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Augmented peripheral chemoreflex in patients with heart failure and inspiratory muscle weakness☆

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ABSTRACT

We hypothesized that heart failure patients with inspiratory muscle weakness (IMW) present greater peripheral chemoreflex responsiveness and augmented exercise ventilatory oscillation compared to patients with preserved inspiratory muscle strength. We studied 19 heart failure patients: 9 with IMW (maximal inspiratory pressure [PImax] < 70% of predicted) and 10 with preserved inspiratory muscle strength. Inspiratory muscle strength was measured via pressure transducer. Peripheral chemoreflex was evaluated by the single-breath CO_2 test. Exercise ventilatory oscillation was determined as the ratio between amplitude and mean of each oscillation during incremental exercise. Patients with IMW had greater peripheral chemoreflex response ($0.11 \pm 0.03\ l\ min^{-1}\ Torr^{-1}$) than those with preserved inspiratory muscle strength ($0.07 \pm 0.03\ l\ min^{-1}\ Torr^{-1}$, $p = 0.02$). Moreover, there was a significant and inverse correlation between PImax and peripheral chemoreflex response ($r = -0.57$, $p = 0.01$). Likewise, there was a significant and inverse correlation between PImax and ventilatory oscillations ($r = -0.46$, $p = 0.04$). Our findings indicate that IMW is linked to increased peripheral chemoreflex and augmented exercise ventilatory oscillation in patients with chronic heart failure.

1. Introduction

Patients with chronic heart failure (CHF) may present abnormal ventilatory response to incremental exercise, including an increased slope of ventilation *vs.* carbon dioxide production ($\dot{V}_E/\dot{V}_{CO_2}$ slope) as well as periodic breathing, and both of these findings have prognostic value (Ribeiro et al., 2006). Several pathophysiological mechanisms have been proposed to explain these ventilatory patterns and a chemoreflex deregulation seems to participate in both (Tumminello et al., 2007). Another ventilatory abnormality with prognostic impact in CHF is inspiratory muscle weakness (IMW) (Frankenstein et al., 2008), which may be related to impaired limb blood flow, most likely due to an abnormal activity of the inspiratory muscle metaboreflex (Chiappa et al., 2008). Interestingly, we have previously shown that in patients with CHF and IMW, inspiratory muscle training improves ventilatory responses to exercise, with reduction in $\dot{V}_E/\dot{V}_{CO_2}$ slope and ventilatory oscillations (Dall'Ago et al., 2006; Ribeiro et al., 2009; Stein et al., 2009; Winkelmann et al., 2009). This effect of inspiratory muscle training on ventilatory responses associated with overactivity of chemoreflex suggests that inspiratory muscle strength and chemoreflex response could be associated in CHF. Therefore, the purpose of this study is to test the hypothesis that patients with CHF and IMW may have an augmented peripheral chemoreflex response when compared to patients with preserved inspiratory muscle strength.

2. Methods

2.1. Patients

We studied 19 patients with stable CHF due to left ventricular systolic dysfunction. Since current evidence suggests that patients with CHF with IMW respond better to inspiratory muscle training than patients without IMW (Arena et al., 2009; Chiappa et al., 2008; Dall'Ago et al., 2006; Ribeiro et al., 2009; Stein et al., 2009; Winkelmann et al., 2009), we evaluated two groups of patients: 9 with IMW (maximal inspiratory pressure [PImax] < 70% of predicted for age and gender [Neder et al., 1999]) and 10 with preserved inspiratory muscle strength. All patients had left ventricular ejection fraction less than 40%, had no history of angina or pulmonary disease, and were not obese or smokers. The protocol

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was approved by the Committee for Ethics in Research of the Hospital de Clínicas de Porto Alegre, and all patients signed an informed consent form. For all patients, measurement of inspiratory muscle strength, peripheral chemoreflex evaluation, and cardiopulmonary exercise test were obtained. Investigators responsible for each of the methods were not aware of the results of the other evaluations.

2.2. Measurement of maximal inspiratory pressure

PImax was measured with a pressure transducer (MVD-500 V.1.1 Microhard System, Globalmed, Porto Alegre, Brazil) during deep inspiration from residual volume against an occluded airway with a minor air leak (2 mm), as previously described (Dall'Ago et al., 2006; Chiappa et al., 2008; Winkelmann et al., 2009). The test was repeated at least 12 times to find 6 measurements with less than 10% of variation (American Thoracic society/European Respiratory Society, 2002).

2.3. Peripheral chemoreflex

Fast peripheral chemoreflex responsiveness was evaluated by the single-breath CO_2 test, as previously described (McClean et al., 1988; Martinez, 2008). Patients rested for 15 min in the supine position and breathed throughout a T-valve connected to a 6-liter reservoir bag containing 13% CO_2 in air. The T-valve was turned during the expiratory phase of the previous breath so that the subject inhaled a single breath of 13% CO_2 in air. $\dot{V}_E$ and end-tidal partial pressure of CO_2 (PET_{CO_2}) were analyzed breath-by-breath (Metalyzer 3B, CPX System, Cortex, Leipzig, Germany). Peripheral chemoreflex responsiveness was determined by the ratio between the change in ventilation and the change in PET_{CO_2} during the first 20 seconds after exposure and was expressed in liters per minute per Torr ($l\,min^{-1}\,Torr^{-1}$). At least 10 tests were applied at 2 min intervals. To evaluate reproducibility, the single-breath CO_2 test was repeated in 7 patients after one week.

