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Pulmonary Limitations in Heart Failure

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Summary

Ultimately in the pathogenesis of heart failure, the disease becomes a systemic illness with a marked impact on the respiratory system. This creates a significant codependence between organ systems that is accentuated as the disease progresses and is further enhanced during exercise where the respiratory system becomes a major contributor to exertional symptoms and an important marker to track disease severity and prognosis.

Keywords

heart failure; cardiopulmonary exercise testing; ventilatory efficiency

Introduction

The heart and lungs are intimately related anatomically and physiologically as they share the enclosed thoracic cavity, are exposed to similar intrathoracic pressures, have a common surface area and are hemodynamically linked as the lungs accept nearly the entire cardiac output¹. Hence, changes in cardiac function may directly influence lung function due to alterations in cardiac preload and afterload including venous return and cardiac transmural pressure. Heart failure directly impacts 1) lung mechanics due to congestion and increased heart size which promote airway obstruction and lung restriction^{1,2}, 2) high pulmonary

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pressures as well as pulmonary congestion contributes to remodeling of the pulmonary capillaries, increased ventilation-perfusion mismatch and decreased alveolar-capillary diffusion^{3,4} and 3) disordered ventilatory control including hyperventilation at rest, during exercise and with sleep⁵⁻⁷. These pulmonary system changes cause decreased breathing reserve combined with enhanced ventilation for a given metabolic demand (minute ventilation ($\dot{V}_E$)/pulmonary carbon dioxide output ($\dot{V}_{CO_2}$) ratio) at rest and during exercise^{7,8}. In this review, we discuss heart failure (HF) related changes in lung mechanics, gas exchange and ventilatory control as well as their impact on the limitation of exercise capacity, sleep disordered breathing and prognosis of HF patients.

Lung Volume and Flow in HF

Pulmonary function is abnormal in HF patients including decreased bronchial conductance and restrictive lung volumes. Moreover, the observed flow limitation and lung restriction may increase the work of breathing which in combination with weak respiratory muscles may increase the sensation of dyspnea in HF patients⁸. Bronchial flow limitation has been attributed to airway compression (by pulmonary edema) and/or mucosal edema due to bronchial congestion (Figure 1)^{1,8-10} which may develop from either an increase in blood flow or an increase in blood volume without a change of flow due to increased cardiac filling pressure or pulmonary artery hypertension¹. Several factors may influence bronchial blood flow in HF patients including increased left atrial pressure causing greater pulmonary vascular pressure and bronchial vessel stasis¹¹; stretching of the left heart chambers which may lead to increased bronchial conductance¹²; rise in inflammatory and vasoactive mediators which may influence vasomotor tone and lead to vasodilatation and congestion of bronchial vessels^{13,14}; and chronic hypocapnia which is a common manifestation of elevated left ventricular filling pressures in HF patients¹⁵ which may also lead to vasodilatation¹⁶.

Experimental studies have shown fluid overload leads to decrease of the diameter of both small¹⁷ and large airways¹⁸. Furthermore, pulmonary function test parameters have been shown to improve with diuresis in HF patients¹⁹. Agostoni et al. observed significantly higher bronchial shunt blood flow in patients with chronic HF than in non-HF patients during surgery on cardiopulmonary bypass suggesting the presence of either dilated or more numerous intrapulmonary bronchial blood vessels in patients with chronic HF¹¹. Pulmonary artery hypertension (PAH), a frequent comorbidity in either HF with reduced (HFrEF) or preserved ejection fraction (HFpEF)²⁰ has been shown to contribute to bronchial airway obstruction by Meyer, et al.,²¹ and others²²⁻²⁴.

Physiologic factors which may counteract hydrostatic forces which promote edema formation in the airways include sympathetic nervous system activation with α -adrenergic receptor mediated vasoconstriction in peri-bronchiolar vessels which may reduce congestion¹. Furthermore, functional capillary remodeling with fibrosis and thickening of the alveolar-capillary membranes due to chronically increased pulmonary capillary pressure may occur²⁵ causing increased resistance to high vascular pressures and interstitial edema development. Lymphatic drainage also progressively increases with the severity of HF²⁶ which may serve as another adaptive mechanism to reduce pulmonary congestion.

