Exercise Pathophysiology in Pulmonary Arterial Hypertension—The Physiologic Explanation for Why Pulmonary Arterial Hypertension Does What It Does

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Pulmonary arterial hypertension (PAH) is a chronic disease that is associated with a significant and progressive limitation of exercise tolerance. The pathophysiological mechanisms of exercise intolerance during exercise are complex, multifactorial, and in fact not limited to the pulmonary circulation and the right ventricle. Disturbance of autonomic nervous function leads to an enhanced chemosensitivity, as well as respiratory and peripheral muscle weakness, and systemic endothelial dysfunction, which together play important roles in PAH pathophysiology and symptomatology. This article is focused on the different pathophysiological mechanisms of exercise intolerance in PAH, their interactions, and their relevance for clinical practice.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a primary disease of the pulmonary vasculature, which is caused by primary structural changes of the pulmonary arteries. These changes lead to an elevation of pressure and resistance in the precapillary part of the pulmonary vasculature, and are therefore characterized by a chronic increase in right ventricular afterload (increased pulmonary vascular resistance)[1] and loss of pulmonary vascular capacitance,[2] potentially leading to right ventricular failure and death. Additionally, the efficiency of alveolar gas exchange of oxygen and carbon dioxide (CO_2) is significantly impaired. Exercise limitation and dyspnea are among the most frequent and distressing symptoms of PAH.[3] In most cases, exercise capacity is limited by a circulatory (heart and/or blood vessel) exhaustion, and not by a lack of breathing (airway) reserve. In addition, autonomic nervous dysfunction leading to an enhanced chemosensitivity, respiratory and peripheral muscle weakness, and systemic endothelial dysfunction play additional and perhaps equally important roles in PAH pathophysiology and symptomatology.

This article focuses on the many pathophysiological mechanisms of exercise intolerance in PAH, their interactions, and their relevance for clinical practice.

FUNCTIONAL AND METABOLIC CHANGES IN THE PULMONARY CIRCULATION DURING EXERCISE IN HEALTHY SUBJECTS

In contrast to the systemic circulation, the pulmonary circulation is a low-pressure and high-compliance system at rest and during exercise. While systolic blood pressure in the systemic circulation rises by about 0.33 mm Hg/W[4] during exercise in healthy subjects and reaches age-dependent peak values of 204 to 213 mm Hg in men and 173 to 192 mm Hg in women,[5] the pulmonary vasculature remains a low-pressure circuit even at an increased cardiac output in normal individuals. The increase in pulmonary arterial mean pressure (mPAP) during exercise is dependent on age and pulmonary blood flow; however, mPAP rarely exceeds 30 mm Hg in healthy subjects.[6] At progressing exercise levels and elevated cardiac output, a modest decrease in total pulmonary resistance and a very modest decrease in pulmonary vascular resistance can be observed.[7] The most recent definition of "exercise pulmonary hypertension" by the European Respiratory Society[7] is based on the relationship between mPAP and cardiac output. According to this reference, an abnormal hemodynamic response to exercise is defined by the presence of a resting mPAP below 25 mm Hg with an increase in mPAP to > 30 mm Hg during exercise, with total pulmonary resistance > 3 Wood units.

These physiological considerations suggest that in normal individuals, an increase in cardiac output must be associated with a significant pulmonary vasodilatation and an increase in the total pulmonary vascular cross-sectional area; in other words, with exercise, a significant recruitment of additional pulmonary vascular bed and thus recruitment of additional lung areas participating in gas exchange occurs.

Gas exchange during exercise is regulated by arterial CO_2 levels, reflecting acid-base balance.[8,9] Minute ventilation($\dot{V}E$) is closely and necessarily linked to CO_2 output ($\dot{V}CO_2$) during exercise. At the beginning of exercise, an improvement of ventilatory efficiency is the norm. The ratio of $\dot{V}E$ to $\dot{V}CO_2$ decreases, as venous CO_2 content excessively rises due to elevated exercise metabolism and—at the same time—CO_2 is more efficiently exhaled due to an improved perfusion and additional recruitment of alveolar areas. Nadir values are reached at higher levels of exercise, at or near the respiratory compensation point.[10] In general, the lowest $\dot{V}E/\dot{V}CO_2$ relationship during

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exercise is considered to be the preferred noninvasive method to estimate ventilatory efficiency.

Another important parameter reflecting ventilatory efficiency is the end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$). It is the highest alveolar PCO_2 during the respiratory cycle, approaching the mixed venous PCO_2.[11] An improved efficiency of pulmonary CO_2 elimination during incremental exercise intensity leads to an increase in $P_{ET}CO_2$, also reaching peak values at the respiratory compensation point. Both $P_{ET}CO_2$ and the $\dot{V}E/\dot{V}CO_2$ relationship reflect the matching of ventilation to perfusion during exercise.

