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Impaired Pulmonary Diffusion in Heart Failure With Preserved Ejection Fraction

Thomas P. Olson, PhD, Bruce D. Johnson, PhD, Barry A. Borlaug, MD

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 ± 2.3 ml/mm Hg/min vs. 14.4 ± 3.3 ml/mm Hg/min; $p < 0.01$) related to reductions in both D_M (18.1 ± 4.9 ml/mm Hg/min vs. 23.1 ± 9.1 ml/mm Hg/min; $p = 0.04$), and V_C (45.9 ± 15.2. ml vs. 58.9 ± 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 ± 4.2 ml/mm Hg/min vs. 24.7 ± 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).

SEE PAGE 499

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

diffusing capacity of the lungs for nitric oxide (NO) was conducted using the rebreathing technique, with gases sampled on a mass spectrometer (Perkin-Elmer 1100, Perkin-Elmer, St. Louis, Missouri) and NO analyzer (Sievers Instruments, Boulder, Colorado) using a custom analysis software package (9,11). A 5-L rebreathe bag was filled with 0.3% carbon monoxide ($C^{18}O$), 40-ppm NO (diluted immediately before each measurement in the rebreathe bag from an 800-ppm gas mixture), 35% oxygen, and balanced nitrogen. The isotope $C^{18}O$ was used in place of the more common $C^{16}O$ as the test gas because the molecular mass of $C^{16}O$ is nearly identical to that of balanced nitrogen, making these gases indistinguishable by the mass spectrometer (9,11).

The volume of gas used to fill the rebreathe bag was determined by the V_T of the subject. Consistent bag volumes were ensured by using a timed switching circuit that, given a consistent flow rate from the tank, resulted in the desired volume. For each maneuver, subjects were switched to the rebreathe bag at the end of a normal expiration (end-expiratory lung volume) and instructed to nearly empty the bag with each breath for 10 consecutive breaths. The fb during the rebreathe maneuver was controlled with a metronome at a rate of 32 breaths/min unless the intrinsic frequency was >32 breaths/min, at which time the metronome was switched off. The rebreathe bag was then emptied with a suction device and refilled immediately before the next maneuver. All analyses of pulmonary diffusion and its subcomponents were conducted offline in a blinded fashion.

TABLE 1 Clinical Characteristics and Resting Cardiovascular Function

	Control (n = 26)	HFpEF (n = 20)	p Value
Clinical characteristics			
Age (yrs)	65 ± 9	67 ± 11	0.4
Sex (% female)	69	75	0.7
Body mass index (kg/m^2)	29.1 ± 5.5	34.5 ± 6.8	0.004
NYHA functional class I/II/III	26/0/0	0/9/11	<0.0001
Hypertension (%)	62	85	0.11
Smoking history (%)	0	10	0.18
eGFR (ml/min)	80 ± 18	82 ± 39	0.8
Plasma BNP (pg/ml)	37 (16–61)	175 (58–200)	0.0003
Hemoglobin (g/dl)	14.0 ± 1.8	13.1 ± 1.3	0.08
Loop diuretic agent (%)	0	60	0.0005
Resting hemodynamics and echocardiography			
Heart rate (beats/min)	70 ± 11	68 ± 13	0.7
Systolic BP (mm Hg)	133 ± 15	129 ± 20	0.4
LV mass index (mg/m^2)	82 ± 24	87 ± 27	0.5
Ejection fraction (%)	58 ± 5	60 ± 6	0.2
LA volume index (ml/m^2)	31 ± 7	45 ± 14	0.0001
E/E′ ratio	11 ± 4	20 ± 8	0.0004
Cardiac index (l/min*m^2)	2.3 ± 0.6	2.3 ± 0.6	0.6

Values are mean ± SD, %, or mean (range). Final column reflects 2-tailed unpaired *t* test or Fisher exact test for sex.

BNP = B-type natriuretic peptide; BP = blood pressure; E = early mitral inflow velocity; E′ = early mitral valve tissue inflow velocity; GFR = glomerular filtration rate; LA = left atrium; LV = left ventricular; NYHA = New York Heart Association.

MEASUREMENT OF CARDIAC OUTPUT. Transthoracic echocardiography was used to measure stroke volume from the left ventricular (LV) outflow dimension and pulse wave Doppler as previously described (7). Stroke volume was multiplied by heart rate to calculate cardiac output. Echo-Doppler measurements were interpreted offline in a blinded fashion and represent the mean of ≥3 consecutive beats collected by a trained cardiac sonographer.

