Respiratory system as the main determinant of dyspnea in patients with pulmonary hypertension

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Abstract
Dyspnea on exertion is a devastating symptom, commonly observed in patients with pulmonary hypertension (PH). The pathophysiology of dyspnea in these patients has been mainly attributed to cardiovascular determinants and isolated abnormalities of the respiratory system during exercise, neglecting the contribution of the control of the breathing system. The aim of this review is to provide a novel approach to the interpretation of dyspnea in patients with PH, focused on the impact of the control of the breathing system during exercise. Exercise through multiple mechanisms affects the (1) ventilatory demands, as dictated by respiratory center activity, (2) actual ventilation, and (3) metabolic hyperbola. In patients with PH, exertional dyspnea can be explained by exercise-induced alterations in these variables. Compared to healthy subjects, at a given CO2 production during exercise, ventilatory demands in patients with PH are higher due to metabolic acidosis (early reaching the anaerobic threshold), hypoxemia, and excessive upward movement of metabolic hyperbola owing to abnormal exercise response of dead space to tidal volume ratio. Simultaneously, dynamic hyperinflation and respiratory muscles weakness decreases the actual ventilation for a given respiratory center activity, creating a dissociation between demands and ventilation. Consequently, a progressive increase in ventilatory demands and respiratory center activity occurs during exercise. The forebrain projection of high respiratory center activity causes exertional dyspnea despite the relatively low ventilation and significant ventilatory reserve. This type of analysis suggests that the respiratory system is the main determinant of exertional dyspnea in patients with PH, with the cardiovascular system being an indirect contributor.

Keywords
brain curve, exercise, metabolic hyperbola, ventilation curve

Abbreviations: CPET, cardiopulmonary exercise testing; PH, pulmonary hypertension; PaCO2, partial pressure of carbon dioxide in arterial blood; RCO, respiratory center output; V′/Q′, ventilation–perfusion; V′CO2, CO2 production; VD/VT, dead space to tidal volume ratio; V′E, minute ventilation; VT, tidal volume.
INTRODUCTION

In patients with pulmonary hypertension (PH), exertional dyspnea is the most frequent symptom for which patients seek medical attention.\(^1\)\(^{-3}\) The severity of dyspnea on exertion progresses even to resting dyspnea as the disease advances, contributing considerably to a reduced quality of life.\(^4\)\(^{-5}\) Previous studies addressing the mechanisms of dyspnea in patients with pulmonary arterial hypertension (PAH, Group 1) and chronic thromboembolic PH (CTEPH, Group 4) have mainly focused on the cardiovascular determinants and isolated abnormalities of the respiratory system during exercise, such as dynamic hyperinflation and respiratory muscle weakness.\(^6\)\(^{-10}\) Reports of cardiopulmonary exercise testing (CPET) in these patients usually point out the significant ventilatory reserve at exercise termination, which leads to the conclusion that cardiovascular and gas exchange abnormalities are the main determinants of exercise limitation.\(^11\) Nevertheless, dyspnea is not linked to actual ventilation, but to forebrain projection of respiratory center activity (corollary discharge) and further increases when ventilatory demands are not met.\(^12\)\(^{-15}\) In patients with PH, ventilatory demands, as reflected by respiratory center output (RCO) per minute (RCO/min), are higher than actual ventilation for several reasons, a dissociation that is greatly augmented during exercise.\(^16\)\(^{-17}\) Without consideration of this dissociation, the management of dyspnea in patients with PH may not be effective and the interpretation of CPET is inaccurate. In this review, we will apply in patients with PH our currently published analysis that relates arterial carbon dioxide levels with respiratory center response to this stimulus, contrasting the brain’s responses to the patient’s ability to generate effective alveolar ventilation, both at rest and during exercise.\(^16\) This analysis may facilitate comprehension of the pathophysiology of dyspnea in patients with PH. Although in this review we will consider only patients with PAH and CTEPH, since in these patients exertional dyspnea occurs with significant ventilatory reserve,\(^11\)\(^,18\) the same principles also apply to patients in other groups. However, mainly in patients of Group 3 and in a minority of patients in Group 2 with interstitial lung edema, lung and chest wall involvement decreases the maximum voluntary ventilation, and because of that, at the end of the exercise, the patients may have a little ventilatory reserve, making obvious the contribution of the respiratory system to exercise termination.

