Exercise intolerance in pulmonary arterial hypertension: insight into central and peripheral pathophysiological mechanisms

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Shareable abstract (@ERSpublications)
Cardiorespiratory, cerebrovascular and skeletal muscle (impaired skeletal muscle morphology, convective O_2 transport, capillarity and metabolism) dysfunctions contribute symbiotically to reduce exercise capacity in patients with PAH https://bit.ly/3hOQxJB

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Abstract

Exercise intolerance is a cardinal symptom of pulmonary arterial hypertension (PAH) and strongly impacts patients' quality of life (QoL). Although central cardiopulmonary impairments limit peak oxygen consumption (V'_{O_2peak}) in patients with PAH, several peripheral abnormalities have been described over the recent decade as key determinants in exercise intolerance, including impaired skeletal muscle (SKM) morphology, convective O_2 transport, capillarity and metabolism indicating that peripheral abnormalities play a greater role in limiting exercise capacity than previously thought. More recently, cerebrovascular alterations potentially contributing to exercise intolerance in patients with PAH were also documented. Currently, only cardiopulmonary rehabilitation has been shown to efficiently improve the peripheral components of exercise intolerance in patients with PAH. However, more extensive studies are needed to identify targeted interventions that would ultimately improve patients' exercise tolerance and QoL. The present review offers a broad and comprehensive analysis of the present literature about the complex mechanisms and their interactions limiting exercise in patients and suggests several gaps in knowledge that need to be addressed in the future for a better understanding of exercise intolerance in patients with PAH.

Introduction

Pulmonary hypertension (PH) is a complex clinical entity currently classified into five groups according to clinical presentation, pathological findings, pulmonary vascular haemodynamics and management characteristics [1]. The haemodynamic definition of pulmonary arterial hypertension (PAH; Group 1) was recently updated at the 6th World Symposium on Pulmonary Hypertension (WSPH), being now characterised by the concomitant presence of mean pulmonary artery pressure (mPAP) >20 mmHg, a pulmonary artery wedge pressure (PAWP) ⩽15 mmHg and a pulmonary vascular resistance (PVR) ⩾3 Wood units (WU) at rest [2]. Fatigue, exertional dyspnoea and a progressive reduction in daily life activities are its prime symptoms [3]. Exercise intolerance is therefore of paramount importance in limiting quality of life (QoL) in patients (figure 1). Contrary to initial beliefs, reduced exercise capacity is not solely triggered by central cardiopulmonary impairments. Several research reports published in the last decade suggest that skeletal muscle (SKM) and cerebrovascular impairments contribute in limiting exercise capacity [12–15].

This review aims to discuss measurement of exercise intolerance in patients with PAH and salient mechanisms responsible for the reduced exercise capacity in patients with PAH, which include cardiorespiratory alterations, but also intrinsic dysfunction of peripheral and respiratory SKM morphology and function. The role of exercise training as a treatment option, as well as several gaps in the knowledge that need to be addressed to better understand exercise intolerance in those patients, is also discussed.

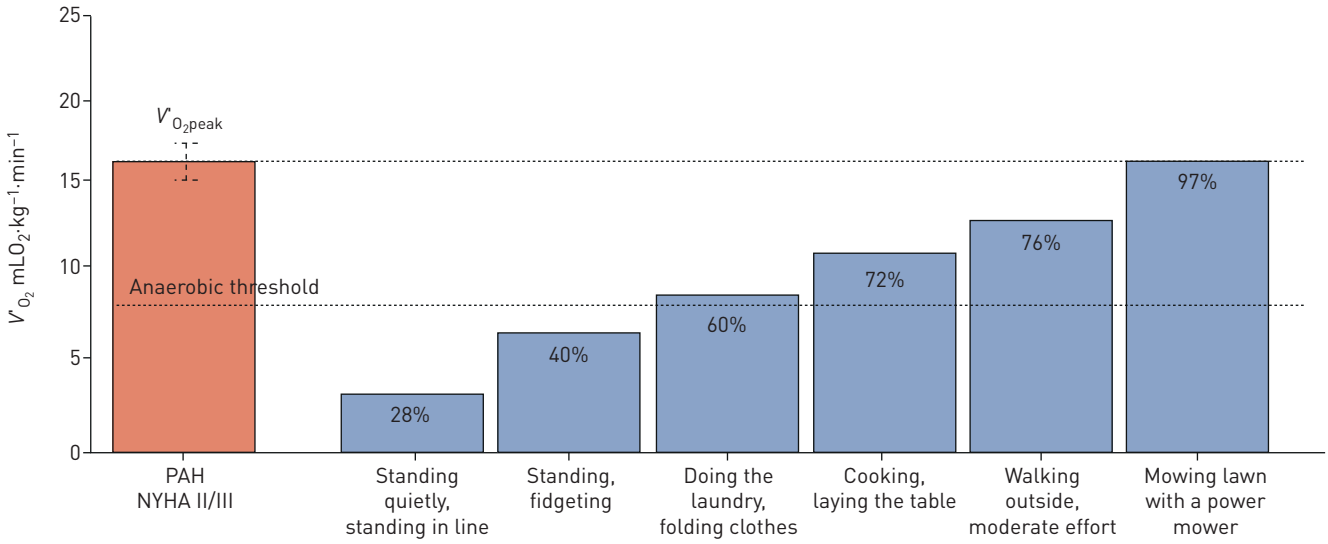

FIGURE 1 Exercise intolerance has a major impact on daily life activities. Patients rapidly reach anaerobic threshold in their daily activities, making sustained efforts difficult. Average peak oxygen uptake (V'_{O_2peak}) used for comparison was 16.1 (1.4) mL O_2.kg^{-1}·min^{-1} based on six studies [4–9]. V'_{O_2}: standing quietly in a queue: 4.6 mL O_2·kg^{-1}·min^{-1}; standing, fidgeting: 6.3 mL O_2·kg^{-1}·min^{-1}; doing the laundry, folding clothes: 9.8 mL O_2·kg^{-1}·min^{-1}; cooking, laying the table: 11.6 mL O_2·kg^{-1}·min^{-1}; walking outside, moderate effort: 12.3 mL O_2·kg^{-1}·min^{-1}; mowing the lawn, with a power mower: 15.6 mL O_2·kg^{-1}·min^{-1}. Specific physical activity intensity was determined using the 2011 Compendium of Physical Activities [10]. NYHA: New York Heart Association; PAH: pulmonary arterial hypertension. Data from [11].