STATISTICAL ANALYSIS. Continuous variables are reported as mean ± SD. Between-group differences were compared by the chi-square test for categorical variables, analysis of variance for normally-distributed continuous variables, and by Wilcoxon rank sum or Kruskal-Wallis tests for non-normally distributed continuous variables. Normality was evaluated for each variable by the Shapiro-Wilk W test. Bonferroni correction was applied for multiple comparisons. Bivariate (Pearson's coefficient) linear regression was performed to test associations between diffusing capacity of the lungs and its subcomponents and peak exercise capacity, ventilatory drive, and symptomology during exercise. Because patients with HFpEF reach lower exercise workload on average than subjects without HF, comparisons were made at both matched, low-level workload (20 W), and at peak exercise. All statistical analyses were performed using SPSS version 20.0 (IBM, Armonk, New York), with graphical representation using GraphPad Prism 6 (GraphPad Software, La Jolla, California).

RESULTS

SUBJECT CHARACTERISTICS. Patients with HFpEF had higher body mass than control subjects, but age, sex, comorbidity burden, and renal function were similar in the 2 groups (Table 1). Patients with HFpEF reported New York Heart Association functional class II to III symptoms and displayed elevated B-type natriuretic peptide levels along with higher left atrial volume and greater early mitral inflow velocity/medial mitral annular velocity ratios, which were all consistent with elevated LV filling pressures. LV mass was higher in patients with HFpEF,

whereas EF, heart rate, and BP were similar in HFpEF and control subjects. None of the subjects were treated with amiodarone or had sleep-disordered breathing.

EXERCISE PERFORMANCE. Exercise time, peak workload, VO_2 at ventilatory threshold, peak VO_2, and percent predicted peak VO_2 were all markedly impaired in patients with HFpEF compared with control subjects (Table 2). Borg effort and dyspnea scores in HFpEF subjects were higher at matched submaximal workload (20 W), which indicated greater perceived difficulty with low-level exercise at matched workload (Figure 1). At peak, Borg scores were similar between patients with HFpEF and control subjects, which was consistent with maximal subjective effort in all groups, but Borg scores relative to work performed were higher in patients with HFpEF. There was no difference in the peak respiratory exchange ratio between the patients with HFpEF and control subjects.

VENTILATION, GAS EXCHANGE, AND LUNG DIFFUSION AT REST AND DURING EXERCISE. There were no differences in VO_2 or measures of ventilation and breathing pattern at rest (Table 3). In contrast, DL_{CO} was significantly lower in the patients with HFpEF compared with control subjects. Compared with control subjects, patients with HFpEF displayed lower D_M, which reflected impaired membrane gas transfer, along with lower V_C, which reflected pulmonary capillary oligemia despite evidence of higher left heart filling pressures, as noted previously (Table 3, Figure 2).

During matched submaximal workload (20 W), VO_2 tended to be lower in the patients with HFpEF ($p = 0.06$) (Table 3). The DL_{CO} was lower in the HFpEF group compared with control subjects at 20 W, which was mediated exclusively by reduced D_M (Table 3). Notably, V_C increased dramatically from baseline in the HFpEF group to 20-W exercise to a level that was not different from control subjects (Figure 2). Despite lower absolute values in patients with HFpEF, relative changes in DL_{CO} and D_M from rest to 20-W exercise were similar in patients with HFpEF and control subjects. In contrast, the relative change in V_C was 2-fold greater in patients with HFpEF than control subjects during low-level exercise (Figure 3A). This greater increase in V_C at 20 W was coupled with higher V_E and V_T/T_I (index of ventilatory drive) in the HFpEF group compared with the control group (Table 3). The increase in V_E in HFpEF was due to higher fb, with no difference in V_T, indicating a more tachypneic breathing pattern (Figure 1).

TABLE 2 Exercise Performance

	Control Values (n = 26)	HFpEF (n = 20)	p Value
Exercise time (s)	840 ± 239	495 ± 210	<0.001
Peak workload (W)	93 ± 27	55 ± 23	<0.001
Peak VO_2 (ml/kg/min)	18.6 ± 3.3	12.7 ± 3.2	<0.001
% Predicted peak VO_2 (%)	94 ± 22	57 ± 19	<0.001
Peak respiratory exchange ratio	1.09 ± 0.07	1.05 ± 0.09	0.11
VO_2 at VAT (ml/kg/min)	14.2 ± 2.5	10.4 ± 2.3	<0.001
V_E/VCO_2 slope	33.5 ± 3.0	36.0. ± 5.0	0.05
20-W Borg effort (6–20)	8.6 ± 1.4	11.3 ± 2.4	<0.001
20-W Borg dyspnea (0–10)	0.8 ± 0.7	2.8 ± 1.5	<0.001
Peak Borg effort (6–20)	16.2 ± 1.8	15.7 ± 2.2	0.45
Peak Borg dyspnea (0–10)	5.2 ± 1.9	5.5 ± 2.0	0.61

Values are mean ± SD. Final column reflects 2-tailed unpaired *t*-test.
VAT = ventilatory anaerobic threshold; V_E = minute ventilation; VCO_2 = carbon dioxide production; VO_2 = oxygen consumption.

