Exercise ventilation inefficiency in heart failure: pathophysiological and clinical significance

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Introduction

Heart failure (HF) is a complex syndrome characterized by myocardial dysfunction and a poor prognosis. Among multiple markers of severity, an exercise ventilation inefficiency has important clinical and prognostic value. The pathophysiology determining exercise ventilatory inefficiency is complex and not definitively clarified. Three different mechanisms have been identified: (i) increased dead space, (ii) early occurrence of lactic acidosis, and (iii) abnormal chemoreflex and/or metaboreflex activity. Besides its prognostic value, abnormal ventilation can be influenced by pharmacological and non-pharmacological therapies such as β-blockers, selective cyclic 3’-5’ guanosine monophosphate phosphodiesterase inhibitors, physical training, and nocturnal continuous positive airway pressure. There is an increasing interest for the exercise periodic breathing, which is frequently associated with HF syndrome and has prognostic importance. The precise mechanisms sustaining exercise periodic breathing are not fully defined but ventilatory and metabo-haemodynamic hypotheses have been proposed.

Increased VE/VCO2 slope

Measuring VE/VCO2 slope is of peculiar clinical relevance because this variable has been repeatedly identified as a strong and independent prognostic marker in a large subset of HF patients with exercise limitation of mild-to-intermediate severity.4–12 Mathematically, the VE/VCO2 slope is determined by three factors: the amount of CO2 produced (VCO2), the physiological dead space/tidal volume ratio (VD/VT), and the arterial CO2 partial pressure (PaCO2) according to the following equation: VE = 863 × VCO2/[PaCO2 {1–VD/VT}]. Three different mechanisms for an increased ventilatory requirement to a given CO2 production have been reported (Figure 1): (i) increased dead space and consequent waste ventilation;10,11,13 (ii) early occurrence of haemtic lactic acidosis,11 and (iii) abnormal chemoreflex and/or metaboreflex activity.14,15

In HF patients, a reduction in static lung mechanics (i.e. reduced vital capacity and forced expiratory volume in 1 s) is a common finding.11 The occurrence of restrictive lung changes is implicated in a lower rate of increase in tidal volume (VT), higher respiratory rate (RR), and dead space to tidal volume ratio (VD/VT) for a given workload.13 Consonant with an increased dead space ventilation is the demonstration that lung interstitial fibrosis and remodelling of alveolar-capillary membrane are additional features of changes occurring at the lung level.16,17 Thus, the abnormalities in alveolar gas membrane conductance along with the occurrence of ventilation/perfusion mismatch due to the combination of impaired regional lung perfusion and abnormal increase in pulmonary capillary pressure seem to be implicated in the increased ventilatory requirement during exercise.18

A limited increase in cardiac output is certainly the initial determinant of exercise intolerance and muscle fatigue in these patients. The imbalance between cardiac output and metabolic request by working muscles explains the development of early lactic acidosis during exercise, favoured by...
concomitant muscle deconditioning and increased type IIb muscular fibres expression. Early lactic acidosis may explain the occurrence of an increased inefficient ventilation since the early stages of exercise. It has been demonstrated that patients with severe HF exhibit a significant PaCO₂ reduction at peak exercise and even during a submaximal constant workload at 50 W. Evidence for a major putative role of lactic acidosis in the augmented ventilatory response is supported by the finding of reduced PaCO₂ levels in HF compared with control subjects. PaCO₂ is stable or gradually increase during an incremental exercise up to the beginning of respiratory compensation for lactic acidosis. Subsequently, for the higher levels of developing lactic acidosis, PaCO₂ decreases accordingly until exercise termination. The demonstration that patients with a lower PaCO₂ at peak exercise are those exposed at a high risk of death supports this hypothesis. This mechanism is nevertheless debated. Wensel et al. recently showed that during the recovery phase of exercise, high levels of lactate do not correlate with VE/VCO₂ slope. Moreover, the decrease in PaCO₂ may also be primarily related to the hyperventilatory response necessary to overcome ventilation-perfusion mismatch and high dead space ventilation.

There is, however, no doubt that most of the pathophysiological evidence for an increase in the ventilatory response to exercise is related to an impaired breathing control. This may occur at several levels and involve the peripheral and/or central chemoreflex control as well as the increased neural reflexogenic activity arising from working muscle ergoreceptors. Chemoreflex deregulation may occur early in the natural history of HF. In 60 patients with ischaemic heart disease without overt HF, VE/VCO₂ slope was found to correlate with the level of central chemosensitivity. Changes in VE/VCO₂ slope correlated with an improved chemoreflex sensitivity after a 3-month period of exercise training. Although an increased chemoreflex activation in patients with overt HF is well established, the relative contributory role of central vs. peripheral activation is still undefined. Interestingly, Ciarka et al. have recently reported that in heart transplant recipients, central chemoreflex activity may reverse to normal despite persistent peripheral impairment, which correlates positively with the increased VE/VCO₂ during exercise.