Measurement of exercise intolerance in patients with PAH

Exercise testing in patients with PAH

The most commonly used test to comprehensively assess subjects' exercise tolerance remains the cardiopulmonary exercise test (CPET) that quantifies peak oxygen consumption (V'_{O_2peak}), carbon dioxide production (V'_{CO_2}) and minute ventilation (V'_E) using inspiratory and expiratory gas analysis at both rest and exercise [16]. In patients with PAH, compared with control groups, patients are characterised by lower V'_{O_2peak}; higher V'_E/V'_{CO_2} rate and slope; lower arterial CO_2 tension and end-tidal CO_2 tension (P_{aCO_2} and P_{ETCO_2}); lower O_2 pulse (oxygen uptake over heart rate ratio (V'_{O_2}/HR)); and lower pulse oxygen saturation (S_{pO_2}) [17–19]. Moreover, CPET has the ability to detect exercise right-to-left shunt through a patent foramen oval when patients present a sharp and sudden increase in V'_E/V'_{CO_2} rate accompanied by an equally sharp and sudden decline in P_{ETCO_2} and S_{pO_2} [20]. CEPT might have a utility in patients where PH remains a possibility (systolic PAP ⩽36 mmHg on transthoracic echocardiography) instead of a likely diagnosis [21]. However, CPET is not sensitive enough to differentiate right ventricle (RV) from left ventricle (LV) dysfunction as only cardiac echography or invasive right heart catheterisation is able to make the differential diagnosis between these conditions. Consistently, invasive CPET with concomitant right heart catheterisation has recently gained in popularity to delineate the specific cardiorespiratory components responsible for exercise intolerance in more complex clinical settings [22, 23]. Conversely, the 6-min walk test (6MWT), which is inexpensive, safe, easy to perform, and familiar to patients and hospital staff [1], remains the most commonly applied test to assess exercise tolerance in patients with PAH on a clinical basis. Although being considered a submaximal test in healthy subjects, this test induces similar V'_{O_2peak} responses as those observed during incremental CPET [24]. Interestingly, the 6MWT draws a parallel with daily life activity. Patients who walk an average of 5000 steps·day^{-1} or less engage in fewer moderate-to-intense daily life physical activities (>3.0 METs (metabolic equivalent of task)) compared with their healthy counterparts [25, 26], correlating with the 6MWT results [25, 26]. Therefore, it is easy to understand how a low V'_{O_2peak} may dramatically limit patient capacity to accomplish several domestic activities (figure 1).

Exercise intolerance, disease severity and prognosis

V'_{O_2peak}, P_{ETCO_2}, V'_E/V'_{CO_2} slope, as well as changes in O_2 pulse, peak systolic blood pressure and HR during CPET were found to be related to survival in patients with PAH [27]. Nonetheless, only V'_{O_2peak} (⩽10.4 mL·kg^{-1}·min^{-1}) and systolic peak blood pressure (⩽120 mmHg) were independent predictors of mortality. A low 6MWT distance has also been associated with a lower survival [28]. Consistently,

exercise capacity is now a key component of the REVEAL 2.0 [29] and European Society of Cardiology (ESC)/European Respiratory Society (ERS) [30] risk stratification tools, and current guidelines recommend measurement of exercise tolerance for decision-making [1, 14]. As such, patients with V'_{O_2peak} >15 mL·kg^{-1}·min^{-1} (>65% of predicted value), V'_E/V'_{CO_2} slope <36 and a 6MWT >440 m have the lowest risk of mortality at 1 year [31]. While both CPET and 6MWT may be used to risk stratifying patients using the ESC/ERS risk score, CPET appears to have limited added discriminative value in prognosticating patients already evaluated by a 6MWT [32]. However, a celling effect has been described in patients with higher walking distance, in particular in those walking >450 m [33, 34]. Therefore, using CPET instead of the 6MWT or using both tests in more fit patients may be more sensitive for risk stratification compared with 6MWT only. While patients' age, sex, height and weight influence exercise capacity independently of PAH severity, adjusting 6MWT results according to patients' characteristics has no impact on the exercise test's discriminative properties [35]. Interestingly, geographical location should be considered in risk stratification [36]. In a Brazilian cohort of 104 patients, individuals with a lower 6MWT distance had worse survival agreeing with international guidelines, but with a higher cut-off value for worse survival (250 m instead of 165 m) potentially attributed to older age and sociocultural conditions [37].

Changes in exercise capacity as a marker of treatment response

Beside its discriminative property for disease severity and patients' prognosis, the 6MWT has been successfully used as a primary end-point in most randomised controlled trials in patients with PAH [38], likely because its responsiveness to clinical changes is enhanced in patients with PAH owing to its repeatability and simplicity of administration in clinical practice [4]. The minimal important difference in the 6MWT in previously untreated PAH patients is approximately 33 m [39]. However, improvements in 6MWT were generally ∼10% and ∼5% from baseline in monotherapy and combination therapy trials respectively [37, 40], and mean changes in 6MWT only modestly predicted the occurrence of morbidity/mortality events [37, 40, 41]. To address some of the limitations of the 6MWT as a primary outcome measure in clinical trials, researchers progressively included composite end-points reflecting time to clinical worsening [42]. It is noteworthy, however, that PAH worsening, which accounted for 55–75% of clinical worsening defining events in most trials, has been commonly defined by signs of PAH progression together with a 10–20% decrease in 6MWT. Conversely, CPET suffers from a lack of responsiveness following therapeutic intervention in patients with PAH, especially in the setting of a multicentre randomised controlled trial [43–45], in keeping with previous studies documenting that peak exercise capacity is not typically responsive to intervention in COPD [46]. This is contrasting to individual changes in 6MWT following the addition of sildenafil to PAH monotherapy [38], individual CPET values [47] or a heart rate recovery ⩾16 bpm after the 6MWT as predictors of subsequent clinical worsening [48].

Mechanisms of exercise intolerance in patients with PAH

Physical exercise requires the interaction of several physiological mechanisms. Both respiratory and cardiovascular systems are coupled to meet the metabolic demand of the contracting SKM. In patients with PAH, several respiratory and cardiovascular anomalies dampen the efficacy of O_2 transport to active muscles.