Olson, et al. have demonstrated a significant relationship between HF severity, heart size, intrathoracic volume and lung restriction². Cardiac enlargement in HF has been shown by Agostoni et al., to promote restrictive lung function²⁷. A close relation between pulmonary function and decrease in cardiac volume with heart transplantation was demonstrated by McCormack et al.²⁸

Gas Exchange Change in HF

Gas exchange is often abnormal in patients with HF and correlates with disease severity²⁹. Several studies have shown decreased lung diffusion factor for carbon monoxide (D_LCO) in patients with HF^{3,4}. The cause is probably multifactorial and involves interstitial edema as well as alveolar-capillary membrane remodeling^{3,4}. Furthermore, bronchial obstruction caused by peri-bronchial edema may reduce ventilation to some pulmonary units, increasing the ventilation-perfusion mismatch and further impairing gas exchange.

Pulmonary edema increases the distance between alveolar gas and red blood cells and may therefore also impair D_LCO . However, in healthy subjects, infusion of normal saline has been associated with worsening of lung mechanics, though not D_LCO ³⁰, suggesting alveolar-capillary remodeling may have a higher impact on the D_LCO changes observed in HF patients. Alveolar-capillary remodeling involves fibrosis, thickening of the alveolar-capillary membranes²⁵ and β -adrenergic receptor insufficiency of the alveolar epithelium³¹ which may result in inability to effectively clear alveolar fluid.

Impaired D_LCO has been associated with poor prognosis³² as well as low exercise performance³³. Unfortunately, adverse remodeling of the alveolar-capillary membrane may not be fully reversible with HF treatment³⁴. Only partial improvement of D_LCO with heart transplantation was shown by Mettauer et. al³⁵ and no change to D_LCO with cardiac resynchronization therapy was shown by our group³⁶.

Surfactant protein B appears to be a promising marker of alveolar-capillary membrane damage as it is not increased in edema with no alveolar damage³⁷ and has been shown to correlate with HF severity³⁸. Moreover, surfactant protein B has been shown to be associated with HF re-hospitalization³⁹ and to be related to D_LCO ⁴⁰, peak oxygen consumption (VO_2) and V_E/VCO_2 slope³⁸. Indeed, surfactant protein B may be a stronger prognostic marker than D_LCO ⁴¹ and unlike D_LCO may decrease with HF clinical improvement³⁹.

Ventilatory Control in HF

Ventilatory control is frequently abnormal in patients with advanced HF and manifests as hyperventilation at rest⁵, during exercise⁶ and with sleep⁷. The presence of hyperventilation has been associated with decreased functional capacity⁶, more severe symptoms⁴² and increased mortality⁴³ in HF patients.

The etiology of hyperventilation in HF patients has not been fully elucidated, and may include activation of pulmonary C-fiber receptors due to congestion, activation of atrial stretch receptors, ventilation-perfusion mismatch and low systemic oxygen transfer capacity as well as increased activation of central and peripheral chemoreflexes and the

ergoreflex^{6,42,44–49}. Lactate acidosis was formerly believed to be a major cause of hyperventilation in HF patients^{50,51} though this concept has since been refuted⁵².

Cardiopulmonary exercise testing (CPET) allows evaluation of the ventilatory response to exercise which is abnormal in HF patients despite normal breathing reserve⁸. Normal ventilatory response includes an increase of minute ventilation (V_E) caused by both increase in tidal volume (V_T) at the beginning of exercise followed by an increase of breathing frequency (f_b) towards peak exercise¹³. In HF, V_E is significantly increased because of the increase in f_b with little or no increase in V_T ⁵³. Ventilatory parameters routinely measured during CPET also include ventilatory efficiency (V_E/V_{CO_2}) and partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$).