INSPIRATORY FLOW-GENERATION PATHWAY

The respiratory center, a network of interconnected neurons in the medulla and pons, receives rather tonic input from various sources that are translated into an output with an oscillatory pattern.\(^16\)\(^,19\) This output can be divided into rhythm and pattern-generating signals and controls the three phases of the respiratory cycle: inspiratory, post inspiratory, and expiratory.\(^16\)\(^,19\) The duration of these phases determines the timing of the breath and thus breathing frequency, whereas the intensity of the output is referred to as respiratory drive.\(^16\)\(^,20\)\(^,21\) The RCO during the inspiratory phase travels through the inspiratory flow-generation pathway\(^16\) from the brainstem and upper cervical spine neurons to the nucleus of respiratory motoneurons, leading to activation and contraction of the inspiratory muscles that generate inspiratory muscle pressure (\(P_{musI}\)).\(^22\) \(P_{musI}\) at time \(t\) of inspiration is dissipated to overcome resistance (\(R_{Rs}\)) and elastance (\(E_{rs}\)) of the respiratory system and causes inspiratory flow (\(V'_I\)) according to the following equation of motion:

\[
P_{musI}(t) = V'_I(t) \times R_{Rs} + \Delta V(t) \times E_{rs} + P_{EE}
\]

where \(\Delta V(t)\) is volume above end-expiratory lung volume at time \(t\) and \(P_{EE}\) is elastic recoil pressure at end expiration.\(^22\)\(^,23\) The latter will be zero if end-expiratory lung volume is at functional residual capacity (FRC) and positive and negative if it is above and below FRC, respectively. End-expiratory lung volume decreases below FRC when expiratory muscle activity is present during the expiratory phase and the subject does not exhibit flow limitation.\(^24\) This strategy is invariably used during exercise and assists the inspiratory muscle function since the relaxation of expiratory muscles generates inspiratory flow (Figure S1).\(^25\)\(^,26\) Therefore, when the inspiratory flow-generation pathway is intact, the RCO per breath, including output both to inspiratory and expiratory muscles, corresponds to tidal volume (\(V_T\)) (Figure S1), and RCO/min to actual minute ventilation (\(V'_E\)).\(^16\)

METABOLIC HYPERBOLA AND \(CO_2\) RESPONSE CURVES

The main inputs to the respiratory center affecting RCO per breath (and thus defining effort per breath) are the chemical feedback and the metabolic rate.\(^16\)\(^,22\) Reflex feedback affects mainly the respiratory rate, which increases when RCO per breath is several fold higher.
than that at resting ventilation. Cortical inputs may affect both the respiratory drive and breath timing, overriding the automatic control of breathing.

The chemical feedback operates through changes in pH and partial pressures of arterial carbon dioxide (PaCO₂) and oxygen (PaO₂), which are sensed by peripheral and central chemoreceptors. PaCO₂ is an important variable in this process since small changes in PaCO₂ elicit considerable changes in RCO, while PaO₂ and pH significantly affect the RCO response to CO₂.

At rest, PaCO₂ is determined by the intersection of metabolic hyperbola and the PaCO₂-ventilation response curve. The metabolic hyperbola is the graphical representation of the alveolar equation for CO₂ and describes PaCO₂ as a function of V′E, as follows:

\[
\text{PaCO}_2 = 0.863 \frac{V'_{\text{CO}_2}}{[V'_E \times (1 - V_D/V_T)]},
\]  

where V′CO₂ is CO₂ production (ml/min) and V_D/V_T is dead space to tidal volume ratio. The PaCO₂-ventilation response curve describes V′E as a function of PaCO₂.

In unconscious humans, the ventilatory response to CO₂ is described by a linear function and predicts zero V′E (apnea) when PaCO₂ reaches a certain value (apneic threshold) that is few mmHg lower than resting PaCO₂.

In awake state above resting PaCO₂, the relationship is also linear, but below it, the wakefulness drive to breath (cortical cortex efferents) prevents apnea.

