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Impairment of pulmonary diffusion correlates with hypoxemic burden in central sleep apnea heart failure patients

Henrik Fox*, Britta Koerber, Thomas Bitter, Dieter Horstkotte, Olaf Oldenburg

Clinic for Cardiology, Herz- und Diabeteszentrum NRW, Ruhr-Universität Bochum, Georgstrasse 11, D-32545 Bad Oeynhausen, Germany

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ABSTRACT

Purpose: Central sleep apnea (CSA) and Cheyne-Stokes respiration (CSR) are highly prevalent in heart failure (HF) and are linked to increased mortality. Impaired pulmonary diffusion capacity [DLCO] and [KCO]) have been suggested to play a key role in CSA-CSR pathophysiology. This study investigated the relationship between HF, CSR, DLCO and KCO in well-characterized HF patients.

Methods: This prospective study included HF patients with CSR, all patients underwent full overnight polysomnography (PSG) and lung function testing.

Results: A total of 100 patients were included (age 70.7 ± 9.7 years, 95% male, body mass index 28.9 ± 5.3kg/m^2, left ventricular ejection fraction 33.5 ± 7.7%, New York Heart Association class III 65%. DLCO and oxygenation were significantly correlated with hypoxemic burden ($p < 0.05$). Mean oxygen saturation, oxygen desaturation, C-reactive protein level and pH were significantly associated with CSA-CSR severity ($p < 0.05$).

Conclusion: The finding that lung diffusion capacity is significantly associated with hypoxemic burden in HF patients with CSA-CSR highlights the important of lung function in HF patients.

1. Introduction

Sleep-disordered breathing (SDB) is a highly prevalent comorbidity in patients with heart failure (HF). The prevalence of moderate to severe SDB in HF patients is more than 50% (Javaheri, 2006; Oldenburg et al., 2007; Schulz et al., 2007). There is a high level of interest in understanding the relationship between SDB and HF because SDB has been shown to be associated with worse prognosis and increased mortality in HF patients (Bitter et al., 2011; Jilek et al., 2011; Oldenburg et al., 2014).

HF is accompanied by elevation of pulmonary capillary wedge pressure (Gehlbach and Geppert, 2004), which is proportional to the extent of underlying cardiac dysfunction. Interstitial pulmonary edema and structural changes in the lung lead to progressive thickening of the alveolar-capillary membrane (West and Mathieu-Costello, 1992). Function of the alveolar-capillary membrane can be determined by measuring the diffusing capacity of the lung for carbon monoxide (DLCO) and the transfer coefficient of the lung for carbon monoxide (KCO), which have shown to be reduced in patients with HF (Guazzi, 2003). DLCO detects transfer capabilities for pulmonary gas exchange, making it a marker of ventilatory control system stability. In addition, DLCO has been associated with reduced exercise capacity in patients with chronic HF (Puri et al., 1995).

Theoretically, reduced gas exchange in HF patients would favor respiratory instability, which in turn might favor central sleep apnea (CSA) (Khoo et al., 1991), but this relationship has not been well studied to date. Recent data showed that impaired pulmonary diffusion capacity and hypoxia were correlated with CSA severity in patients with HF (Szollosi et al., 2008). HF might predispose patients to CSA because it provokes hypocapnia secondary to pulmonary congestion caused by pulmonary irritant receptor stimulation (Solin et al., 1999). Szollosi et al. hypothesized that in HF patients with predominant CSA during sleep, where relevant ventilatory control instability is present, reduced DLCO would be associated with more severe respiratory disturbance during sleep (Szollosi et al., 2008). However, published data on CSA and DLCO are scarce.

This study investigated the relationship between DLCO and CSA-CSR in patients with HF. The aim was to determine whether impaired pulmonary diffusion capacity correlates with CSA severity in HF patients. Established SDB severity metrics were used, including the apnea-hypopnea index (AHI), apnea index (AI), and central apnea index (cAI) as well as markers of hypoxemia and hypoxemic burden (time with oxygen saturation of < 90%) because hypoxemic burden has recently been reported to be an independent predictor of mortality in

* Corresponding author.
E-mail address: akleemeyer@hdz-nrw.de (H. Fox).

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patients with HF and SDB (Oldenburg et al., 2016).

2. Methods

This prospective study included HF patients with nocturnal CSR during full overnight polysomnography (PSG). Inclusion criteria were stable chronic HF of ≥3 months' duration, age > 18 years, New York Heart Association (NYHA) class ≥II, left ventricular ejection fraction (LVEF) ≤45%, and CSA with an AHI > 15/h. Exclusion criteria were acute coronary syndrome within 3 months prior to enrollment, active myocarditis, complex congenital heart disease, constrictive pericarditis, clinical evidence of digoxin toxicity, need for mechanical hemodynamic support, chronic hypoxemia as evidenced by sustained oxygen saturation ≤90%, transient ischemic attack (TIA) or stroke within 3 months prior to enrollment, post-heart transplant or LVAD, prescribed inotrope therapy, known amyloidosis, arteriovenous fistulas, primary hemodynamically significant uncorrected valvular heart disease (obstructive or regurgitant), pregnancy, advanced structural lung disease (forced expiratory volume in 1 s [FEV_1] ≤ 30% of predicted, FEV_1/vital capacity [VC] < 70% or FEV_1 < 50% of predicted plus chronic respiratory insufficiency) and participation in pharmaceutical or treatment-related clinical study within 6 months of enrollment. The study was approved by the institutional ethical committee and was conducted in accordance with the Declaration of Helsinki. All patients gave informed consent before undergoing study investigations.

