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Review

Cardiopulmonary interaction in heart failure

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Abstract

In heart failure lung dysfunction is frequent and is greater the greater the heart failure severity. It can be evaluated in terms of lung mechanics and gas diffusion. Indeed heart–lung interaction is related to heart dimensions and lung fluid content; furthermore heart–lung interaction is influenced by the body position. Lung diffusion is also altered in patients with chronic heart failure, and a low gas diffusion is associated with a reduced performance. During exercise, heart–lung interaction becomes more evident. Heart failure patients show an abnormal hyperventilation due to a progressively increased respiratory rate, and a lower tidal volume; hyperventilation is due to different causes including enhanced responses from chemo- and metabolo-receptors, increased CO_2 production and increased dead space ventilation. Several drugs affect the ventilatory pattern in heart failure patients: ACE-inhibitors and anti-aldosteronic drugs improve lung diffusion and ventilatory efficiency during exercise; beta-blockers reduce exercise-induced hyperventilation. Furthermore, ultrafiltration improves lung mechanics, both at rest and during exercise, through body fluid content reduction.

Keywords: Cardiomegaly; Exercise; Heart failure

Contents

This paper reviews the physiological basis of cardiopulmonary interaction in patients with chronic heart failure. Lung dysfunction can be evaluated in terms of lung mechanics and gas diffusion. The former has been studied for many years while the correlation between gas diffusion abnormalities and chronic heart failure has been suggested more recently. This is due to the fact that, differently from patients with chronic pulmonary diseases, hypoxaemia is rare in heart failure patients in stable clinical conditions so that the well-documented correlation between lung diffusion abnormalities and exercise capacity in heart failure has been considered as occasional and free from a physiological meaning.

Independently from the presence of co-morbidity, resting pulmonary function is either normal or characterized by a restrictive pattern [1]. Pulmonary function of 190 chronic heart failure patients is reported in Table 1. Patients were grouped according to heart failure severity as assessed by exercise capacity. Lung dysfunction increases in parallel with the severity of heart failure [2]. This is likely due to the greater amount of fluid present in the lungs of patients with severe heart failure. A role is also played by the enlarged heart [3]. Indeed a correlation between volume of the chest occupied by the enlarged heart and lung function has been reported, so that the strongest correlation is the cardiothoracic index (relationship between chest and heart size at chest X-ray), and the lowest correlation is with lung

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Table 1
Pulmonary function in series of 190 heart failure patients

Group	FVC (l/min)	FVC (%)	FEV_1 (l/min)	FEV_1 (%)	FEV_1/FVC	MVV (l/min)
1 ($n=25$)	2.3±0.4	67±16	1.9±0.2	76±13	89±15	78±15
2 ($n=75$)	3.0±0.7°	80±14°	2.4±0.6°	85±18*	84±17	92±24*
3 ($n=64$)	3.3±0.8°	85±16°	2.7±0.6°	90±15°	89±19	102±25°
4 ($n=26$)	3.7±0.5°	87±18°	3.0±0.4°	98±16°	88±15	104±24°
Group	DLCO (ml/mmHg/min)	DLCO (%)	DM (ml/mmHg/min)	V_c (ml)	DM/V_c	DM/V_A
1 ($n=25$)	16.1±4.2	65±18	27.7±11.8	83±49	0.49±0.39	6.3±2.8
2 ($n=75$)	20.5±5.6°	80±22°	30.3±10.0	104±44	0.34±0.19*	6.1±1.9
3 ($n=64$)	21.4±5.4°	80±15°	31.1±9.5	103±37*	0.35±0.17*	5.8±1.7
4 ($n=26$)	25.0±5.9°	90±21°	42.3±11.4°	111±42*	0.46±0.29	7.3±2.7

Definition groups: 1 = peak $VO_2<12$ ml/kg/min; 2 = peak $VO_2>12$ and <16 ml/kg/min; 3 = peak $VO_2>16$ and <20 ml/kg/min; 4 = peak $VO_2>20$ ml/kg/min.
FVC = forced ventilatory capacity. FEV_1 = forced expiratory volume in the first second; MVV = maximal voluntary ventilation; DLCO = lung diffusion for CO; DM = membrane diffusion; V_c = capillary volume; V_A = alveolar volume.*$p<0.05$ vs. Group 1; °$p<0.01$ vs. Group 1.

function [3]. Moreover in a recent report, Palermo et al. [4] showed, in chronic heart failure patients, that lung dysfunction varies in relationship with the position of the body, being the worst in the lateral decubitus. The greater the heart dimensions the greater is the difference in lung function between the sitting position and the lateral decubitus. This information explains why heart failure patients feel a greater discomfort in the lateral position compared with sitting, prone or supine, and why they avoid, during sleeping, both left and right lateral decubitus.