The V_E/V_{CO_2} slope identifies and quantifies the magnitude of hyperventilation and has been found to be elevated^{54,55} and inversely correlated with cardiac output in HF patients⁵⁵. Importantly, many studies in HF patients have shown V_E/V_{CO_2} to be a better predictor of clinical outcome than peak VO_2 ^{56–60}. Ventilatory efficiency is inversely related to the partial pressure of arterial CO_2 ($PaCO_2$) and positively to the dead space / tidal volume ratio (V_D/V_T) by the alveolar gas equation $V_E/V_{CO_2} = 863 / (PaCO_2 \times (1 - V_D/V_T))$. From this relationship, it is clear the V_E/V_{CO_2} may be increased by lowering of the $PaCO_2$ or increasing the V_D/V_T ratio. Increased stimulation or increased sensitivity of pulmonary receptors, increased sympathetic nerve activity, peripheral and central chemoreceptors and ergoreceptors may cause hyperventilation and reduction of $PaCO_2$. Conversely, the V_D/V_T ratio may be effected by ventilation-perfusion mismatch including a rapid and shallow breathing pattern⁶. Woods et al., quantified the contribution of $PaCO_2$ and V_D/V_T to the increased V_E/V_{CO_2} in HF patients and found nearly similar contribution of $PaCO_2$ and V_D/V_T ⁶ (Figure 2).

Low $P_{ET}CO_2$ during exercise has also been shown to reflect functional, ventilatory and cardiac performance in HF patients by Myers et al.⁶¹. Furthermore, rest $P_{ET}CO_2$ has also been shown to be useful in HF prognostication⁶², and to add incremental prognostic value to V_E/V_{CO_2} slope⁵. Rest $P_{ET}CO_2$ has also been demonstrated to be an independent predictor of left ventricular assist device implantation⁶³. $P_{ET}CO_2$ has been integrated into two CPET scoring systems for adverse event prediction in HF^{64,65}. $P_{ET}CO_2$ may be decreased by hyperventilation and by increased dead space ventilation, i.e., by the same factors which determine V_E/V_{CO_2} ⁶, suggesting the parameters are closely related⁶¹. In our previous studies we have shown HF patients with low $P_{ET}CO_2$ and increased V_E/V_{CO_2} at peak exercise also exhibit low $P_{ET}CO_2$ and increased V_E/V_{CO_2} at rest^{7,66} suggesting factors which promote high V_E/V_{CO_2} and low $P_{ET}CO_2$ may not be limited to exercise.

Periodic Breathing, Exercise Oscillatory Ventilation and Central Sleep Apnea

Periodic breathing (PB) is a consequence of respiratory control system instability characterized by waxing and waning of tidal volume with or without interposed apnea⁴⁹ due to oscillations of central respiratory drive⁶⁷. PB may appear either at rest⁶⁸, during exercise⁶⁹ or with sleep⁷⁰. It has been shown that PB occurs mostly in the situations where

ventilation is mainly under metabolic control. During sleep it occurs with non-rapid eye movement sleep⁷⁰ and during exercise it is the time when the increased metabolic demand for O₂ consumption and CO₂ production cause respiratory control to fall mainly under the influence of the metabolic respiratory control system⁷¹.

Oxygen delivery and CO₂ excretion are physiologically maintained by the respiratory and circulatory systems. Stability of these systems is maintained by several feedback loops involving a central controller comprised of peripheral and central chemoreceptors stimulating the brainstem respiratory motor neurons and a peripheral working unit comprised of lungs, rib cage and respiratory muscles⁶⁷. Several factors may destabilize the respiratory control system and produce the PB pattern observed in HF patients. Prolonged circulatory time may cause delay in the information transfer between lungs and chemoreceptors⁷²; increased CO₂ chemosensitivity with increased chemoreceptor gain may lead to over-correction of PaCO₂ deviations from the arterial CO₂ setpoint⁶⁹; and the CO₂ setpoint may be lowered closer to the apnea threshold by hyperventilation caused by either activation of pulmonary C-fibers due to congestion, activation of left atrial stretch receptors by volume overload, ventilation-perfusion mismatch, increased sympathetic nerve activity or modulation of the ergoreflex^{6,44–49,73}. Taken together, PB is a manifestation of control system failure, caused by signal underdamping with periodic over and undershooting of ventilation⁶⁷. During sleep, the development of apnea depends mainly on the frequency of oscillations; the lower the frequency, the higher the amplitude and the higher the chance of crossing the CO₂ apnea threshold⁷⁰. Indeed, inhalation of 3% CO₂ eliminates Cheyne Stokes respiration of patients with HFrEF⁷⁴.

