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Impaired Pulmonary Diffusion in Heart Failure With Preserved Ejection Fraction

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ABSTRACT

OBJECTIVES The purpose of this study was to compare measures of gas exchange at rest and during exercise in patients with heart failure and preserved ejection fraction (HFpEF) with age- and sex-matched control subjects.

BACKGROUND Patients with HFpEF display elevation in left heart pressures, but it is unclear how this affects pulmonary gas transfer or its determinants at rest and during exercise.

METHODS Patients with HFpEF ($n = 20$) and control subjects ($n = 26$) completed a recumbent cycle ergometry exercise test with simultaneous measurement of ventilation and gas exchange. Diffusion of the lungs for carbon monoxide (DL_{CO}) and its subcomponents, pulmonary capillary blood volume (V_C) and alveolar-capillary membrane conductance (D_M), were measured at rest, and matched for low-intensity (20 W) and peak exercise. Stroke volume was measured by transthoracic echocardiography to calculate cardiac output.

RESULTS Compared with control subjects, patients with HFpEF displayed impaired diastolic function and reduced exercise capacity. Patients with HFpEF demonstrated a 24% lower DL_{CO} at rest (11.0 $\pm$ 2.3 ml/mm Hg/min vs. 14.4 $\pm$ 3.3 ml/mm Hg/min; $p < 0.01$) related to reductions in both D_M (18.1 $\pm$ 4.9 ml/mm Hg/min vs. 23.1 $\pm$ 9.1 ml/mm Hg/min; $p = 0.04$), and V_C (45.9 $\pm$ 15.2. ml vs. 58.9 $\pm$ 16.2 ml; $p = 0.01$). DL_{CO} was lower in patients with HFpEF compared with control subjects in all stages of exercise, yet its determinants showed variable responses. With low-level exercise, patients with HFpEF demonstrated greater relative increases in V_C, coupled with heightened ventilatory drive and more severe symptoms of dyspnea compared with control subjects. At 20-W exercise, D_M was markedly reduced in patients with HFpEF compared with control subjects. From 20 W to peak exercise, there was no further increase in V_C in patients with HFpEF, which in tandem with reduced D_M, led to a 30% reduction in DL_{CO} at peak exercise (17.3 $\pm$ 4.2 ml/mm Hg/min vs. 24.7 $\pm$ 7.1 ml/mm Hg/min; $p < 0.01$).

CONCLUSIONS Subjects with HFpEF display altered pulmonary function and gas exchange at rest and especially during exercise, which contributes to exercise intolerance. Novel therapies that improve gas diffusion may be effective to improve exercise tolerance in patients with HFpEF. (J Am Coll Cardiol HF 2016;4:490–8)

Elevation in pulmonary venous pressures with exercise is pathognomonic of heart failure with preserved ejection fraction (HFpEF) (1). Many studies have examined the hemodynamic mechanisms underlying filling pressure elevation in HFpEF (2-4), but very little is known about how these mechanisms might alter pulmonary gas exchange and ventilatory mechanics to produce dyspnea. It is important to understand how the hemodynamic abnormalities that develop during exercise in HFpEF affect the alveolar-pulmonary capillary interface so novel therapeutics can be designed.

Acute elevation in pulmonary venous pressure can cause interstitial or alveolar edema, whereas sustained increases can cause pulmonary vascular remodeling (5). Increases in venous pressure during exercise in HFpEF may alter forces that govern fluid distribution between the vascular, capillary wall, and

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alveolar spaces in the lung, which potentially results in interstitial edema, impaired gas conductance, stiffer lungs, a more tachypneic pattern of breathing, and greater ventilatory drive and ventilatory inefficiency, all of which may increase the work and cost of breathing, and heighten symptoms of dyspnea during exercise (6).

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The aim of this study was to comprehensively examine the pulmonary response to exercise in HFpEF by assessing measures of gas exchange, ventilatory drive and efficiency, and the diffusion capacity of the lungs for carbon monoxide (DL_{CO}) and its subcomponents (pulmonary capillary blood volume [V_C] and alveolar-capillary membrane conductance [D_M]) in subjects with HFpEF compared with healthy control subjects at rest and during exercise. We hypothesized that subjects with HFpEF would demonstrate reduced lung diffusion at rest and with exercise related to distinct patterns of change in capillary blood volume and membrane conductance.

