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The alveolar to arterial oxygen partial pressure difference is associated with pulmonary diffusing capacity in heart failure patients

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ABSTRACT

In chronic heart failure (HF), the alveolar-capillary membrane undergoes a remodeling process that negatively affects gas exchange. In case of alveolar-capillary gas diffusion impairment, arterial desaturation (SaO_2) is rarely observed in HF patients. At play are 3 factors: overall pulmonary diffusing capacity (assessed as lung diffusion for CO, DLCO), global O_2 consumption (VO_2) and alveolar (A) to arterial (a) pO_2 gradient ($AaDO_2$).

In 100 consecutive stable HF patients, DLCO, resting respiratory gases and arterial blood gases were measured to determine VO_2, paO_2, pAO_2 and $AaDO_2$.

DLCO was poorly but significantly related to $AaDO_2$. The correlation improved after correcting $AaDO_2$ for VO_2 ($p < 0.001$, $r = 0.49$). Both VO_2 and $AaDO_2$ were independently associated with DLCO ($p < 0.001$). Patients with reduced DLCO showed no differences as regards paO_2 and pAO_2. $AaDO_2/VO_2$ showed a higher gradient in patients with lower DLCO.

$AaDO_2$ increase and VO_2 reduction allow preventing low SaO_2 in HF patients with reduced DLCO. Accordingly, we suggest considering $AaDO_2$ and VO_2 combined and reporting $AaDO_2/VO_2$.

1. Introduction

The alveolar-capillary membrane undergoes an extensive remodeling process in most patients with heart failure (HF). This remodeling includes fibrosis of the lung parenchyma, added connective tissue deposition, and small blood clots in the lung (Agostoni et al., 2000; Puri et al., 1995; Kay and Edwards, 1973). This process negatively influences the main physiological duties of the alveolar-capillary membrane, which are gas exchange and lung fluid homeostasis. Gas exchange across the alveolar-capillary membrane is usually assessed using inert gases as tracers, such as carbon monoxide (CO) and nitric oxide; the former is most often utilized in the clinical field by means of pulmonary diffusing capacity for CO (DLCO). It is well known that DLCO impairment is greater the greater the severity of HF (Agostoni et al., 2006a), that DLCO has an independent prognostic role in HF (Guazzi et al., 2002), and that the alveolar-capillary membrane is recognized as a target of HF treatment (Contini et al., 2013). Indeed, several categories of HF drugs, such as ACE-inhibitors (Guazzi et al., 1997) and anti-aldosteronic drugs (Agostoni et al., 2005), improve gas diffusion across the alveolar-capillary membrane, while others have a nil influence, such as AT1-blockers (Guazzi et al., 1999), or even a negative action, such as β1–β2 blockers (Contini et al., 2013). All the above-mentioned reasons have generated a lot of interest in the physiology of the alveolar-capillary membrane in HF.

Lungs have a relevant capacity to overcome alveolar-capillary membrane impairment avoiding low arterial hemoglobin O_2 saturation (SaO_2). Indeed, a low SaO_2 is very rarely observed in HF patients at rest and even during effort (Clark and Coats, 1994), except in patients with particularly severe or unstable HF (Taylor et al., 2013). This common, undeniable finding casts many doubts about the real clinical meaning of a low DLCO in HF patients, and it suggests the need to evaluate the events that are possibly activated to prevent the occurrence of systemic hypoxia. Indeed, SaO_2 is a

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function of ventilation, pulmonary diffusing capacity, ventilation-perfusion matching, and the alveolar to arterial pO_2 difference ($AaDO_2$). To our surprise, the latter has not been investigated at rest in patients with various degrees of HF.

The purpose of the present study was to determine the association between pulmonary diffusing capacity, measured at rest, and the $AaDO_2$, also measured at rest, in HF patients.

2. Methods

2.1. Patient population

We prospectively analyzed the clinical data, obtained as part of routine HF patients' follow-up program, of 100 consecutive patients with stable HF (age 69 ± 11 years; 78 males and 22 females, BMI 27 ± 7kg/m^2, and left ventricle ejection fraction (LVEF) of 32 ± 8%) who underwent full clinical evaluation at our HF Unit between March and July 2015 (Table 1). All tests were performed on the same day within a 4-h window. We evaluated HF patients in stable clinical condition, in New York Heart Association (NYHA) functional class I–III, capable of performing standard pulmonary functional and DLCO maneuvers.

We excluded from data analysis patients with preserved left ventricular ejection fraction (LVEF > 50% at echocardiography), primary pulmonary hypertension, intracardiac shunt, pulmonary embolism and respiratory comorbidities such as severe obstructive pulmonary disease as defined by clinical diagnosis and/or forced expiratory volume in one second (FEV_1) < 50% of the predicted value.

HF etiology was: ischemic heart disease (42 patients), idiopathic cardiomyopathy (48 patients) and valvular heart disease (10 patients).

HF severity was assessed by NYHA class, brain natriuretic peptide (BNP) measurements, echocardiography and cardiopulmonary exercise test.