In contrast, no association between PaCO₂ at rest and during exercise and EOv (presence, duration, amplitude) was found in the study of Murphy et al⁷⁵. And in the same study, EOv was shown to be associated with increased cardiac filling pressure⁷⁵ supporting the concept of activation of pulmonary C-fibers and hyperventilation. However, this observation has been questioned by others who found EOv to disappear during late exercise despite an increase in pulmonary capillary wedge pressure⁷⁶. These observations suggest that EOv pathophysiology is complex and likely involves multiple factors.

The American Heart Association has defined EOv as an oscillatory ventilatory pattern that persists for at least 60% of exercise at an amplitude of 15% or more of the average resting value^{77,78} (Figure 3). By CPET, EOv has been detected in 19–51% of HFrEF patients⁷⁵ and similar prevalence has been observed in HFpEF patients⁷⁹. EOv has been associated with increased risk of death^{73,80}. Moreover, the risk of death is further increased in HF patients with EOv and increased V_E/VCO₂ slope⁸¹. Guazzi et al. found EOv to be the strongest predictor of cardiac events in HFpEF patients⁷⁹ and in patients without clinical manifestations of HF⁸². The risk of death is further increased if EOv is combined with abnormal breathing during sleep⁸³. The prevalence of EOv is similar to the prevalence of CSA and the presence of EOv is highly predictive of the presence of CSA⁸⁴ suggesting shared pathophysiology.

In HF patients, CSA is characterized as a crescendo-decrescendo breathing pattern with hyperventilation alternating with compensatory apnea^{85,86}. CSA is considered a

consequence of HF^{86–90}, is linked to the hemodynamic severity of HF^{91,92} and associated with increased hospital readmission rates⁹³ and mortality⁹⁴. In a previous study by our group, we have shown HF patients with CSA exhibit higher central CO₂ chemosensitivity, increased V_E and lower P_{ET}CO₂ at rest, higher V_E, V_T and V_E/VCO₂ ratio and lower P_{ET}CO₂ during exercise, and higher V_E/VCO₂ ratio and lower P_{ET}CO₂ at peak exercise⁷. Moreover, we have shown central CO₂ chemosensitivity, peak P_{ET}CO₂ and peak V_E/VCO₂ ratio to be independently associated with the presence of CSA and to correlate with CSA severity⁷. These observations suggest the presence of abnormal ventilatory control of HF patients with hyperventilation at rest, during exercise and with sleep and may promote recognition of the CSA phenotype during CPET⁷.

Special Considerations for HFpEF

HFpEF is frequent and accounts for more than half of HF cases⁹⁵. Moreover, HFpEF is associated with increased risk of hospitalization and death^{96,97}. Guazzi et al showed V_E/VCO₂ but not peak VO₂ to be associated with all cause and cardiac related mortality and hospitalization in patients with HFpEF^{79,98}. These result were supported by Yan et al., who also showed V_E/VCO₂ but not peak VO₂ to be associated with all-cause mortality in patients with HFpEF⁹⁹. In contrast, Shafiq et al. showed an association of peak VO₂ but not V_E/VCO₂ with all-cause mortality and cardiac transplant¹⁰⁰. Finally, Nadruz et al showed both V_E/VCO₂ and peak VO₂ to be independent prognostic tools in HFpEF¹⁰¹.

Special Considerations for Pulmonary Artery Hypertension

Chronically increased cardiac filling pressure is a common cause of PAH in both patients with HFrEF and HFpEF²⁰. The prevalence of this comorbidity is high in patients with HFrEF (up to 72%)¹⁰² and in patients with HFpEF (up to 83%)¹⁰³. PAH is associated with exercise dyspnea, increased V_E/VCO₂ slope and poor prognosis¹⁰⁴. Physiologically, V_E/VCO₂ decreases and P_{ET}CO₂ increases from rest to peak exercise¹⁰⁵. This physiological pattern may also be observed in patients with HF^{7,106}. In contrast, in patients with moderate to severe PAH, V_E/VCO₂ was found to increase¹⁰⁷ and P_{ET}CO₂ to decrease during exercise because of poor pulmonary perfusion¹⁰⁸. In patients with PAH, ventilatory response to exercise seems to be more closely related to ventilatory-perfusion mismatch and increased ventilatory drive than altered pulmonary mechanics¹⁰⁹.