EFFECT OF STRUCTURAL PULMONARY VASCULAR DAMAGE IN PRECAPILLARY PULMONARY HYPERTENSION

From a pathology point of view, PAH is an obstructive pulmonary panvasculopathy,[12] with loss and obstructive remodeling of the pulmonary vascular bed, leading to stiffening of large, lobar, or segmental pulmonary arteries. Additionally, distal arteries may be affected by medial hypertrophy or hyperplasia, fibrosis, and thrombotic or plexiform lesions.[13] Both the loss of small pulmonary arteries in the micrometer range and a reduced elasticity in the larger pulmonary arteries contribute to an elevation of pulmonary vascular resistance and the mPAP/cardiac output slope.[7] As a consequence, cardiac output cannot be increased during exercise without an excessive increase of pulmonary arterial pressure. If the right ventricle (RV) is not able to overcome this pressure elevation, pulmonary blood flow will not adequately increase during exercise in PAH patients, potentially leading to a relative underfilling of the left ventricle (LV), systemic hypotension, and reduced systemic perfusion. In addition, due to the loss of pulmonary vascular bed and diminished perfusion of ventilated lung areas seen in PAH, central venous CO_2 is eliminated with a higher minute ventilation compared to healthy subjects. Thus, there is an elevated ventilatory requirement for any given CO_2 output during exercise.

The pathophysiological changes of the pulmonary circulation during exercise in PAH are summarized in Figure 1.

Impairment of Pulmonary Blood Flow Increases With Exercise

Early works reported that cardiac output can increase 4- to 5-fold during exercise, while pulmonary arterial pressure may rise to about 2 to 3 times that of the resting value in healthy subjects.[14] More recent studies have consistently reported increases in pulmonary arterial pressure with a concomitant increase in cardiac output. As a result, total pulmonary resistance and pulmonary vascular resistance actually decrease (slightly) during exercise.[6,7,15] An mPAP/cardiac output slope (total pulmonary resistance) of more than 3 Wood units (240 dynes · sec · cm^{-5}) has been suggested for defining an abnormal hemodynamic response to exercise.[7]