Impaired ventilation and blood gas during exercise

Impaired ventilation in patients with PAH has multiple complex origins. PAH is characterised by heightened ventilatory response to exercise (V'_E/V'_{CO_2} slope) partially attributed to pulmonary vascular remodelling leading to increased physiological dead space (V_D/V_T) ratio and high ventilation-perfusion (V'/Q') heterogeneity (figure 2) [17, 49, 50]. An interesting hypothesis about the negative V'_E axis-intercept from the V'_E/V'_{CO_2} slope has been raised by Agostoni *et al.* [51] and further reviewed by her team [52]. When passing the respiratory compensation point, the V'_E/V'_{CO_2} slope becomes steeper and the V'_E axis-intercept becomes negative, potentially showing a sheer increase in dead space ventilation toward the end of exercise [52]. However, the prognostic value of V'_E/V'_{CO_2} slope analysis beyond the respiratory compensation point remains to be investigated. While patients are frequently hypoxemic at rest, which even worsens during exercise [17, 53], they also have hypocapnia even in the absence of hypoxemia [52, 54]. Therefore, ventilatory inefficiency is not solely explained by increased V_D/V_T. Using the modified rebreathing protocol, increased ventilation at rest and exercise ventilatory inefficiency was recently shown as the result of increased central chemoreflex activity [5]. Consistently, Farina *et al.* [55] used hypoxia and hypercapnia tests to further demonstrate that hyperventilation results from a combination of both increased dead space and central chemoreflex activity (figure 2). Taken together, ventilatory inefficiency and hypocapnia appear to be related, at least in part, to an increased central chemoreflex sensitivity that may contribute to dyspnoea in patients.

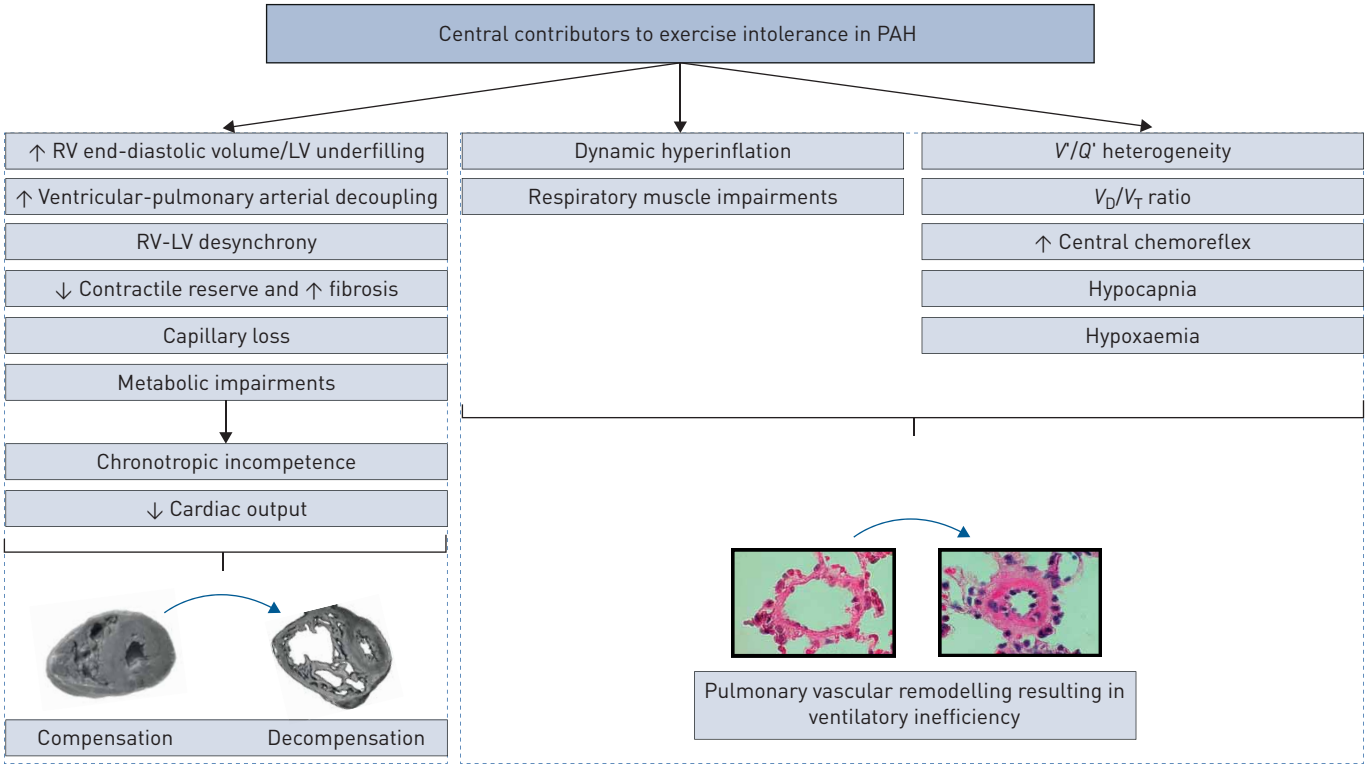

FIGURE 2 Impaired cardiac adaptation and ventilatory response to exercise in patients with pulmonary arterial hypertension (PAH). RV: right ventricle; LV: left ventricle; V_D/V_T: dead space/tidal volume ratio; V'/Q': ventilation-perfusion ratio (normal ratio average 0.8).

Intriguingly, patients with PAH exhibit a more dyspnoeic pattern in relation to higher V'_E/V'_{CO_2} slope and lower O_2 pulse compared with patients with left heart failure (HF) at comparable exercise state [56]. Conversely, patients with HF are much more likely to present exercise oscillatory ventilation (EOV) [57, 58], a respiratory pattern expected to result from delay in information transfer between pulmonary gas exchanging capillaries and the peripheral and central chemoreceptors secondary to a fall in cardiac index [59], increased peripheral and central chemoreflex sensitivity [60] and a reduced baroreflex damping capacity [61]. Indeed, Vicenzi *et al.* [62] found no EOV in a sample of 109 patients with PAH, whereas it was identified in 22% of the 107 patients with HF reaching 40% in patients with isolated post-capillary PH. The differential mechanisms responsible for EOV in HF compared with PAH remains, however, elusive.