To better understand the dissociation between RCO/min and the actual ventilation, we have recently introduced the terms “brain curve” and “ventilation curve.” Although the concepts of brain and ventilation curves were used to describe abnormalities in respiratory drive in critically ill patients, the same principles apply to any patient with an underlying disease that affects the inspiratory flow-generation pathway. The term brain curve refers to the V′E that would theoretically result in a response to PaCO₂ changes if the inspiratory flow-generation pathway was intact; the ventilation desired by the respiratory centers at any PaCO₂ level. The term ventilation curve refers to the actual changes in V′E in response to changes in PaCO₂, as modified by any impairment in the inspiratory flow-generation pathway (Figure S2). Hence, in healthy humans, the brain curve is identical to the ventilation curve, and the desired ventilation that corresponds to RCO/min is equal to actual ventilation (Figure S3A). On the contrary, when the inspiratory flow-generation pathway is impaired, the brain and ventilation curves dissociate, and at a given level of RCO/min, the resulting ventilation is lower and the PaCO₂ is higher than the brain desires (Figure S3B).

This increased PaCO₂ stimulates a further increase in RCO/min according to the brain curve, and the resulting increase in ventilation is determined by the ventilation curve. A steady state is reached at the intersection of the actual ventilation curve and the metabolic hyperbola (Figure S3B). It follows that any deviation between the brain and the ventilation curve increases RCO, which is projected to the forebrain and is a major contributor to dyspnea.

### BRAIN AND VENTILATION CURVES IN PH

Hypocapnia is commonly present at rest in patients with PH and is associated with poor outcomes. Indeed, 74% and 80% of patients with PAH and CTEPH, respectively, exhibited a resting PaCO₂ < 37 mmHg. This finding indicates that at rest the intersection point between ventilation curve and metabolic hyperbola is at low PaCO₂ due to a left, upward shift of brain curve. The mechanisms of this shift are incompletely understood, but increased chemosensitivity to CO₂ because of hypoxemia, disturbances of autonomic control, increased sympathetic activation, high vascular pressures in pulmonary circulation, and stimulation of lung and chest wall receptors might be involved.

Indeed, Farina et al. studied stable patients with PAH and CTEPH and showed that compared to healthy subjects, central hypercapnic chemosensitivity on average increased by 90% (4.48 vs. 2.35 L/min/mmHg).

To which extent actual PaCO₂ is similar to that desired by the respiratory centers depends exclusively on the integrity of the inspiratory flow-generation pathway (Figures 1 and S3A). In patients with PH, this pathway may not be intact, mainly due to respiratory muscle dysfunction and abnormal respiratory system mechanics. Studies have shown that respiratory muscle strength is impaired in many patients with PH, while airway resistance, and to a lesser extent respiratory system elastance, is often increased. Therefore, ventilation decreases for a given RCO/min. As a result, the ventilation curve deviates from the brain curve, and the actual PaCO₂ is higher than that desired by respiratory centers. This discrepancy between actual and desired PaCO₂ increases the RCO/min. Nevertheless, at resting breathing and the initial stage of the disease, the deviation may be relatively small (Figures 2 and S3B). Under this circumstance, the slightly increased RCO may not be associated with dyspnea at rest.

Exercise affects both the brain and ventilation curves through multiple mechanisms. Early in exercise brain curve may be unaffected, but as the workload is increased, the patient reaches the anaerobic threshold, and after that point, the accumulation of lactate and the
associated increase in [H+] augments CO2 sensitivity, and the brain curve is shifted upward/left. Compared to healthy subjects, in patients with PH, the anaerobic threshold is reached at a relatively low workload, due to an inappropriate increase in cardiac output. This is caused by the inability of the pulmonary circulation to dilate or recruit additional pulmonary vessels to accommodate for the increased cardiac output, causing a progressive increase in the afterload of the right ventricle.43 This limits the exercise-induced augmentation of stroke volume resulting in increased right ventricular diastolic volume and pressure. The dilation of the right ventricle shifts the interventricular septum to the left, impairing the diastolic filling of the left ventricle and decreasing its preload, thus prohibiting the normal, exercise-induced increase in cardiac output. The compensatory increase in heart rate is not sufficient to restore the normal cardiac output response to exercise, while it may further decrease the preload of the left ventricle via shortening of the diastolic time.6,44