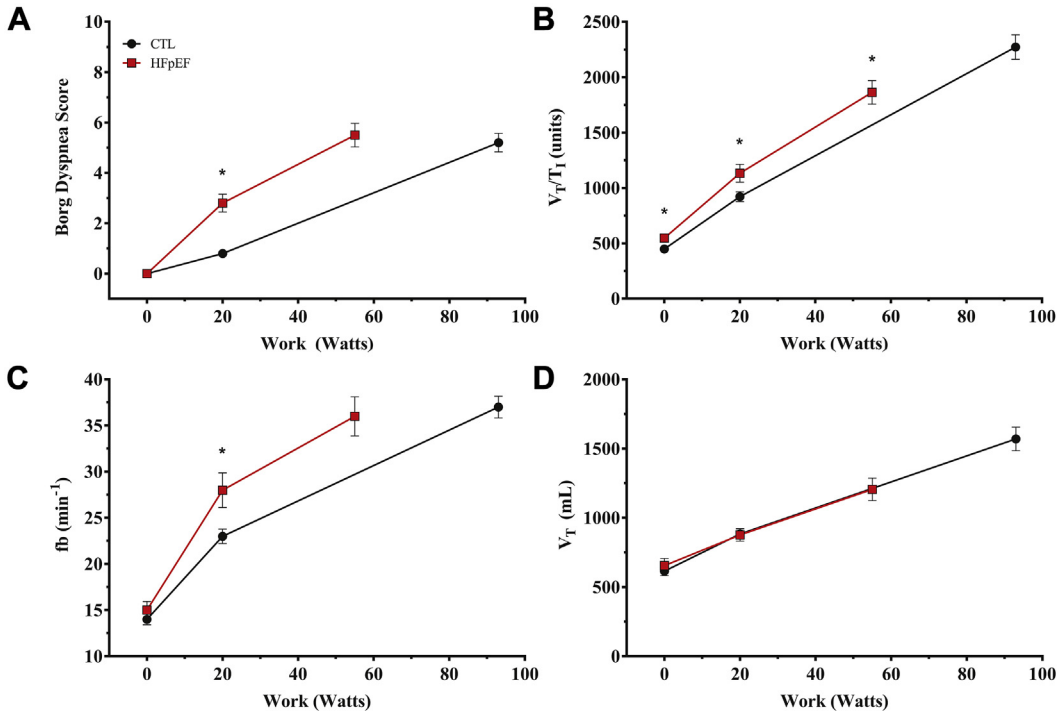
At peak exercise, V_E was lower in the HFpEF group compared with the control group, mediated by reduced V_T (Table 3). However, relative to the work performed, V_T responses were similar in the 2 groups, whereas fb was persistently elevated in HFpEF relative to exercise workload (Figure 1). The DL_{CO} during peak exercise in patients with HFpEF was again lower compared with the control subjects, as a function of both a reduction in D_M and V_C (Table 3, Figure 2). From 20-W exercise up to peak, there was proportionately greater increase in DL_{CO}, D_M, and V_C in control subjects compared with patients with HFpEF (Figure 3B). Notably, there was no further increase in V_C from 20 W to peak exercise in patients with HFpEF, indicating that pulmonary capillary blood volume reserve became saturated during low-level exercise.

At any cardiac output, absolute DL_{CO} and D_M values were consistently lower in patients with HFpEF than control subjects, whereas V_C was lower in patients with HFpEF only at baseline and peak exercise (Figure 2). Peak VO_2 was directly correlated with exercise increases in DL_{CO} ($r = 0.68$; $p < 0.0001$) and D_M ($r = 0.69$; $p < 0.0001$). In contrast, peak VO_2 was only modestly associated with changes in V_C ($r = 0.33$; $p = 0.02$).