Mechanical and respiratory muscle impairments

A significant reduction in maximal inspiratory and expiratory pressure were documented in patients with PAH [63–65] and modestly correlated with exercise performance (figure 2) [63]. Human biopsy samples of diaphragm muscle fibres revealed atrophy, hypocontractility and decreased capillary density [66, 67]. Furthermore, reduced nonvolitional and isolated fibre respiratory strength were also documented in rodent PH models [68]. These abnormalities may contribute to respiratory mechanical disadvantage that leads the inability of the V_T to properly expand at the beginning of exercise to increase ventilation [69, 70]. More recently, dynamic hyperinflation, an increase in end-expiratory lung volume traditionally observed in patients with COPD, was also described in 60% of patients with PAH in the absence of obvious obstructive lung abnormalities or impaired inspiratory flow-generating reserve of the inspiratory muscles. Although its cause remained unknown, hyperinflation was associated with sensory consequences, including increased breathing effort and unsatisfactory inspiration [70]. Boucly *et al.* [69] further demonstrated that during exercise in patients with PAH, an inflection in tidal volume ($V'T$) response when inspiratory reserve becomes critically reduced marks a transition from increased breathing effort to unsatisfied inspiration, a far more unpleasant sensation associated with anxiety.

Impaired cardiac adaptation and reserve during exercise

In patients with PAH, RV function prevails as an important prognostic factor. Using cardiac magnetic resonance imaging, van Wolferen *et al.* [71] determined that elevated RV end-diastolic volume index,

low end-diastolic LV volume index (a direct consequence of LV underfilling) and low stroke volume (SV) index were strong independent predictors of mortality in patients with PAH. Compared with the LV, the RV demonstrates a heightened sensitivity to afterload changes [72], which markedly increases upon exercise in patients with PAH [73]. Moreover, according to the Frank-Sterling mechanism, when RV pre-load extends the capacity of shortening of the longitudinal circumferential oblique muscle fibres it results in insufficient myocardium contraction and low SV [74]. As such, increased pre-load forces the RV to adapt, causing hypertrophy in an attempt to maintain normal SV, a process that ultimately leads to maladaptive remodelling, followed by dilation and failure [75, 76]. Over time, RV maladaptation is characterised by progressive O_2 supply–demand imbalance resulting from coronary arterial remodelling [77] and loss of capillaries [78], myocardial fibrosis [79] and metabolic remodelling from mitochondrial-based fatty acid oxidation to O_2-sparing anaerobic glycolysis (figure 2) [80]. As both ventricles work in series and because of pericardial restraints [81, 82], an altered RV will also impact the LV with an important impact on its geometry, structure, and function [83] that contribute in decreasing global cardiac output (CO), especially during exercise [79, 84].

Consistently, several studies demonstrated that changes in cardiac and pulmonary haemodynamics during exertion accurately predict improvements in exercise capacity and prognosis compared with changes in resting haemodynamics [73, 85, 86], indicating that the incapacity of the RV to increase CO is an important determinant of exercise intolerance [87, 88]. Indeed, in addition to increased afterload, impaired chronotropic response to exercise [89], ventricular–pulmonary arterial decoupling amplified with exercise [90], RV desynchrony [91], absence of RV end-systolic volume decrease with exercise [87] and depressed contractile reserve [87, 92] were demonstrated to result in this blunted increase in CO during exercise (figure 2) [56, 93]. In addition, in patients with a preserved systolic function adaptation, RV desynchrony is associated with a lower V'_{O_2peak} [91]. Although its specific contribution to exercise intolerance in patients with PAH remains also understudied, significant tricuspid regurgitation may also limit increases in CO to meet exercise metabolic demands consistent with impaired LV pre-load [94].

Impaired cerebrovascular function and oxygenation

The regulation of cerebral blood flow (CBF) remains complex. Known determinants include systemic blood pressure, CO, arterial blood gas content, autonomic nervous system and neurovascular coupling for meeting local cerebral metabolic demand [95]. Sustained intense exercise leads to a mild cerebral deoxygenation and metabolic perturbation in healthy individuals [96], similar to that seen in hypoxic environment such as high altitude [97]. In heathy individuals, exercise in experimental hypoxic condition leads to central fatigue that correlates with decreased cerebral oxygenation [96], suggesting that exercise tolerance could be affected by impaired cerebral oxygenation. Recent evidence suggests that lower CBF and oxygenation may be limiting exercise capacity in patients with HF [98–100]. Lower CO and higher ventilatory response to exercise are also hypothesised to be involved in lower cerebral perfusion and oxygenation [98, 101]. In addition, impaired CBF regulatory mechanisms are impaired as well in HF and as a possible consequence, blood pressure modulations is buffered less efficiently and may fail to meet increased metabolic demands with exercise [102–104]. Recently, we [5] and others [105, 106] demonstrated that patients with PAH also have lower CBF and impaired regulatory mechanisms, altering the buffering of blood pressure changes and potentially explaining why patients with PAH are more prone to syncope after Valsalva-induced decreases in blood pressure [107]. At exercise, cerebral oxygenation was also markedly impaired during incremental [5, 106] and endurance exercise [108], tightly correlating with the exercise capacity of patients with PAH [5]. Interestingly, oxygen supplementation significantly enhanced cerebral oxygenation, maximal workload and endurance time during exercise, attesting of its probable relevance for exercise tolerance in patients with PAH [109].

Peripheral skeletal muscle limitation to exercise in patients with PAH

Morphological abnormalities

Several morphological and functional impairments have been observed in peripheral SKM (figure 3), including reduction in both volitional [6, 7, 63, 110] and nonvolitional strength [6, 7]; and endurance [66]. The force-generating capacity of muscle fibres are typically proportional to their cross-sectional area (CSA). Manders *et al.* [111] reported that the maximal force of isolated permeabilised fast-twitch quadriceps fibres, normalised to fibre CSA, was significantly lower in patients with PAH. This diminished maximal force was related to a decreased active stiffness in fast-twitch muscle fibres, suggesting a reduction in the number of available active actin-myosin cross-bridge from a loss of the major contractile protein myosin. In addition, numerous signalling abnormalities associated with SKM dysfunction have been described in recent years. These include suppression of signalling pathways responsible for SKM hypertrophic response, elevation of signalling pathways responsible for atrophic response and engagement of ubiquitin-proteasome-mediated muscle proteolysis signalling [112–115]. A recent plasma metabolomics

