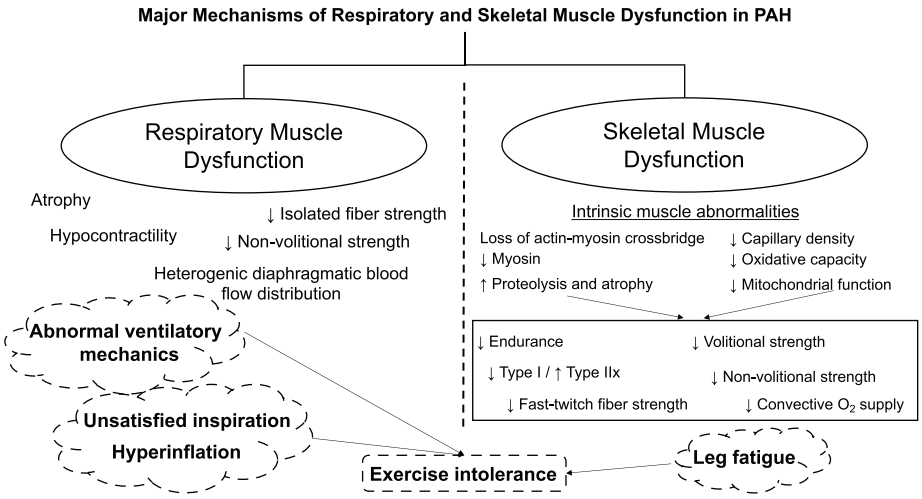

Figure 1: Pathophysiology and mechanisms of respiratory and peripheral skeletal muscle dysfunction in pulmonary hypertension. Volitional and nonvolitional strength correspond to voluntary and nonvoluntary skeletal muscle strength. Abbreviation: PAH, pulmonary arterial hypertension.

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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