Lung diffusion is also altered in patients with chronic heart failure. Indeed, several lines of evidence suggest that gas diffusion across the alveolar–capillary membrane influences exercise capacity in heart failure patients: (a) lung diffusing capacity for carbon monoxide (DLCO) correlates with exercise capacity [5–8]; (b) clinical and exercise capacity improvement with ACE-inhibitors is associated with and positively correlates with the increase in DLCO [9,10]; (c) oxygen uptake kinetics can be altered with lung diffusion manipulation [11]; and (d) exercise performance can be improved in heart failure patients by increasing oxygen partial pressure physiologically, i.e. by exercising patients below sea level [12] or, artificially, by increasing the inspired oxygen fraction [13], or by positive pressure ventilation [14]. All together these observations suggest a link between lung diffusion and exercise capacity. Lung diffusion can be further evaluated by considering its two subcomponents, capillary volume and membrane resistance. The term capillary volume, if correction for haemoglobin content is made, refers to the volume of blood which is seen by gas exchange molecules (experimentally CO); in other words, it includes the concepts of vessels and blood flow. In previous studies it was demonstrated by Puri et al. [7] that the membrane resistance decreases and the capillary volume increases in relationship with the severity of the disease. The capillary volume increase was interpreted as a compensatory mechanism aimed, by pulmonary vessels recruitment, at preserving alveolar–capillary gas diffusion. Table 1 reports lung diffusion values at rest from the same 190 chronic heart failure patients previously reported. In this series of patients capillary volume decreased in patients with severe heart failure. The difference between our results and those of Puri et al. [7] is probably due to the greater heart failure severity of our patients. The reduction of capillary volume in patients with severe heart failure may be related to a low cardiac output, occlusion of pulmonary vessels and increased intrapulmonary shunt.

Physical exercise, however, is the condition during which cardiopulmonary interaction becomes more evident. In normal individuals, during exercise there is a progressive increase of ventilation due to both tidal volume and respiratory rate increase. Tidal volume increase is mainly at the beginning of exercise, while respiratory rate increase is more relevant toward peak exercise. Abnormal hyperventilation is a striking characteristic of the integrated response to exercise in heart failure patients. For a given work-rate, heart failure patients show higher ventilation when compared with normal subjects, associated with a progressively increased respiratory rate and lower tidal volume [1]. Several observations relate heart failure severity to hyperventilation: (a) hyperventilation is associated with dyspnoea, one of the most common symptoms of heart failure patients [15]; (b) a low ventilatory efficiency, defined as a high ventilation relative to CO_2 production, is a strong negative predictor of prognosis, independent of peak $V'O_2$ [16,17]; and (c) abnormal ventilation is among the limiting factors of exercise capacity [18–20]. In heart failure patients, hyperventilation is due to several causes including: alteration of lung mechanics, reduced lung diffusion, increased ventilatory needs due to increased CO_2 production, increased dead space ventilation, and overactive reflexes from metabolo-receptors, baro-receptors and chemo-receptors, all of which are part of the widespread derangement of the cardiovascular reflex control in heart failure [21–24]. At sea level, ventilation depends on $V'CO_2$,

$PaCO_2$ and V_D/V_T according to the formula:

$$V'_E = V'CO_2 \times 863/[PaCO_2(1 - V_D/V_T)],$$

where V'_E is the ventilation, $V'CO_2$ the CO_2 production, $PaCO_2$ the CO_2 arterial pressure and V_D/V_T is tidal volume/dead space ratio [1]. In heart failure, during exercise hyperventilation is associated with an increased V_D/V_T and $V'CO_2$ and with a lower arterial PCO_2, if compared with a similar percent intensity of exercise in normal subjects. Furthermore, the $V'_E/V'CO_2$ slope, which is increased in heart failure patients, is both the best index of the efficiency of ventilation and a strong prognostic indicator. Robbins et al. [25], in a population of 470 patients undergoing CPET, demonstrated that an increased $V'_E/V'CO_2$ slope >34 is a relevant prognostic indicator whose power increased when combined with a reduced chronotropic index. Moreover, Ponikowski et al. [23] analysed 123 patients with a peak $V'O_2 > 18$ ml/min/kg. In this subset of patients, they found that, for those with a steeper $V'_E/V'CO_2$ (>34), the 3-year survival rate was 57% compared with 93% in those with a normal $V'_E/V'CO_2$. The V'_E vs. $V'CO_2$ relationship is linear with two components, below and above the end of the isocapnic buffering period. Indeed, before the end of the isocapnic buffering period, at sea level, the major stimulus to ventilation is CO_2, and the amount of ventilation needed to eliminate CO_2 is an index of efficiency of ventilation. Above the isocapnic buffering period, ventilation is guided mainly by acidosis and, under particular circumstances, by thermoregulatory mechanisms. Accordingly, the $V'_E/V'CO_2$ slope, as an index of efficacy of ventilation, should be measured from the beginning of exercise to the end of the isocapnic buffering period and not throughout the entire exercise. In hypoxic conditions, such as at altitude, the chemical stimulus of ventilation is the low oxygen level. The value of the $V'_E/V'CO_2$ relationship in studies performed at high altitude is still unknown. The equation