Overactivation of ergoreceptors (amielinic fibres located in the skeletal muscles) to metabolic products such as K⁺ and H⁺ triggers a series of reflex responses such as sympathetic activation, vasoconstriction, and hyperventilation. Ergoreflex activation independently correlates with VE/VCO₂ slope and inversely with exercise tolerance in HF patients. The central nervous system processing involvement in the deregulated ventilatory response to exercise has been evaluated. Rosen et al. did not report major differences between the regional brain activation at rest, after exercise, and during isocapnic hyperventilation in HF patients and controls. Leptin, an hormone that may be involved in the control activity of central chemosensitivity, was found be a marker of increased VE/VCO₂ slope.

Impaired ventilation during exercise is a common finding in HF patients even in right HF due to primary pulmonary hypertension (PPH). PPH patients present a ventilation profile similar to HF patients, consisting in increased VE/VCO₂ slope, ventilated dead space, and concomitant reduced PaCO₂. The difference between the two patterns is the underlying pathophysiological mechanisms. PPH results primarily from the abnormalities of pulmonary vasculature consisting in intimal fibrosis, medial hypertrophy leading to increased pulmonary vascular resistances, and loss of the physiological vasodilator response to exercise. These changes determine a ventilation/perfusion...
mismatch and increased VD/VT ratio, due to hypoperfusion of ventilated alveoli, resulting in an increased VE/VCO₂ ratio. Another trigger for the increased ventilatory response to exercise is the early lactic acidosis at low work rate and the consequent production of CO₂ due to the bicarbonate dissociation, as it buffers the newly formed lactic acid. The last mechanisms are the arterial hypoxemia and failure in delivering the requested O₂ to the exerting muscles due to: (i) reduced pulmonary capillary bed with short red blood cell transit, (ii) possible right-to-left shunt through a patent foramen ovale, and (iii) failure in cardiac output. The right ventricle is unable to increase the pulmonary and consequent systemic blood flow against the elevated vascular resistance. Interestingly, the role of an impaired chemoreflex and ergoreflex control in PPH has not been tested. Nevertheless, in PPH patients, VE/VCO₂ better correlates with the NYHA class than the resting pulmonary haemodynamics. The ventilatory pattern is also important for unmasking the presence of a right-to-left shunt as evidenced by an abrupt decrease in end-tidal CO₂ with concomitant increase in end-tidal O₂ and respiratory exchange ratio (RER).

VE/VCO₂ slope: prognostic relevance and therapeutic implications

VE/VCO₂ slope (Figure 2) has repeatedly emerged as an independent powerful prognostic marker in HF patients with intermediate exercise limitation. Following the landmark paper published by Mancini et al., in the early 1990s, the prognostic superiority of VE/VCO₂ slope over peak VO₂ has been progressively documented and strengthened by a series of studies. As originally proposed by Chua et al., the majority of these studies have identified and confirmed the prognostic value of a cut-off of 34. Remarkably, VE/VCO₂ slope provides incremental prognostic value in patients with preserved peak VO₂ (>18 mL/min/kg) and in patients with diastolic HF. Although the exercise ventilation inefficiency is not considered as a specific target of HF therapeutic strategies, an improvement in VE/VCO₂ slope has been demonstrated after several therapeutic approaches.

Exercise ventilation inefficiency in HF

In a retrospective analysis performed in 614 HF patients, an association was found between β-blocker administration and an improved ventilatory efficiency. Multiple explanations have been proposed for this favourable interaction. β-Blockers may attenuate catecholamine activation of central and peripheral chemoreceptors. Moreover, HF is associated with cardiac β-adrenoceptor desensitization and the process may also involve the pulmonary system; a resensitization receptor process induced by β-blockers may favourably influence pulmonary ventilation-perfusion matching and haemodynamics during exercise, leading to a more efficient ventilation during exercise. An intriguing hypothesis is the postulated effects of β-blockers on metabolic activity. In the early and intermediate exercise stages, energy is supplied predominantly by fatty acids while at further exercise stages, it is supplied by carbohydrates. Fatty acid oxidation yields to an RER, which is given by VCO₂/VO₂ ratio of 0.7 compared with 1.0 when glucose is the only energy substrate. Sympathetic nervous system activation during exercise shifts the metabolic substrate towards carbohydrate utilization pathway. β-Blockers may delay the switch from fatty acid to carbohydrate substrate utilization keeping exercise VCO₂/VO₂ ratio at lower levels. As a result, for a given O₂ consumption, less CO₂ is produced. In other words, an improved ventilation efficiency could be driven by a lower CO₂ production due to a prolonged utilization of fatty acid substrate.

Modulation of the nitric oxide pathway by selective cyclic 3’-5’ guanosine monophosphate phosphodiesterase inhibition, such as sildenafil, has provided evidence for a VE/VCO₂ slope lowering effect. This therapeutic effect was found to correlate with an improvement in alveolar-capillary membrane conductance.

Non-pharmacological therapy that directly influences the inefficient ventilation includes physical training and nocturnal continuous positive airway pressure (CPAP). Treating central sleep apnoea with CPAP improves inefficient ventilation probably through a combined positive effect on LV ejection fraction, sympathetic activity, and chemosensitivity. Similarly, exercise-training programs improve inefficient ventilation by several mechanisms: (i) reduced sympathetic nerve activity and catecholamine concentration, (ii) restoration of normal muscular metabolism, (iii) reduction in metabolic mediators involved in ergoreflex activation, and (iv) improved alveolar-capillary membrane diffusion properties.