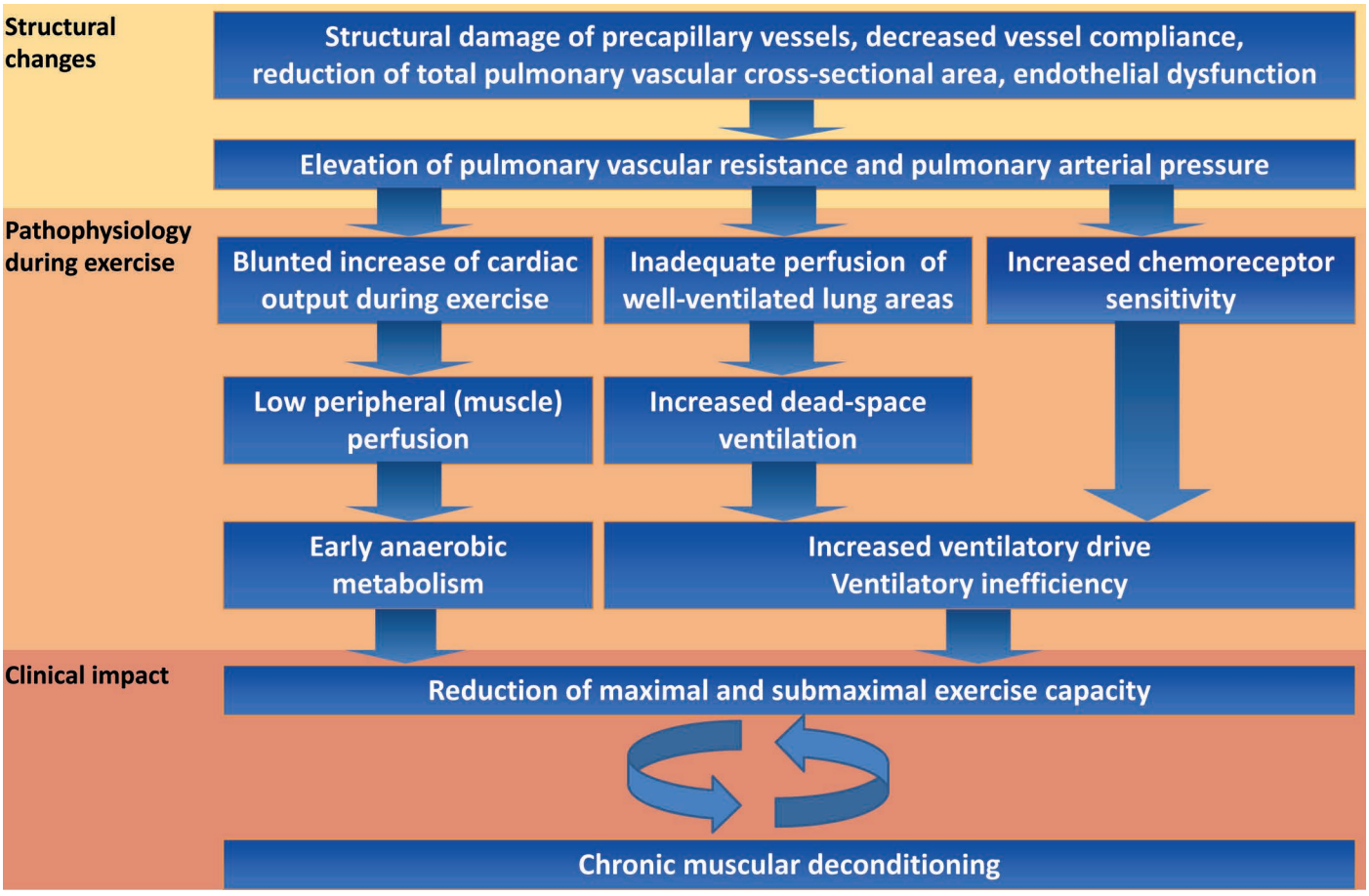

Figure 1: Overview of the pathophysiological mechanisms that may become relevant during exercise in pulmonary arterial hypertension patients.

Normal RV function is primarily determined by RV afterload. The RV ejection fraction is inversely correlated to pulmonary arterial pressure.[16] As the pulmonary circulation is normally a high-compliance and low-resistance system, the RV adapts to changes in volume rather than to changes in pressure.[17] With rising pulmonary vascular resistance, a decline in RV stroke volume is seen, which is significantly steeper than the decline in LV stroke volume.[18] Additionally, "ventricular interdependence" may become relevant. A flattening or a leftward shift (toward the LV) of the interventricular septum may reduce LV transmural filling pressure and/or restrict diastolic LV filling, potentially influencing systemic perfusion.[19] In summary, the increased circulatory demand during exercise, and the relatively sudden rise in pulmonary arterial pressure resulting, poses a hemodynamic challenge for the RV,[20] potentially impeding the requisite increase in cardiac output.

Based on these pathophysiological considerations, it is obvious that the increase of cardiac output needed in PAH patients during exercise requires significantly more energy than in normal individuals. Because the RV may not be able to adequately increase stroke volume during exercise, cardiac output is particularly dependent on the ability to increase heart rate in these patients.

Previous studies have consistently demonstrated that flow-related hemodynamic abnormalities have prognostic relevance. At rest, stroke volume index is an independent predictor of survival in patients with idiopathic, drug- or toxin-induced, or heritable PAH[21] and in patients with scleroderma-associated PAH.[22] Wensel et al[23] showed that peak systemic blood pressure during exercise, reflecting LV filling, was a strong and independent predictor of survival. In a cohort of patients with PAH and chronic thromboembolic pulmonary hypertension, the pressure-flow relationship predicted transplant-free survival and correlated with established markers of disease severity and outcome.[24] As exact measurement of cardiac output during exercise is technically demanding, data on the quantification of the cardiac output increase in PAH patients are limited. Immediately after modest exercise (30 W constant work rate), magnetic resonance imaging (MRI) data show that peak aortic blood flow is similar between PAH patients and matched controls, however with a significantly lower stroke volume and—as a compensation mechanism—a significantly steeper heart rate increase in PAH patients.[25] In that study, real-time cardiac MRI was able to unmask depleted contractile reserves. In contrast to healthy control subjects during acute normobaric hypoxia, PAH patients had a lower peak cardiac index, were not able to augment stroke volume index, and showed an impaired RV reserve, despite comparable resting function to controls.[26]