Patients with PH often exhibit hypoxemia on exertion due to worsening of ventilation–perfusion (V′/Q′) inequalities, diffusion limitation, and the drop in mixed venous PO2 because of the inability of cardiac output to increase. In some patients, the increased pressure in the right atrium results in the intracardiac right to left shunt and this contributes to hypoxemia.11,35 Hypoxemia increases the sensitivity of respiratory centers to CO2, causing a further leftward shift of the brain curve.45,46

To summarize in patients with PH, the early reaching of anaerobic threshold and hypoxemia are the two main reasons for the upward/leftward shift of the brain curve during exercise. It follows that compared to healthy subjects, at a given V′CO2, the ventilatory demands, as dictated by the RCO/min, are considerably higher. Ventilatory demands are further increased during exercise because the ventilation
curve may be shifted downwards, resulting in a progressively larger deviation between these two curves. There are two mechanisms of a downward shift of ventilation curve during exercise in these patients. First, the development of dynamic hyperinflation, and second, the presence of inspiratory and expiratory muscles weakness.9 Studies have shown that, in nonsmoking patients with PH and no spirometric obstruction at rest, dynamic hyperinflation developed from early on during exercise in approximately 50% of patients, likely due to small airway dysfunction.7,10 The development of dynamic hyperinflation causes a downward shift of the ventilation curve, first by preventing the normal decrease of end-expiratory lung volume below passive FRC, and second, because a portion of the inspiratory muscle pressure must be dissipated to overcome the positive elastic recoil pressure at the end of expiration (Figure S2). Obviously, as exercise progresses, the magnitude of dynamic hyperinflation increases due to the increasing ventilatory demands, which, combined with tidal volume restriction, lead to a relatively early increase in respiratory rate (rapid shallow breathing pattern), placing the patient in a vicious cycle.10,27 These events can further shift the ventilation curve downwards,
progressively widening the deviation between the brain and the ventilation curve (Figure 3). As a result, the sense of dyspnea is increased, and this forces the patient to terminate the exercise. The exercise-induced increased deviation between brain and ventilation curves is supported by Dorneles et al.,17 who measured in patients with PAH, P0.1 (an index of RCO), and showed at low workload a sudden rise in P0.1 and dyspnea perception when dynamic hyperinflation (estimated using inspiratory capacity) reached a certain threshold.

The second major cause of the downward shift of the ventilation curve during exercise in patients with PH is respiratory muscle weakness, which further disrupts the integrity of the inspiratory flow-generation pathway. It has been shown that compared to healthy subjects, inspiratory and expiratory muscle strength is reduced in patients with PH.8,38,39 The mechanisms of the respiratory muscle dysfunction are not clear, but might be part of generalized skeletal muscle weakness, possibly linked to decreased oxygen delivery to cells, reduced maximal tension and
cross-sectional area of the slow-twitch fibers, increase in easily fatigable fast-twitch fibers, reduced heavy-chain myosin concentration, abnormal intracellular calcium profile, decreased oxidative enzymes and mitochondria, and metabolite profile. The degree of respiratory muscle weakness is related to 6 min walking test, exercise capacity, and the degree of dyspnea for a given level of minute ventilation and work rate. In patients with CTEPH and respiratory muscle weakness, Rolim et al. showed an abrupt increase in severity of dyspnea as exercise progresses. Furthermore, they demonstrated that at a given level of workload and minute ventilation severity of dyspnea is considerably higher in patients with respiratory muscles weakness than that in patients without. These observations strongly suggest that respiratory muscle weakness as the intensity of exercise increases may cause a downward shift of the ventilation curve.

**METABOLIC HYPERBOLA IN PH**

The upward or downward shift of metabolic hyperbola entirely depends on $V'_{CO_2}$ and $V_D/V_T$ ratio (Equation 2). An increase in $V'_{CO_2}$ and $V_D/V_T$ moves the metabolic hyperbola upwards, while a decrease moves it downwards. Abnormalities in $V_D/V_T$ significantly affect the position of metabolic hyperbola both at rest and during exercise, while $V'/Q'$, which is generally low at rest, during exercise increases several fold, and shifts the metabolic hyperbola upwards.