All patients underwent clinical examination and questioning, transthoracic echocardiography, ECG, laboratory tests, cardiopulmonary exercise testing (CPX), 6 min walk test, blood gas analysis, and hypercapnic ventilatory response (HCVR) test; DLCO and KCO were also determined. Body plethysmography and single-breath DLCO was measured according to American Thoracic Society/European Respiratory Society guidelines (Robinson et al., 2013). All DLCO results were corrected for hemoglobin using the method described by Cotes (Cotes, 1963) using hemoglobin values obtained from arterial blood gas samples. DLCO corrected for alveolar volume (KCO) was calculated as the DLCO divided by the alveolar volume (VA).

All PSG recordings were independently analyzed by two sleep specialists according to current guidelines (Berry et al., 2012). The definition of oxygen desaturation index (ODI) used in this study was the number of ≥3% arterial oxygen desaturations per hour (Berry et al., 2012), and hypopneas were not scored in relation to an arousal. All patients were naïve to any ventilation therapy or chronic oxygen treatment.

2.1. Definition of central sleep apnea (CSA) and Cheyne-Stokes respiration (CSR)

A central apnea was defined as a 10 s pause in ventilation with no associated respiratory effort; a central apnea index (CAI) of > 5/h is considered abnormal. Patients needed to have > 50% of events on PSG as central apneas to be classified as having CSA. CSR was determined based on the presence of a characteristic crescendo-decrescendo pattern of breathing with a central apnea or hypopnea at the nadir of ventilatory effort.

2.2. Statistical analysis

Statistical analysis was performed using IBM SPSS 21.0.0.2, IBM Corporation, Armonk, NY, USA, for Mac, Apple Inc., Cupertino, CA, USA. A *p*-value of < 0.05 was defined as statistically significant. Data are expressed as percentages for discrete variables and as means ± standard deviation for continuous variables. Normality of data distribution was checked and continuous variables were compared by one-way ANOVA, for post-hoc analysis Bonferroni was used. Categorical comparisons were compared using Chi-square analysis and correlations were performed using Pearson's correlation.

Table 1
Patient demographics and characteristics at baseline.

	All patients (n = 100)
Age (years)	70.7 ± 9.7
Male (% patients)	95.0
Height (cm)	175.7 ± 7.8
Weight (kg)	89.6 ± 18.4
BMI (kg/m^2)	28.9 ± 5.3
BSA (m^2)	1.9 ± 0.2
NYHA class	2.6 ± 0.5
Systolic blood pressure (mmHg)	114.8 ± 21.8
Diastolic blood pressure (mmHg)	70.0 ± 12.2
Heart rate (beats/min)	71.9 ± 11.9
Atrial fibrillation (% patients)	24
Ischemic cardiomyopathy (% patients)	68
Diabetes (% patients)	48
Pulmonary hypertension (% patients)	18
COPD (% patients)	12
Former smoker (% patients)	31
ACEI/ARB (% patients)	97
Diuretics (% patients)	91
Beta blocker (% patients)	90
LVEF (%)	33.5 ± 7.7
LA diameter (mm)	50.7 ± 7.7
LVEDD (mm)	66.1 ± 10.4
Systolic PAP (mmHg)	41.4 ± 12.7

Abbreviations: ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; BSA, body surface area; BMI, body mass index; COPD, chronic obstructive pulmonary disease; Hb, hemoglobin; LA, left atrial; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; pCO_2, carbon dioxide pressure; pO_2, oxygen pressure; SaO_2, oxygen saturation.

3. Results

A total of 100 patients with HF with reduced ejection fraction (HFREF) and CSA-CSR were enrolled. Patients were generally elderly and the majority were male (Table 1); all were naïve to ventilation therapy and had reduced exercise capacity and 6 min walk distance (Table 2). Laboratory parameters at baseline are shown in Table 3, and the results of PSG evaluation are shown in Table 3.

There was no significant correlation between DLCO or the partial pressure of oxygen (PaO_2) and total AHI, total apnea index (AI), obstructive AI, central AI, mixed AI or the hypopnea index (HI) (p = 0.377). BMI was significantly associated with AHI (p < 0.05, r = 0.43). Hypoxemic burden (time with oxygen saturation < 90%; T < 90) was significantly associated with both DLCO and KCO

Table 2
Functional parameters.

	All patients (n = 100)
CPET max workload (watt)	76.9 ± 33.9
CPET VO_2 anerobic threshold (mL/min)	11.1 ± 3.5
CPET VO_2 peak (mL/min)	13.4 ± 12.6
CPET VO_2 predicted (%)	56.8 ± 16.9
VE/VCO_2 slope > 35 (% of patients)	43
VE/VCO_2 slope	30.3 ± 3.5
HCVR (L/min/mmHg)	3.0 ± 2.2
DLCO (Hb) (mL/mmHg/min)	6.1 ± 1.9
DLCO (%)	67.4 ± 17.5
KCO (Hb) (mL/mmHg/min)	1.1 ± 0.3
KCO (%)	86.4 ± 20.5
Inspiratory vital capacity (%)	79.9 ± 16.9
FEV_1 (% predicted)	79.3 ± 18.5
FEV_1/VC (%)	95.8 ± 15.6
6 min walk test (meters)	380 ± 328.8

Abbreviations: CPET, cardiopulmonary exercise test; VE, minute volume; VO_2, oxygen uptake; DLCO, diffusing capacity of carbon monoxide; FEV1, forced expiratory volume in 1 s; HVCR, hypercapnic ventilatory response; KCO, lung carbon monoxide transfer coefficient; VC, vital capacity.