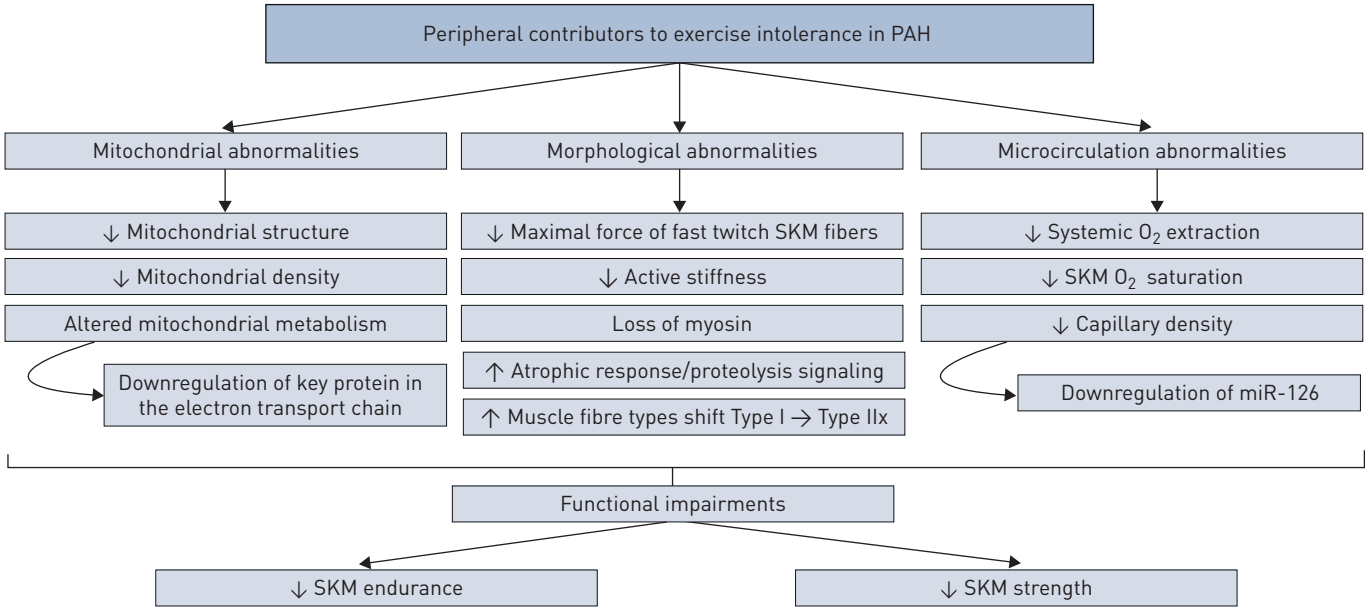

FIGURE 3 Skeletal muscle (SKM) determinants of exercise intolerance in patients with pulmonary arterial hypertension (PAH).

profile also found that patients with PAH are characterised by increased levels of circulating modified fatty oxidation residues [116]. These metabolites could act as pro-inflammatory modulators, ultimately promoting muscle catabolism. Interestingly, pharmacological blockade of excessive fatty oxidation was shown to protect human myotubes and protect peripheral muscle against atrophy in cancer cachexia models *in vivo* [117]. Pre-clinical data also indicates a potential role for nutrition, as supplementing mice with an anti-inflammatory diet resulted in decreased RV hypertrophy, fibrosis and inflammation while preventing SKM atrophy [118]. It is noteworthy, however, that despite molecular abnormalities promoting atrophy being documented in patients with PAH, most studies in human PAH documented no changes in whole muscle [6, 7, 63, 66] or fast-twitch fibre CSA [111].

SKM typology and oxidative capacity are also affected in patients with PAH (figure 3). A significant shift in muscle fibre types from oxidative type I toward more glycolytic type IIx has been documented in most studies involving human PH [6, 112, 119] and experimental PH [114] although this was not uniformly observed [7, 66]. Consistently, a significant reduction in SKM oxidative capacity [6, 119, 120] were repeatedly documented in muscle samples from both humans and rodents with PAH.

Skeletal muscle microcirculation abnormalities

Under normal physiologic circumstances, skeletal and respiratory muscles account for around 40% of the body mass and are responsible for up to 30% of resting O_2 consumption [121]. During exercise, the proportion of the CO diverted to respiratory [122–124] and skeletal [125] muscles increase markedly, a situation where the O_2 cost of breathing approaches 10–15% of the total V'_{O_2Max} in healthy subjects [126]. TOLLE *et al.* [127] first documented profound impairments in systemic O_2 extraction at the end of maximal exercise in patients with PAH compared with patients with preserved and reduced ejection fraction HF (HFpEF and HFrEF respectively). These results were substantiated by evidence from our group where patients with PAH exhibited a decrease in muscle O_2 saturation and increased deoxyHb-Mb during both normoxic and hyperoxic submaximal exercise at the same workload despite near-normal systemic oxygen delivery [7] and compatible with reduced total systemic O_2 extraction and O_2 utilisation from exercising muscles [128]. These impairments were related to a lower capillary density rather than impaired systemic blood flow and oxygen delivery, and correlated with V'_{O_2peak}, suggesting that impaired convective and diffusive muscle O_2 supply contributes to exercise intolerance [7], but also contribute to reduced daily physical activity (figures 3 and 4) [129]. SKM capillary rarefaction was shown to be mediated, at least in part, by a downregulation of the microRNA (miR)-126 resulting in the downregulation of the downstream effectors of the vascular endothelial growth factor pathway (figure 3) [66]. This phenomenon was unique to patients with PAH and not found in equally exercise intolerant patients with COPD [66]. Interestingly, the restoration of miR-126 levels in monocrotaline-induced PH rats resulted in improved SKM perfusion