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Abbreviations

CPET	cardiopulmonary exercise testing
CSA	central sleep apnea
D_LCO	lung diffusion factor for carbon monoxide

EOV	exercise oscillatory ventilatory
f_b	breathing frequency
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
Pa	arterial partial pressure
PAH	Pulmonary artery hypertension
PB	periodic breathing
P_{ET}CO₂	end-tidal partial pressure for carbon dioxide
ṡCO₂	pulmonary carbon dioxide output
VD	dead space
ṡE	minute ventilation
ṡO₂	pulmonary oxygen uptake
V_T	tidal volume

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Synopsis:

The heart and lungs are intimately linked. Hence, impaired function of one organ may lead to changes in the other. Accordingly, heart failure is associated with airway obstruction, loss of lung volume, impaired gas exchange and abnormal ventilatory control. Cardiopulmonary exercise testing is an excellent tool for evaluation of gas exchange and ventilatory control. Indeed, many parameters routinely measured during cardiopulmonary exercise testing including the level of minute ventilation per unit of carbon dioxide production (V_E/VCO_2 slope) and the presence of exercise oscillatory ventilation have been found to be strongly associated with prognosis in HF patients.

Key points:

1. Heart failure is associated with airway obstruction, reduced lung volume, impaired gas exchange and abnormal ventilatory control.
2. Abnormal ventilatory control in heart failure patients manifests as hyperventilation at rest, during exercise and even with sleep.
3. Cardiopulmonary exercise testing detects abnormalities of gas exchange and ventilatory control.
4. Selected cardiopulmonary exercise testing parameters including V_E/VCO_2 slope and oscillatory breathing have been strongly associated with prognosis of heart failure patients.

Airflow limitation (due to airway compression by pulmonary edema and/or mucosal edema secondary to bronchial congestion) and lung restriction (linked to cardiomegaly and increased lung elastic recoil) are common consequences of chronic heart failure.

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The efficiency of intra-pulmonary gas exchange can be decreased in heart failure due to a highly variable combination of interstitial edema, alveolar-capillary membrane remodeling and ventilation-perfusion mismatch. These abnormalities can be appreciated by the degree of impairment in hemoglobin-corrected $D_L CO$.

A high V_E/V_{CO_2} in heart failure reflects an excessive ventilation for the prevailing metabolic demand due to alveolar hyperventilation secondary to increased stimulation or sensitivity of pulmonary receptors, increased sympathetic nerve activity and chemo-receptor overactivation and/or high “wasted” ventilation as a consequence of ventilation-perfusion mismatch and a rapid and shallow breathing pattern.

Abnormalities in the ventilatory control system are commonly found in advanced chronic heart failure: these derangements are exacerbated in physiological situations in which afferent stimulation is strongly influenced by metabolism e.g., exercise and sleep.

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Figure 1.

Bronchial flow limitation in heart failure may be caused by mucosal edema due to bronchial congestion which may develop from either an increase in blood flow or an increase in blood volume (Theory A) or by bronchial compression which may be caused by reduction of intrathoracic space by either increase in heart size or by pulmonary edema (Theory B) (reprinted with permission from reference #1, figure #2, Ceridon et al 2009).

Figure 2.

In heart failure, both the increased ventilatory drive (low partial pressure of carbon dioxide ($PaCO_2$)) and ventilation/perfusion mismatch (high dead space volume to tidal volume ratio (V_D/V_T)) contribute nearly equally to the increase in ventilatory inefficiency (higher V_E/V_{CO_2}) (reprinted with permission from reference #6, figure #3C, Woods et al, 2010).

Figure 3.

Exercise oscillatory ventilation is a consequence of respiratory control system instability characterized by waxing and waning of tidal volume (V_T), breathing frequency (RR) and minute ventilation ($\dot{V}_E$) without interposed apnea due to oscillations of central respiratory drive. (Reprinted with permission from reference #78, figure #10, Olson et al 2006)