Contrary to general belief, dead space and tidal volume are not the only variables that affect $V_D/V_T$. $V'/Q'$ inequalities and right to left shunt are equally important determinants of $V_D/V_T$. In patients with PH, gas exchange at rest is characterized by a shift of ventilation to high ventilation-perfusion ratios, mild to moderate increase in perfusion to low ventilation-perfusion ratios, variable degrees of intracardiac or intrapulmonary right to left shunt, and increased physiologic dead space. It follows that in patients with PH at rest, an excessive upward shift of the metabolic hyperbola due to increased $V_D/V_T$ is the rule. This shift further increases the already high ventilatory demands due to the left-ward shift of the brain curve and contributes to high resting minute ventilation in these patients.

**METABOLIC DRIVE IN PH**

RCO is tightly linked to metabolic rate and this has an enormous impact on the ventilatory response to exercise. Exercise increases metabolic rate, and thus $V'_{CO_2}$ causing an upward shift in the metabolic hyperbola. In healthy subjects, this shift is limited by the significant fall in $V_D/V_T$ as workload increases, but in any case, any upward shift results in a new intersection point between metabolic hyperbola and ventilation curve, which is at higher minute ventilation and PaCO2 (Figure 1). However, during exercise PaCO2 remains rather constant to resting levels, while minute ventilation is higher than that predicted by the intersection point between metabolic hyperbola and ventilation curve (Figure 1). This excessive ventilation is due to metabolic drive, mediated by poorly explained mechanisms, involving various sources of afferents to the respiratory center.

In patients with PH at a given $V'_{CO_2}$ production, RCO/min due to metabolic drive is considerably higher than that of healthy subjects for two reasons. First, resting hypocapnia, a common finding in patients with PH, moves PaCO2 to the ascending part of metabolic hyperbola, and thus to maintain constant PaCO2 during exercise, the amount of ventilation and RCO/min increases (Figure 2). Second, contrary to healthy subjects in whom $V_D/V_T$ decreases and limits the $V'_{CO_2}$-induced upward shift of metabolic hyperbola, $V_D/V_T$ fails to decrease. This is mainly due to further increase in $V'/Q'$ mismatch and right to left shunt and in patients with $V_T$ constraint due to dynamic hyperinflation and/or weak muscles, in rapid shallow breathing pattern. As a result, compared to healthy subjects, the upward shift of metabolic hyperbola at a given $V'_{CO_2}$ is larger, and thus to maintain constant PaCO2 during exercise, RCO/min and minute ventilation are considerably higher (Figure 2). High ventilation places the patient at risk of dynamic hyperinflation, which is a significant burden on the already weak inspiratory muscles.

**OVERVIEW OF THE MECHANISMS CONTRIBUTING TO THE DISSOCIATION BETWEEN ACTUAL VENTILATION AND VENTILATORY DEMANDS DURING EXERCISE IN A PATIENT WITH PH**

Figure 3 shows a simulation of the brain and ventilation curves and metabolic hyperbola at rest and during exercise, in a patient with PAH or CTEPH exhibiting weak respiratory muscles and/or exercise-induced dynamic hyperinflation. The curves have been created using data obtained from several studies.

In this patient, compared to the patient in Figure 2, the initial small deviation of the ventilation from the brain curve becomes progressively larger during
exercise since metabolic acidosis (early reaching the anaerobic threshold)\textsuperscript{11,18,37} and hypoxemia\textsuperscript{11} shift the brain curve to the left, while dynamic hyperinflation\textsuperscript{10,17,42} and/or respiratory muscle weakness\textsuperscript{8,38,39} move the ventilation curve downwards. During exercise at $V'C_{O_2}$ of 600 ml/min actual ventilation is 32 L/min, and to achieve this, total $R'C_{O_2}$/min corresponds to 85 L/min, of which 29 L/min is due to metabolic drive, whereas unmet ventilatory demands rise from 4 L/min at rest to 53 L/min. These values sharply contrast to a healthy subject, in whom during exercise at similar $V'C_{O_2}$, $R'C_{O_2}$/min corresponds to 16 L/min, of which only 1 L/min is due to metabolic drive (Figure 1).