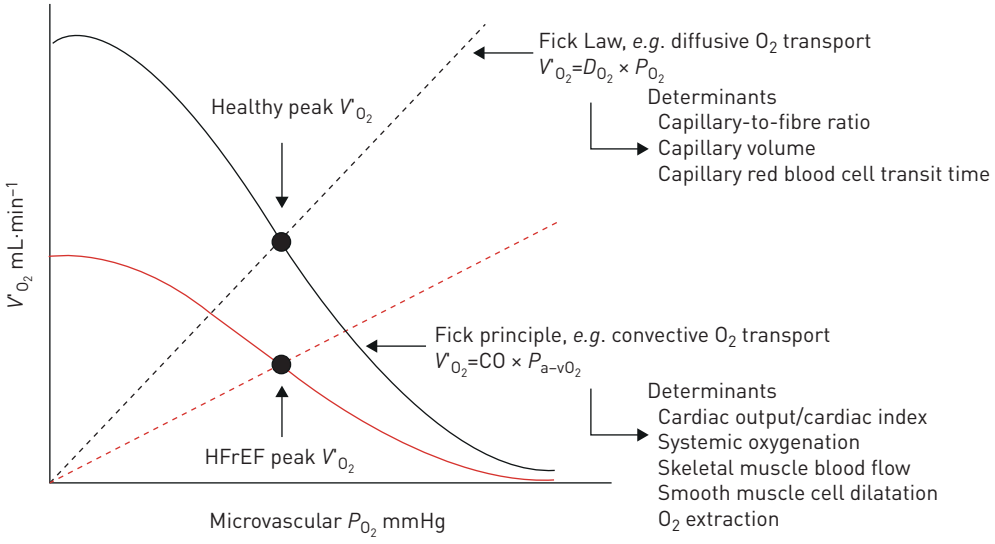

FIGURE 4 The Wagner diagram. Oxygen uptake is plotted as a function of microvascular oxygen pressure. Black line: diffusive (Fick law) and convective (Fick principle) components that interact to determine peak oxygen uptake (V'_{O_2peak}). The Fick principle line is not straight because it directly represents the haemoglobin dissociation curve (greater haemoglobin O_2 affinity), resulting in a lower venous O_2 partial pressure [130]. The slope of the straight line (Fick law) is determined by the diffusing capacity of the muscles [130]. Red line: in patients with heart failure, a left-shifted haemoglobin dissociation curve (greater haemoglobin O_2 affinity), resulting in a lower venous O_2 partial pressure, and a lower slope of the Fick law line results in earlier bisection of both diffusive and convective components and reduced V'_{O_2peak}. P_{a-vO_2}: arterio-venous difference in partial pressure of oxygen; D_{O_2}: oxygen delivery; HFrEF: heart failure with reduced ejection fraction; P_{O_2}: partial pressure of oxygen; CO: cardiac output.

and treadmill distance while artificial diminution of miR-126 levels in the SKM of healthy rats has the opposite effect [66], demonstrating a relatively maintained SKM plasticity in patients with PAH.

Diminished O_2 transport might also result from endothelial dysfunction that characterises PAH and markedly influences peripheral endothelium-dependent flow-mediated vascular tone [46, 131, 132]. For example, slow-twitch muscle fibre vessels are more prone to endothelin-1 (ET-1)-induced vasoconstriction than fast-twitch muscle fibre vessels, influencing endogenous vascular tone in the forearm and leg of healthy subjects [132–135]. Similarly, detrained slow-twitch fibre vessels have less eNOS expression than fast-twitch fibres [136, 137], and the combined inhibition of NO and prostaglandins markedly reduces SKM blood flow [138, 139]. Consistently, endothelin receptor antagonists were recently shown to improve angiogenesis of Sugen/hypoxia-induced PH [78, 140]. Interestingly, reduced capillary density was partly restored by ET-1 receptor antagonist macitentan within the lungs, RV and muscles of treated rats [140], raising questions on whether the pulmonary and systemic vascular defects could be connected by similar molecular mechanisms.

Skeletal muscle mitochondrial function abnormalities

The reduction in SKM oxidative capacity previously described suggests significant mitochondrial impairment in patients with PAH [112]. This hypothesis was further supported by the whole proteomic profile of human PAH SKMs realised by our group, showing significant downregulation of key proteins involved in the electron transport chain complex I, III, ATP synthase complex, citric acid cycle, mitochondrial metabolism, ADP/ATP translocase and the fatty acid metabolism [119]. Bioinformatics analyses from Gene Ontology enrichment confirmed a significant downregulation of protein complex involved in oxidative metabolism and mitochondrial integrity, whereas electronic microscopy and enzymatic activity confirmed abnormal mitochondrial crest structure and density [119]. Note that similar mitochondrial dysfunction also occurs in PAH RV [141], but Enache *et al*. [142] reported that SKM mitochondrial dysfunction precedes RV impairment in an experimental model of PAH supporting the hypothesis that SKM defect is an early characteristic of the disease. However, no studies have explored the impact of disease severity on mitochondrial function. One potential avenue to explore may be if peripheral

muscle inflammation impact muscle mitochondrial function in a similar fashion than in pulmonary artery smooth muscle cells [143]. Contrary to previous studies, SITHAMPARANATHAN *et al.* [144] showed a prolonged phosphocreatine recovery time and abnormal SKM pH suggesting an altered O_2 delivery over an altered O_2 utilisation as the main contributor to exercise intolerance, but normal mitochondrial function and subunit protein abundance in the electron transport chain. However, the absence of paired control subjects, the lack of measurements of the ATP cost of contraction or the limited details regarding the exercise done to measure phosphocreatine recovery time preclude confident conclusions to be made from that study. Interestingly, MCCULLOUGH *et al.* [145] demonstrated plasticity in mitochondrial function after endurance exercise training in Sugen/hypoxia PAH rat model, especially for mitochondrial complex I and III.

Exercise as an adjunct treatment strategy

For several years, exercise was contraindicated for patients with PAH who were considered at risk for exercise-induced RV failure, syncope or sudden death [146]. In line with earlier concerns, HANDOKO *et al.* [146] demonstrated that exercise training could be detrimental in monocrotaline rats with severe and progressive PH, but resulted in improved exercise capacity, pulmonary haemodynamics and RV capillarisation in their counterparts with stable PH. In humans, MERELES *et al.* [147] conducted the first prospective randomised trial evaluating the effect of exercise and respiratory training in severe symptomatic patients under optimised medical therapy. The first 3 weeks of training were in-hospital while the remaining weeks of the program were done at home, supervised by phone. After 15 weeks of training, the 6MWT distance decreased in control group (−15±54 m) while it increased in the training group (+96 ±61 m) with a mean difference of 111 m (95% CI 65 to 139 m, p<0.001), combined with a significant improvement in QoL [147]. Since then, similar beneficial exercise training effects were demonstrated in patients with PAH [148, 149], patients with PAH associated with connective tissue disease [150] and patients with congenital heart disease [151], as well as patients with chronic thromboembolic PH [152]. Inspiratory muscles training as an add-on therapy to cardiopulmonary rehabilitation has also been associated with a decreased sensation of dyspnoea [153, 154]. A meta-analysis of 16 studies confirmed that exercise was likely associated with significant improvement in exercise tolerance and potentially better pulmonary haemodynamics in patients with PAH [155]. Safety was also assessed. Adverse events were more frequent in outpatients, including episodes of dizziness, pre-syncope, syncope, palpitations, arrhythmia, fatigue, hypotension or O_2 desaturation being observed in 4.7% of patients with overall protocol dropout <1% [14, 155].