2.2. Pulmonary function evaluation

FEV_1 and forced vital capacity (FVC) were measured in triplicate and calculated according to the American Thoracic Society criteria (Pellegrino et al., 2005), using a mass flow sensor (229D Spectra metabolic cart, Sensor Medics; Yorba Linda, CA). DLCO was measured in the standard sitting position with the single breath technique (229D Spectra metabolic cart, Sensor Medics; Yorba Linda, CA), and it was corrected for gender and for the patient's hemoglobin concentration. Alveolar volume was measured by methane dilution. Spirometry and overall DLCO data are reported as absolute values, as a percentage of predicted value (Huang et al., 1994; Miller et al., 1983).

2.3. Laboratory data

Hemoglobin concentrations and BNP levels were determined from peripheral blood samples. All patients underwent conventional two-dimensional and Doppler echocardiography to confirm the diagnosis of HF with low ejection fraction.

2.4. Alveolar–asrterial pO_2 gradient

Arterial blood was sampled at rest after at least 10 min of quiet breathing (sitting position). These samples were used to measure arterial oxygen (paO_2) and carbon dioxide tensions ($paCO_2$), pH and SaO_2, the latter by co-oxymetry (GEM Premier 4000, Instrumentation Laboratory, Bedford, Massachusetts, USA). Gas analysis was done immediately after arterial blood samples were obtained. Respiratory gases were measured after 10 min of resting in the sitting position (229D Spectra metabolic cart, Sensor Medics; Yorba Linda, CA).

Alveolar pO_2 (pAO_2) was determined from the equation:

$$pAO_2 = [(Bp(mmHg) - 47) \times FiO_2 - paCO_2/R]$$

where Bp = barometric pressure, FiO_2 = oxygen inspired fraction, and R = respiratory gas exchange ratio. The $AaDO_2$ is reported as absolute value or normalized for measured VO_2.

We also calculated end tidal pO_2 ($PetO_2$) as an index of pAO_2.

2.5. Cardiopulmonary exercise testing

A maximal cardiopulmonary exercise test was performed (229D Spectra metabolic cart, Sensor Medics; Yorba Linda, CA) on a cycle ergometer in patients without contraindications to the test and capable of cycling (Erg 800S, Sensor Medics, Yorba Linda, CA), using a personalized ramp protocol aimed at achieving peak exercise in around 10 min (Hansen et al., 1988). Peak VO_2 is reported as absolute value or as a percentage of the VO_2 max predicted value (Hansen et al., 1984). The ventilation (VE)/carbon dioxide flow (VCO_2) slope was calculated as the slope of the relationship between VE and VCO_2 from approximately 1 min after the beginning of loaded exercise to the end of the isocapnic buffering period. All patients underwent respiratory gas measurements (VO_2, VCO_2 and respiratory exchange ratio – RER), obtained at rest during quiet breathing for at least 5 min.

2.6. Statistical analysis

Data are presented as mean ± SD unless otherwise reported. Differences between groups were assessed by unpaired T-test.

Multivariable linear regression with stepwise selection of variables was employed to assess the independent predictors of paO_2; among the potential candidates, we included age, sex, weight, DLCO, VO_2 at rest, FVC, LVEF. A further analysis was run by forcing age and sex into the model.

Another multivariable linear regression analysis was run to show the independent relationship between $AaDO_2$, VO_2 and DLCO.

Pearson's correlation analysis was performed between $AaDO_2$ and DLCO and between $AaDO_2/VO_2$ and DLCO, and the two correlation coefficients were compared by bootstrap method, with 1000 resampling replications. Statistical analyses were performed using SAS statistical package v.9.4 (SAS Institute Inc., Cary, NC, US). Significant differences were accepted if $p < 0.05$.

3. Results

The HF patients we studied had moderate to severe HF, as demonstrated by NYHA class, BNP, LVEF, peak VO_2 and ventilation efficiency during exercise (Table 1). Spirometry, DLCO and resting gas exchange data were obtained in all patients. 75 patients were able to perform a maximal cardiopulmonary exercise test.

On average, DLCO was slightly reduced. Average paO_2 was 78.8 ± 11.5 mmHg, alveolar pO_2 (pAO_2) was 103 ± 5.6 mmHg with a mean $AaDO_2$ difference of 24.5 ± 11.2 mmHg. Average $PetO_2$ was 110.7 ± 5.8 mmHg. Average SpO_2 was 97.4 ± 1.6%. Measured VO_2 was 0.25 ± 0.06 L/min at rest (Table 1). FVC was 86.9% and FEV1 was 83.7%.

A first analysis was done by grouping patients according to DLCO values, ≥ or < 80% of the predicted value (Table 1). This allowed us to identify a group of patients with clearly normal DLCO and a group with abnormal DLCO or with a DLCO value in the lowest range of normality. As expected, in patients with reduced DLCO, peak VO_2 was lower, BNP was higher ($p = 0.06$), while VE/VCO_2 slope