2.4. Cardiopulmonary exercise testing

Maximal incremental exercise test was performed on a treadmill (INBRAMED 10200, Porto Alegre, Brazil) using a ramp protocol, starting at a speed of 2.4 km h^{-1} and 2% slope, with 20-s increments of speed and slope to reach volitional fatigue at approximately 10 min, as previously described (Dall'Ago et al., 2006). Gas exchange variables were measured breath-by-breath by a validated system (Metalyzer 3B, CPX System, Cortex, Leipzig, Germany) (Meyer et al., 2001). Heart rate was determined using the R–R interval from a 12-lead electrocardiogram. Cardiopulmonary exercise variables were calculated as previously described (Dall'Ago et al., 2006). In short, peak oxygen uptake ($\dot{V}_{O_2}$ peak) was defined as the highest value achieved during the test for 20 seconds. $\dot{V}_E/\dot{V}_{CO_2}$ slope was obtained by linear regression model using all data points obtained during the exercise test. The quantification of ventilatory oscillations was performed as originally proposed by Francis et al. (1999) and modified by Dall'Ago et al. (2006). For every 2 adjacent 20-s period of $\dot{V}_E$, the amplitude of oscillation was calculated as difference between the 2 points divided by their mean. This value was again divided by the mean to obtain the relative amplitude, and the values of the entire cardiopulmonary test were averaged to convey in a single ratio. Therefore, similarly to what was done in our previous studies on inspiratory muscle training (Dall'Ago et al., 2006; Winkelmann et al., 2009), we quantified ventilatory oscillations during incremental exercise, but we did not evaluate the presence of periodic breathing, as done in other investigations (Agostoni et al., 2008; Ribeiro, 2006).

2.5. Statistical analysis

Descriptive data are presented as mean ± SD. Considering that inspiratory muscle strength as measured by PImax is a continuous variable and that from the clinical point of view it is useful to classify patients with or without IMW, we performed two analyses. First, groups were compared by the Student's *t*-test and afterwards the Pearson correlation coefficient was used to evaluate associations using the whole sample. Finally, stepwise multiple regression was used to predict peripheral chemoreflex responsiveness, using as regressors variables which presented correlations with p values less than 0.1 in the univariate analysis. Statistical significance for the other tests was set at $p < 0.05$.

3. Results

Table 1 presents the clinical characteristics as well as the results of inspiratory muscle strength, peripheral chemoreflex, and exercise responses for patients with and without IMW. The groups were similar in respect to age, gender distribution, height, weight, etiology, use of medications, and left ventricular ejection fraction. As by protocol, patients with IMW had lower PImax. $\dot{V}_{O_2}$ peak and $\dot{V}_E/\dot{V}_{CO_2}$ were not significantly different between the groups. Exercise ventilatory oscillation tended to be greater in patients with IMW than in those with preserved inspiratory muscle strength ($p = 0.1$).

The coefficient of variation for the single-breath CO_2 test in two different days was 13 ± 11%. Peripheral chemoreflex responsiveness was significantly increased in patients with IMW compared those with preserved inspiratory muscle strength (Table 1). As shown in Fig. 1, there was a significant inverse correlation between the peripheral chemoreflex response and PImax expressed in absolute units (panel a) as well as in percentage of predicted (panel b). PImax was also significantly and inversely correlated with exercise ventilatory oscillation (Fig. 1 panels c and d). Peripheral chemoreflex responsiveness was not significantly associated with $\dot{V}_{O_2}$ peak ($r = 0.18$, $p = 0.46$), with $\dot{V}_E/\dot{V}_{CO_2}$ ($r = -0.08$, $p = 0.74$) or with exercise ventilatory oscillation ($r = 0.35$, $p = 0.15$). By stepwise multiple regression analysis, PImax was the only independent predictor of peripheral chemoreflex ($p < 0.05$).

4. Discussion

An augmented peripheral chemoreflex is a common finding in CHF patients and may occur in as many as 40% of patients (Chua et al., 1997). The increased chemoreflex may be linked to abnormal ventilatory responses to exercise such as an increased $\dot{V}_E/\dot{V}_{CO_2}$ and exercise periodic breathing (Tumminello et al., 2007). IMW is also frequently found, occurring in more than 30% of our outpatients in a specialized heart failure clinic (Dall'Ago et al., 2006; Ribeiro et al., 2009), but the clinical characteristics associated with this ventilatory abnormality are not well defined. This small, cross-sectional study demonstrates, for the first time, that inspiratory muscle strength, as determined by PImax, is associated with augmented peripheral chemoreflex responsiveness and exercise ventilatory oscillation in CHF patients.

The augmented peripheral chemoreflex responsiveness in patients with IMW in the present study may not be attributed to disease severity, since both groups showed similar $\dot{V}_{O_2}$ peak and left ventricular ejection fraction. Moreover, in our patients, inspiratory muscle strength was found to be an independent predictor of peripheral chemoreflex responsiveness by multivariate analysis. Indeed, the link between peripheral chemoreflex and $\dot{V}_{O_2}$ peak has not been a consistent finding in previous studies (Ponikowski et al., 2001a). A modest association has been described between periph-