The mechanisms for improvements in exercise capacity are still lacking. EHLKEN *et al.* [156] investigates the effects of exercise training on cardiopulmonary function and RV haemodynamics using the same training planning as in MERELES *et al.* [147]. V'_{O_2peak} was significantly improved in the training group (+3.1±2.7 mL $O_2 \cdot min^{-1} \cdot Kg^{-1}$ *versus* −0.2±2.3 mL $O_2 \cdot min^{-1} \cdot Kg^{-1}$), consisting of a 25% increase for the training group *versus* 1% in controls [156]. 6MWT, QoL and resting pulmonary haemodynamics measured invasively were also significantly improved with exercise. The specific mechanisms of pulmonary haemodynamic improvements with exercise remain to be investigated, but the current hypothesis implicates a training-induced reduction in pro-inflammatory cytokines and an antioxidant effect [157].

However, a disproportionate improvement in V'_{O_2peak} compared with resting pulmonary haemodynamics after exercise (25% *versus* 15%) suggests that peripheral mechanisms may also contribute to exercise intolerance. In support of this argument, the loss of capillary density has been closely coupled with SKM fatigue independently of arterial blood flow, leading to long-term exercise intolerance if left untreated following capillary occlusion in rats' hindlimbs [158]. Therefore, muscle dysfunction, but primarily capillary loss in patients with PAH, if left untreated, may curtail exercise rehabilitation improvements. Partially supporting this idea, GONZALEZ-SAIZ *et al.* [8] focused on peak muscle power during bench presses and leg presses in a randomised clinical trial over a 8-week period and found a significant improvement in SKM power and strength, increased V'_{O_2peak} (+17% from baseline) and a better QoL and daily physical activity in patients with PAH. This last study demonstrates that significant results may be achieved over a relatively short period of time.

Gaps in knowledge

Pulmonary pressure, flow and distensibility during exercise

Moderate exercise induces a linear increase in CO and a concomitant minor decrease in PVR secondary to dilation of compliant pulmonary capillaries and, although controversial, the potential recruitment of additional capillaries in the upper lobes. Altogether, this results in relatively mild increases in mPAP [159, 160]. Before 2008, mPAP >30 mmHg upon exercise was defined as exercise PH (ePH), whatever exercise intensity, type and position of exercise [161]. However, a systematic review documented that close to 50%

of healthy individuals over 50 years of age reached such levels upon mild-to-moderate exercise without any symptoms [162], so that this criterion was no longer considered as reflecting an abnormal response to exercise.

More recently, Naeije *et al.* [163] proposed that the limit-of-normal for the mPAP–CO relationship ranges between 0.5 and 3.0 $mmHg \cdot L^{-1} \cdot min^{-1}$, corresponding to a maximal total pulmonary resistance (TPR) of 3 WU during exercise. By testing this proposition, Herve *et al.* [164] confirmed that a TPR of ⩾3 WU and mPAP ⩾30 mmHg reached at maximal exercise delineated controls from patients with early pulmonary vascular disease or left heart disease (LHD) with a sensitivity of 0.99 and a specificity of 0.95 amongst 169 individuals with resting mPAP ⩽20 mmHg. Most recently, Ho *et al.* [165] prospectively analysed a total of 714 patients with dyspnoea on exertion and preserved ejection fraction investigated with invasive CPET using a slightly different approach. Over a median follow-up period of 3.7 years, individuals with a mPAP/CO slope >3 $mmHg \cdot L^{-1} \cdot min^{-1}$ during exercise had a 2-fold increase risk of cardiovascular hospitalisation or all-cause mortality including in the subgroup of patients with a resting mPAP ⩽20 mmHg [165]. Nonetheless, the proposed cut-off values (mPAP ⩾30 mmHg, TPR ⩾3 WU or mPAP/CO slope >3 $mmHg \cdot L^{-1} \cdot min^{-1}$ during exercise) alone are insufficient to distinguish LHD from early pulmonary vascular disease. Moreover, the appropriate interpretation of age-dependency of these measures together with the limited data about the clinical relevance of ePH prevented its re-introduction in the hemodynamic definition of PH [2].

Interestingly, the introduction of ambrisentan in patients with so-called ePH (resting mPAP: 18 mmHg; peak exercise mPAP: 36 mmHg) resulted in a significant decline in peak exercise mPAP (−5.2±5.6 mmHg) and PVR (−0.9±0.7 WU) together with a significant increase in CO (+2.3±1.4 $L \cdot min^{-1}$) and pulmonary vascular compliance (+0.8±1.4 $mL \cdot mmHg^{-1}$) suggesting that ePH may respond to current PAH-specific therapies [166]. Intriguingly, these improvements were not associated with statistically significant increases in $V'_{O_{2peak}}$. The mechanisms responsible for this disconnection remains elusive. However, how this increased blood flow is distributed during exercise or following treatment may be important: if patients are expected to benefit from favourable pulmonary vasodilation (in ventilated areas), these effects may be offset by less favourable vasodilation resulting in V'/Q' mismatch or increased shunt, as previously observed in patients with COPD treated with calcium channel blockers [167] or prostacyclin [168].

Also of interest, the assessment of pulmonary vascular distensibility during exercise may eventually help discriminating early pulmonary vascular disease during exercise prior to symptomatic exercise dyspnoea [169]. Pulmonary vascular distensibility predicts aerobic capacity in healthy individuals. Athletes with the highest maximal aerobic capacity have the greatest distensibility, increase in capillary blood volume and lowest PVR at maximal exercise [170]. In recent cohort studies, decreased distensibility was not only primarily observed in patients with PAH when compared with healthy controls, HFrEF and HFpEF, but was also associated with right ventricle-pulmonary artery (RV-PA) uncoupling and decreased V'_{O_2peak} [171, 172]. The clinical relevance of impaired pulmonary vascular distensibility in term of its ability to distinguish LHD from PAH with confidence remains, however, unknown [173]. Hopefully, an ERS Clinical Research Collaboration called the pulmonary haemodynamics during exercise – research network (PEX-NET) will provide answers regarding prognostic relevance of ePH in terms of mortality/lung transplantation (primary end-point) and hospitalisation, development of PH at rest, or initiation of targeted PAH medication (secondary end-points) [174].