The Pulmonary Ventilation/Perfusion Relationship

Patients with PAH and other forms of relevant precapillary pulmonary vasculopathy, such as chronic thromboembolic pulmonary hypertension, hyperventilate at all metabolic states, potentially even during sleep.[23,27-29] Due to the nature of the disease, with lung areas that are normally ventilated but poorly perfused, these patients do not perform gas exchange with normal efficiency. Compared to healthy subjects, a significantly higher amount of minute ventilation is needed to eliminate any given amount of CO_2. As CO_2 levels are the major driver of ventilation during exercise,[8,9] inefficient CO_2 elimination must trigger an additional ventilatory drive. Early works showed preservation of matching of alveolar ventilation to perfusion, suggesting an active redistribution mechanism of alveolar ventilation as a compensation mechanism.[30] However, in most cases this compensation is not sufficient to achieve a normal, or physiological, $\dot{V}E/\dot{V}CO_2$ relationship during exercise. Unlike healthy subjects, this ventilatory inefficiency in PAH patients is evident by their inability to improve ventilatory efficiency during exercise; the $\dot{V}E/\dot{V}CO_2$ relationship is in fact elevated at rest, and *does not decrease* during exercise. Concomitantly, $P_{ET}CO_2$ is significantly reduced at rest, and *does not increase* during exercise in PAH patients. Patients with more advanced PAH may even show a continuous increase of the $\dot{V}E/\dot{V}CO_2$ relationship and a continuous decrease of $P_{ET}CO_2$ during exercise.[27,28]

Ventilatory inefficiency in terms of the $\dot{V}E/\dot{V}CO_2$ relationship and $P_{ET}CO_2$ may be considered for the differential diagnosis of ventilatory versus circulatory/pulmonary vascular limitation. A low ventilatory efficiency (high $\dot{V}E/\dot{V}CO_2$ relationship, low $P_{ET}CO_2$ at the anaerobic threshold), together with sufficient breathing reserve, hypocapnia, and a high positive gradient between arterial and end-tidal PCO_2 ($P_{(a\text{-}ET)}CO_2$) may indicate a significant pulmonary vascular component of exercise limitation.[31,32]

While elevated $\dot{V}E/\dot{V}CO_2$ relationships may be explained by reduced lung perfusion and an increase of dead space ventilation in the affected areas, *hypocapnia* demonstrates that there is an additional component of hyperventilation present and visible already at rest.[33] Recent studies have shown that autonomic nervous system disturbances may play an important role in ventilatory inefficiency, and that there may be an additional component of increased chemoreceptor sensitivity leading to hyperventilation in PAH.[34] Farina et al[35] demonstrated that ventilatory responses to brief periods of inspiratory hypoxia and steady-state hyperoxic hypercapnia in subjects with PAH were about twofold greater than in matched controls.[29,35] According to this study, hyperventilation in PAH is explained by a combination of increased dead space ventilation and an enhanced sensitivity of chemoreceptors.

Skeletal Muscle Dysfunction in PAH

The pathophysiology of exercise limitation in PAH is not limited to the RV, the pulmonary circulation, and the autonomic nervous system. Exercise intolerance in PAH is a complex phenomenon, additionally involving weakness of respiratory[36] and peripheral muscles.[37,38] Patients with significant chronic cardiopulmonary exercise limitations will undergo a process of progressive muscular deconditioning, affecting exercise capacity and quality of life. The mechanisms of muscle deconditioning are not yet completely understood. The dysfunction of sarcomers, the smallest

contractile unit in the muscle, may play a significant role in PAH.[39-41]

Specific medical PAH therapy alone has been shown to improve submaximal exercise tolerance reflected by an improvement in 6-minute walking distance. However, in several clinical trials with pulmonary vasodilator therapy for the treatment of PAH, peak oxygen uptake as an endpoint was negative.[42,43] Despite recognized limitations in methodology,[44] the results from these studies might indicate that *maximal* exercise tolerance (peak oxygen uptake) in PAH may only be significantly improved by a combination of medical therapy and supervised exercise training.

Systemic Endothelial Dysfunction in PAH

Patients with PAH have abnormal systemic vascular endothelial dysfunction, demonstrated by impaired flow-mediated dilation in the peripheral circulation,[45,46] likely mediated by reductions in endothelial-derived nitric oxide and prostaglandins[47,48] and adenosine,[49] as well as proinflammatory cytokines[50] and increased sympathetic nerve activity.[51] These abnormalities are associated with abnormal skeletal muscle structure and performance[52,53] and therefore likely contribute to the exercise impairment seen in PAH patients.

CONCLUSION

The pathophysiology of PAH during exercise is complex, as the interface between the lung, the pulmonary circulation, and the heart is affected by the disease. Exercise limitation is a multifactorial phenomenon. It is attributable, but not limited, to an impaired increase in cardiac output, a significant reduction in ventilatory efficiency and an increase in dead space ventilation, and enhanced chemosensitivity as well as a progressive weakness or deconditioning of respiratory and/or peripheral muscles. The noninvasive diagnostic evaluation of these mechanisms may be technically challenging in clinical practice, limiting their use for routine workup. Nevertheless, the knowledge of the pathophysiological mechanisms that limit exercise may be helpful for differential diagnosis and the serial follow-up of PAH patients as well as for the design of future clinical trials.

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