Figures 2 and 3 clearly showed the significant impact on $R'C_{O_2}$/min imposed by the exercise-induced further leftward and downward shift of brain and ventilation curve, respectively. At $V'C_{O_2}$ of 600 ml/min and assuming similar $V_D/V_T$ (0.5) in both patients,\textsuperscript{41,42} actual ventilation is 32 L/min. In the absence of exercise-induced further shift of brain and ventilation curve (Figure 2), the ventilatory demands dictated by $R'C_{O_2}$/min corresponds to 44 L/min, of which 7 L/min is due to metabolic drive. In the patient in Figure 3, the corresponding values are 85 and 29 L/min; when compared to the patient in Figure 2, it represents an increase of 93% (metabolic demand: 85 vs. 44 L/min) and 314% (metabolic drive: 29 vs. 7 L/min). It follows that despite similar actual ventilation, dyspnea may be intolerable in the patient of Figure 3. Thus, although at the end of the exercise, in patients with PAH or CTEPH, actual ventilation could be far below the ventilatory ceiling, indicating significant ventilatory reserve, respiratory center activity may well be at near maximum, forcing the patient to stop exercise because of severe dyspnea.\textsuperscript{11,18} It is of interest to note that peak exercise ventilation, expressed as % of maximum voluntary ventilation, decreases with increasing the severity of PAH and remains considerably lower than that in normal humans.\textsuperscript{18}

**CONCLUSION**

Dyspnea on exertion, a cardinal symptom in patients with PH, can be explained by abnormalities in brain and ventilation curves and metabolic hyperbola. During exercise the deviation between brain and ventilation curve, presented already at rest, becomes progressively larger, resulting in high $R'C_{O_2}$ and continuously increasing unmet ventilatory demands. Furthermore, metabolic drive, an important determinant of ventilation during exercise, is significantly higher than that in normal humans. For these reasons, patients with PH have high $R'C_{O_2}$, which is simultaneously transmitted up to the forebrain and leads to the perception of exertional dyspnea at relatively low minute ventilation. In several cases, dyspnea is so severe that exercise is terminated. These patients at peak exercise typically exhibit a reduced maximum $O_2$ consumption, normal, or even high ventilatory reserve and signs of cardiovascular compromise (high heart rate, low $O_2$ pulse, low anaerobic threshold). Although this combination points out the dominance of cardiovascular mechanisms in reducing maximal exercise tolerance, exercise is limited by control of breathing mechanisms, while the cardiovascular compromise indirectly contributes to respiratory system abnormalities. We must emphasize that in patients with PAH or CTEPH, the ventilatory reserve are increased with increasing the severity of the disease.\textsuperscript{11,18} Exercise rehabilitation programs in these patients should focus on (1) decreasing the deviation between brain and ventilation curves and (2) moving the metabolic hyperbola downwards. Preventing exercise-induced hypoxemia (i.e., oxygen prescription during exercise) and delaying reaching the anaerobic threshold (i.e., optimization of therapy for PH, exercise programs to reverse the sedentary lifestyle effects on cardiac function) shift the brain curve downward, to higher $PaCO_2$, while respiratory muscle training and avoiding the occurrence of dynamic hyperinflation (i.e., weight loss in obese patients that may increase FRC, appropriate drug therapy that increases expiratory flow at low lung volume) shift the ventilation curve upward, to lower $PaCO_2$. Finally, decreasing $V_D/V_T$ (optimization of therapy for PH) and $V'C_{O_2}$ (weight loss in obese patients) moves the metabolic hyperbola downwards and this greatly decreases the ventilatory demands. Nevertheless, the whole task is complicated since several variables are involved in the process, including both the respiratory and cardiovascular systems.

**CONFLICTS OF INTEREST**

The authors declare no conflicts of interest.

**ETHICS STATEMENT**

The ethics statement is not available.

**AUTHOR CONTRIBUTIONS**

Ioanna Mitrouska and Dimitris Georgopoulos contributed to the conception of this study. Dimitris Georgopoulos, Ioanna Mitrouska, Maria Bolaki, and Katerina Vaporidi drafted and reviewed the manuscript. All authors finally approved the content of the manuscript.

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**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.