Convective and diffusive O_2 transport

Reduced V'_{O_2} may result from either convective or diffusive O_2 transport limitations [130]. Convective elements include CO, systemic oxygenation, SKM blood flow, leg smooth muscle cells vasodilation and O_2 extraction; while diffusive elements include capillary-to-fibre ratio, capillary density and capillary red blood cells transit time in the active muscle (figure 4) [130, 175, 176]. The specific contributions of convective *versus* diffusive limitations in O_2 transport in patients with PAH remain largely unknown. As we previously mentioned, the proportion of the CO diverted to skeletal muscles increases markedly during exercise [125]. Similarly, blood flow to the respiratory muscles increases substantially during maximal exercise [122–124], a situation where the O_2 cost of breathing in normal subjects approaches 10–15% of the total V'_{O_2max} [126]. In healthy subjects, this "competition" for redistribution of CO is only relevant during strenuous exercise [177]. However, in COPD and HF, increased flow distribution to the respiratory muscles at the expense of the lower limb muscles is observed during submaximal exercise [178, 179], contributing to excessive SKM fatigue, effort perception and decreased exercise capacity [180, 181]. Such "vascular steal" by the respiratory muscles may also occur in patients with PAH since respiratory workload is markedly increased at rest and during exercise secondary to mild obstructive and/or restrictive defects

[53, 182], hyperventilation and increased dead space ventilation [17, 53, 54], resulting in major interference with oxygen delivery to the working muscles.

Oxygen delivery at the microcirculation level may also be involved. Intriguingly, the incapacity to increase V'_{O_2peak} following the addition of ambrisentan in patients with ePH [166] previously mentioned may have resulted from the combination of increased systemic O_2 delivery with a decreased systemic O_2 extraction [183]. Those two physiological mechanisms may explain this finding, in accordance to the Wagner diagram (figure 4). First, a lower SKM capillary-to-fibre ratio and oxidative enzyme capacity [9, 119] combined with a lower capillary density [66] may result in perfusion and oxidative metabolism mismatch following drug-induced increases in limb blood flow resulting in decreased systemic O_2 extraction. Secondly, muscle atrophy and excitation-contraction impairment [112] combined with intrinsic muscle mitochondrial dysfunction [119] may also contribute to impaired systemic O_2 extraction. These studies all argue in favour of the combined contributions of convective and diffusive O_2 defects in patients with PAH leading impaired V'_{O_2peak}.

Furthermore, endothelial dysfunction has also been demonstrated in the peripheral circulation of patients with PAH (reviewed by Nickel *et al*. [12]) and may also limit V'_{O_2}. During exercise, in healthy subjects, regional blood supply progressively shifts from other organs to exercising muscles, and within muscle toward more oxidative fibres. Interestingly, Cano *et al*. [184] determined that heterogeneity in SKM may have a greater impact on limiting V'_{O_2} than V'/Q' heterogeneity in the lungs, especially when mitochondrial metabolic capacity is slightly higher than the potential to deliver O_2 to the mitochondria (*e.g.* lower capillary density hence diffusive component).

In HFrEF, using small muscle mass to prevent exceeding the cardiac pumping capacity that necessitates enhancing sympathetic vasoconstriction within the exercising muscle, Esposito *et al*. [185] first demonstrated that V'_{O_2} limitation comes from both convective and diffusive O_2 transport defects in SKM, whereas isolated lower leg cardiorespiratory rehabilitation restored muscle exercise capacity resulting from increased capillary-to-fibre ratio and oxidative capacity in the trained leg muscles [186, 187]. In HFpEF, the O_2 pathway with the largest impact on exercise capacity was located in the periphery as well, more precisely related to the O_2 diffusion capacity and utilisation within exercising muscles [11, 188, 189]. Similar results were observed in COPD [190]. Therefore, altered convective and diffusive components of O_2 transport remain to be explored in patients with PAH and may explain at least in part the limited increases in peak improvements V'_{O_2} with current therapies.

Contribution of skeletal muscle ergoreflex to exercise intolerance

Within SKM, the ergoreflex consists of contraction-induced mechanical and chemical stimuli that activate thinly myelinated (group III) and unmyelinated (Group IV) afferent nerve fibres projecting *via* the dorsal horn of the spinal cord to various sites within the central nervous system [191]. In HFrEF, muscle ergoreflex activity has been assessed using post-exercise regional circulatory occlusion. Its overactivation was associated with abnormally elevated ventilatory response to exercise, attenuation of baroreflex and peripheral chemoreceptor overactivation, suggesting an interplay between enhanced sympathetic overdrive and exercise intolerance [192]. Furthermore, muscle ergoreflex overactivity was observed in both noncachexic and cachexic patients with a strong association between muscle reflex overactivity and muscle cachexia [193]. Spinal anaesthesia has been used to partially block group III/IV muscle sensory afferents and resulted in reduced exercise ventilatory response to exercise [194], decreased peripheral fatigue sensing leading to more profound muscle fatigue [195, 196] and a higher energy cost of muscle contraction [197] in both healthy individuals and athletes. In COPD, the use of spinal anaesthesia also reduced ventilatory response to exercise, hyperinflation and dyspnoea, resulting in prolonged endurance capacity [198]. Therefore, it remains plausible that ventilatory response to exercise, dyspnoea and enhanced muscle sympathetic overdrive are also at interplay in patients with PAH, contributing to exercise intolerance.

Conclusion

Cardiorespiratory, cerebrovascular and SKM systems are affected in patients with PAH and translate into clinical symptoms such as exertional dyspnoea, fatigue, weakness and RV failure symptoms. Exercise testing is not only an objective measure of the patient's functional status, but also represents an important adjunct to prognostications and the assessment of response to therapy. In addition to currently approved vasodilatory medications, cardiopulmonary rehabilitation also represents a key strategy to alleviate exercise intolerance in patients with PAH. However, further studies are needed to: 1) fully determine the mechanisms and relevance of ePH; 2) elucidate the role of convective and diffusive O_2 transport in limiting V'_{O_2peak}; and 3) elucidate the role of muscle ergoreflex in exercise intolerance in patients.

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