$$V'_E = V'CO_2 \times 863/[PaCO_2(1 - V_D/V_T)]$$

can be rearranged as

$$V_D/V_T = 1 - [863/PaCO_2(V'_E/V'CO_2)]$$

and plotted as in Fig. 1. This plot is useful because it allows us to differentiate specific patterns for various diseases. Indeed, in normal subjects V_D/V_T decreases throughout the entire exercise: $V'_E/V'CO_2$ reduces in the first part of exercise but increases at the end, while $PaCO_2$ decreases, but only toward the end of exercise. The heart failure, pulmonary hypertension and COPD behaviours are also plotted for comparison; each has a peculiar behaviour. Indeed, heart failure patients reduce V_D/V_T and $V'_E/V'CO_2$, as do normal subjects, but to a lesser extent.

The flow/volume curve during exercise provides us with more detailed information about ventilatory abnormalities. Indeed, Johnson et al. [26], showed that the expiratory flow reserve was dramatically reduced throughout exercise, and that the only way that heart failure patients have to keep increasing ventilation is through an increment in FRC during exercise.

Several therapeutic interventions affect the ventilatory pattern in heart failure patients. ACE-inhibitors, but not AT1-receptor blockers, improve lung diffusion due to an

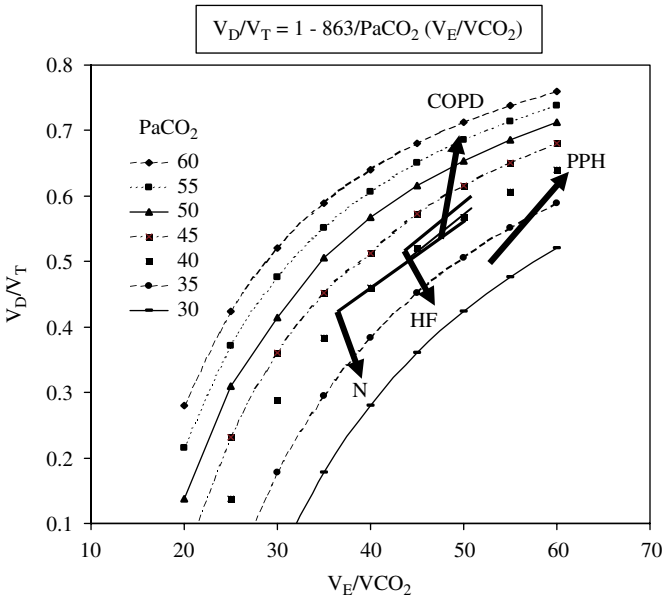

Fig. 1. Ventilatory behaviour during exercise of a normal subject (N), an heart failure subject (HF), a chronic obstructive lung disease patient (COPD) and of a patient with primitive pulmonary hypertension (PPH). V_D/V_T = dead space/tidal volume ratio, $PaCO_2$ = arterial pressure for carbon dioxide, $V'_E/V'CO_2$ = ratio of ventilation vs. carbon dioxide production.

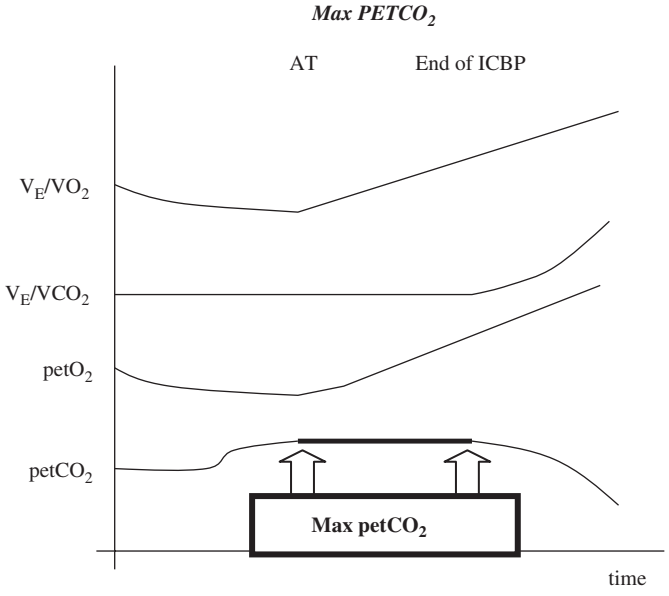

Fig. 2. Schema of ventilatory equivalents for oxygen ($V'_E/V'O_2$), for carbon dioxide ($V'_E/V'CO_2$) end-tidal pressure of oxygen ($PetO_2$) and of carbon dioxide ($PetCO_2$) behaviour with time during an hypothetical ramp protocol cardiopulmonary exercise test. The highest end-tidal carbon dioxide pressure (max $PetCO_2$) is measured between the anaerobic threshold (AT) and the end of the isocapnic buffering period (ICBP).