Exercise periodic breathing

There is an increasing interest for an abnormal breathing disorder, identified as exercise periodic breathing (EPB), which may be observed in HF patients (Figure 3). Since 1986, Weber described a particular ‘saw-toothed’ ventilatory response to exercise in some HF patients. EPB ventilation is characterized by oscillations in ventilation, VO₂ and VCO₂, with a period and amplitude that may be quite different across HF populations. Its definition and classification remain quite arbitrary and definitive criteria are still needed. Kremser et al. classified the periodism as an oscillation of ~1 min, a >15% amplitude of the resting
value, and a duration of up to 66% of the exercise protocol. Leite et al. diagnosed EPB based on the presence of frequent (at least three cycles), regular (standard deviation of three consecutive cycle lengths within 20% of their average), and ample (minimal amplitude of 5 L/min) minute ventilation oscillations.

EPB pathophysiology and prognostic relevance

The precise mechanisms sustaining EPB are unclear but ventilatory and metabo-haemodynamic hypotheses have been proposed (Figure 1).

The ventilatory hypothesis is based on the demonstration of instability of ventilatory control due to an abnormal chemoreceptors feedback. Fluctuating afferent signalling to ventilatory centres could promote oscillatory patterns in VO₂ and VCO₂. In experimental conditions, an increase in chemoreceptor discharge induced an oscillatory ventilation that was abolished by hyperoxia. Ponikowski et al. identified a link between an enhanced chemosensitivity and an oscillatory breathing at rest. Modulation or blockade of peripheral chemoreflex activity by hyperoxia or dihydrocodeine can reduce or abolish the oscillatory ventilatory pattern. The impaired feedback in the ventilatory control could also involve a prolonged circulatory time. A long lung-to-ear circulatory delay has been reported in HF patients and could induce a desynchronization between the lung and the ventilatory control system leading to a periodic respiration. Moreover, administration of milrinone, a positive inotropic and vasodilatory agent, is capable of abolishing the periodic breathing in HF patients.

Some data are, however, against this hypothesis. Gases oscillatory kinetics do not seem to be synchronous with the ventilatory kinetics and voluntary simulated periodic breathing failed to reproduce the magnitude and phase of spontaneous oscillations of HF patients. Francis et al. reported that the magnitude and the synchronism between metabolic and ventilatory fluctuations in spontaneous periodic breathing are also reproducible with a voluntary periodic breathing if the latter is corrected for the workload at which the ventilation is performed. Nonetheless, echocardiographic and radionuclide studies have provided evidence of stroke volume fluctuations.

In patients with severe HF evaluated for heart transplantation, EPB was found to be the single predictor of cardiac death. In a recent report by Corra et al., periodic breathing prevalence was 21% among 150 HF patients, 78% of whom presenting with central sleep apnoea and severe sleep-disordered breathing (apnoea–hypopnea index > 30/h). In this study, a tight pathogenic link between EPB and oscillatory sleep-disordered breathing was observed. The finding of EPB may, therefore, help in the decision making for further investigations, such as screening for a sleep apnoea syndrome. However, several questions on this ventilatory abnormality remain unanswered, such as the real incidence of this phenomenon, the uncertain criteria for EPB definition, its prognostic importance compared with VE/VCO₂ slope, and the most effective therapeutic approach.

Future implications: mitral regurgitation and excessive exercise ventilation

HF is frequently associated with functional mitral regurgitation (MR), which can be due to several mechanisms such as valve annular dilatation, LV distortion, and mitral deformation. MR yields to a significant rise in pulmonary venous, capillary, and arterial pressures. MR quantification is usually performed at rest and despite a relevant and compelling pathophysiological background, it is often overlooked that MR may abruptly rise during exercise. Notably, the degree of MR at rest is not predictive of exercise-induced changes in MR and a strong correlation has been reported between MR exercise-induced changes and transtricuspid pressure gradient. The excessive rise in pulmonary wedge pressure and pulmonary artery pressure is likely related to an increased ventilation during exercise and dyspnoea sensation. Many HF patients, without significant MR at rest, may develop a functional MR during exercise resulting in worsening of dyspnoea and hyperventilation. In order to better quantify the role of functional MR in the development of dyspnoea during exercise in the individual patient, the appreciation of functional MR may be integrated with a contemporary evaluation of the effective ventilation during exercise. Remarkably, the occurrence of exertional hyperventilation may potentially suggest the presence of functional MR, which could play a role in the hyperventilatory response. Finally, the presence of functional MR is a further relevant marker for the prognostic stratification of HF patients by predicting the occurrence of acute pulmonary oedema and guarded prognosis.

Conclusions

HF syndrome is a complex syndrome involving several organ systems. Exercise limitation is a typical manifestation that is accompanied by increased significant dyspnoea and ventilation inefficiency. Characterization of abnormalities in exercise ventilation may help clinicians to better define clinical condition and risk stratification.

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References

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