METHODS

Patients with HFpEF (n = 20) with EF >50% and unequivocal signs and symptoms of heart failure (Framingham criteria) were studied prospectively in as outpatients and were compensated for the study. Exclusion criteria included significant valvular or pericardial disease, infiltrative or hypertrophic cardiomyopathy, cor pulmonale, obstructive or restrictive pulmonary disease, unstable coronary disease, atrial fibrillation, pregnancy, primary renal or hepatic disease, and inability to exercise or to suspend cardiovascular medicines. Healthy control subjects without cardiovascular disease or diabetes (n = 26) were recruited by advertisement.

Some clinical characteristics, cardiovascular function, and exercise capacity data from subjects in this study have previously been published (7); however, none of the data on pulmonary diffusion capacity, its subcomponents, or the relationships presented in this paper have been reported. All participants gave written informed consent after being provided a description of study requirements. The protocol was approved by the Mayo Clinic Institutional Review Board, and all procedures conformed to the Declaration of Helsinki. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the paper as written.

EXERCISE TESTING PROTOCOL. Subjects were instructed to avoid strenuous physical activity for 24 hours before arrival and were studied in the upright position in an ambulatory, compensated, fasting state in a quiet, temperature-controlled room (21°C). In addition, all cardiovascular medicines were withheld for 24 h before study. Ventilatory, gas exchange, heart rate, and oxygen saturation data were measured continuously during exercise.

Exercise testing was conducted on a recumbent electronically braked cycle ergometer (Corival, Lode Medical Technology, Groningen, the Netherlands). The exercise protocol consisted of pedaling at a constant cadence of 65 rpm with an initial resistance of 0 W that was subsequently increased every 3 min by 20 W. Symptoms of fatigue were quantified by the rating of perceived exertion (RPE) on the Borg 6 to 20 scale. Subjects were verbally encouraged to continue the exercise protocol to maximal exertion, identified by RPE ≥17. Symptoms of dyspnea were quantified by the Borg dyspnea score (0 to 10). Brachial blood pressure (BP) was obtained by auscultation by a single investigator during rest and at the end of each stage of exercise.

VENTILATION AND EXPIRED GAS ANALYSIS. Breath-by-breath oxygen consumption (VO_2), carbon dioxide production (VCO_2), minute ventilation (V_E), tidal volume (V_T), breathing frequency (fb), inspiratory time (T_I), and total respiratory cycle time (T_{TOT}) were measured continuously via a metabolic measurement system through a mouth piece and pneumotachograph while wearing a nose clip (CPX/D, Medical Graphic, St. Paul, Minnesota). Manual volume calibration was performed with a 3-L syringe, and gas calibration was performed with manufacturer-recommended gases of known concentration. All calibration procedures were conducted immediately before each testing protocol.

Aerobic capacity was assessed by the peak VO_2 attained during exercise. Objective exercise effort was assessed by the peak respiratory exchange ratio (VCO_2/VO_2). Ventilatory efficiency was assessed by the slope of V_E to VCO_2, and ventilatory drive was assessed by the ratio of V_T to T_I (8). All analyses of ventilation and gas exchange data were conducted offline in a blinded fashion.

PULMONARY DIFFUSING CAPACITY AND SUBCOMPONENTS. The disappearance of carbon monoxide in concert with nitric oxide was measured for the assessment of D_M and V_C as previously described in detail (9–11). Briefly, measurement of the DL_{CO} and

ABBREVIATIONS AND ACRONYMS

BP = blood pressure

DL_{CO} = diffusion of the lungs for carbon monoxide

D_M = alveolar-capillary membrane conductance

EF = ejection fraction

fb = breathing frequency

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

LV = left ventricle

NO = nitric oxide

RPE = rating of perceived exertion

T_I = inspiratory time

T_{TOT} = total respiratory cycle time

V_C = pulmonary capillary blood volume

VCO_2 = volume of carbon dioxide produced

V_E = minute ventilation

VO_2 = volume of oxygen consumed

V_T = tidal volume