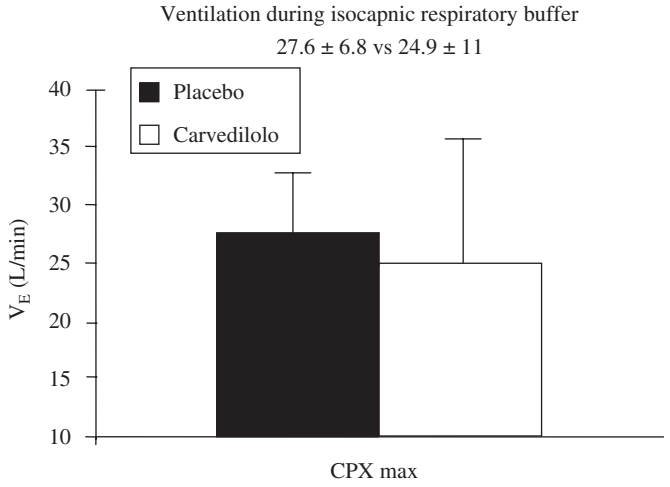

Fig. 3. Ventilation (V'_E) during the ICBP in heart failure patients treated chronically with placebo (black column) and carvedilol (white column). Data from Ref. [27].

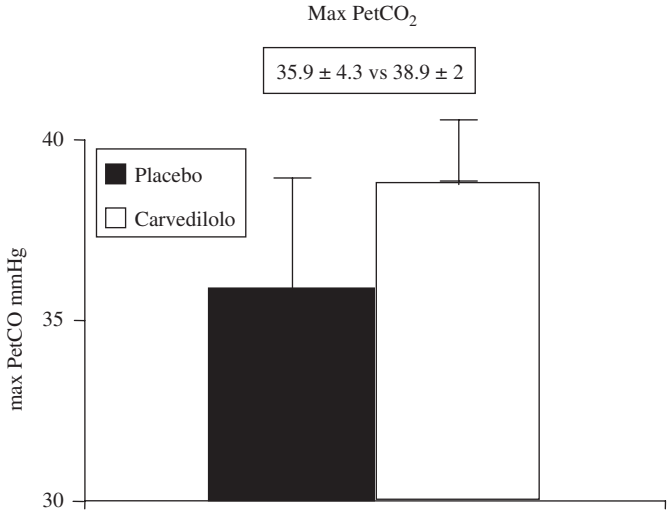

Fig. 4. The highest end-tidal carbon dioxide pressure (max $PetCO_2$) in heart failure patients treated chronically with placebo (black column) and carvedilol (white column). Data from Ref. [27].

increase in bradykinin levels. However, both ACE-inhibitors and AT1-blocking agents improve exercise performance but, most likely, through different mechanisms [6]. Beta-blockers, without affecting exercise performance, reduce exercise-induced hyperventilation, as shown by a lower $V'_E/V'CO_2$ slope, through an up-shifting of the CO_2 set-point. In a recent paper from our group peak $V'O_2$ was 16.2 ± 4.1 ml/min/kg in placebo and 16.4 ± 4.4 ml/min/kg in chronic carvedilol treatment, while the $V'_E/V'CO_2$ slope was 36.4 ± 8.9 and 31.7 ± 3.8 in placebo and carvedilol, respectively ($p < 0.01$) [27]. The maximal end-tidal CO_2 pressure is the highest value of end-tidal CO_2 recorded and is observed between the anaerobic threshold and the end of the isocapnic buffering period (Fig. 2). At this point of exercise carvedilol reduces ventilation and increased $PetCO_2$ (Figs. 3 and 4). This suggests a reduction of the overactive chemo-receptor response. Also antialdosteronic drugs improve lung diffusion as well as exercise performance [28]. Ultrafiltration, a dialitic technique used to reduce the body fluid content, improves lung mechanics, but not lung diffusion, and increase exercise performance [29]. This suggests that, in chronic heart failure patients in optimized drug treatment, the amount of fluid on the alveolar capillary membrane clearable by ultrafiltration is limited while some fluid is cleared from other parts of the lungs.

In conclusion heart and lung behaviours in heart failure are strictly interrelated. Exercise and hypoxia enhance this interrelation. Both lung and heart can be targets of a therapeutic intervention in heart failure.

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