DISCUSSION

This prospective study is the first to evaluate pulmonary gas diffusion both at rest and during exercise in patients with HFpEF, with separation of individual determinants of gas transfer, including D_M and V_C. We demonstrate that patients with HFpEF have

FIGURE 1 Borg Dyspnea Score, V_T/T_I, fb, and V_T as a Function of Workload During Exercise



(A) Borg dyspnea score, **(B)** ventilatory drive (tidal volume/inspiratory time [V_T/T_I]), **(C)** breathing frequency (fb), and **(D)** V_T, as a function of workload during exercise. *$p < 0.05$ versus control subjects.

important limitations to gas transfer as evidenced by a global reduction in DL_{CO}, both at rest and during exercise. Examination of the individual determinants of lung diffusion reveals a complex and dynamic interplay; with the onset of low-level exercise, there is a greater increase in V_C in patients with HFpEF compared with that of control subjects, which is presumably related to the greater increase in pulmonary venous pressures. Despite the greater rise in V_C with low-level exercise in patients with HFpEF, DL_{CO} remains lower than that in control subjects because of persistently decreased D_M. From low level to peak exercise, there is no further increase in V_C in patients with HFpEF, in contrast to the steady increases in V_C with increasing cardiac output observed in control subjects. This indicates a limitation in pulmonary vascular recruitment with maximal exercise, which coupled with impaired D_M, greatly limits gas transfer during exercise in patients with HFpEF. Diffusion abnormalities in HFpEF were associated with lower aerobic capacity and were coupled to greater symptoms of dyspnea, more profound tachypnea, and increased ventilatory drive relative to exercise workload. These data provide new insight into the mechanisms by which hemodynamic abnormalities developing during exercise in subjects with HFpEF alter pulmonary function and gas exchange to contribute to symptoms of exercise intolerance. Novel therapies that improve gas diffusion through either hemodynamic or non-hemodynamic mechanisms may be effective to improve exercise tolerance in subjects with HFpEF.

DETERMINANTS OF PULMONARY DIFFUSING CAPACITY. DL_{CO} describes the conductance of gas from the alveolus across the alveolar-capillary membrane to bind hemoglobin in erythrocytes (9). The reciprocal of this conductance ($1/DL_{CO}$) thus represents the total resistance to gas transfer in the lungs and is determined by the sum of resistances imposed by the $1/D_M$ and $1/\theta \cdot V_C$ (9,12). Previous studies in patients with HF and reduced EF (HFrEF) have shown that DL_{CO} and D_M are reduced compared with that in control subjects when measured at rest, and that the extent of this impairment is correlated with a greater

TABLE 3 Cardiopulmonary Function, Gas Exchange, and Lung Diffusion at Rest and During Exercise

	Controls (n = 26)	HFpEF (n = 20)	p Value
Rest			
VO_2 (ml/kg/min)	3.60 ± 0.51	3.29 ± 0.82	0.13
Q (l/min)	4.4 ± 1.2	4.9 ± 1.2	0.15
SV (ml/beat)	63.9 ± 17.6	74.1 ± 20.9	0.09
HR (beats/min)	70 ± 11	68 ± 13	0.7
V_E (l/min)	8.5 ± 1.9	9.5 ± 2.4	0.14
fb (breaths/min)	14 ± 3	15 ± 4	0.5
V_T (ml)	615 ± 166	655 ± 218	0.5
V_E/VCO_2 (ratio)	38.6 ± 5.0	40.1 ± 6.4	0.4
V_T/T_I (ratio)	448 ± 120	547 ± 122	0.01
DL_{CO} (ml/mm Hg/min)	14.4 ± 3.3	11.0 ± 2.3	<0.001
D_M (ml/mm Hg/min)	23.1 ± 9.1	18.1 ± 4.9	0.04
V_C (ml)	58.9 ± 16.2	45.9 ± 15.2	0.01
Matched workload (20 W)			
VO_2 (ml/kg/min)	9.6 ± 1.2	8.9 ± 1.41	0.06
Q (l/min)	8.2 ± 2.3	7.2 ± 1.4	0.12
SV (ml/beat)	86.2 ± 21.7	77.8 ± 19.1	0.09
HR (beats/min)	85 ± 17	94 ± 15	0.04
V_E (l/min)	20.1 ± 4.4	24.0 ± 5.3	0.01
fb (breaths/min)	23 ± 4	28 ± 8	0.02
V_T (ml)	883 ± 197	876 ± 188	0.9
V_E/VCO_2 (ratio)	34.3 ± 4.2	36.0 ± 5.0	0.2
V_T/T_I (ratio)	922 ± 225	1,133 ± 340	0.02
DL_{CO} (ml/mm Hg/min)	17.4 ± 3.6	14.5 ± 4.0	0.01
D_M (ml/mm Hg/min)	26.9 ± 6.6	21.5 ± 6.1	0.008
V_C (ml)	67.6 ± 23.3	64.9 ± 24.9	0.7
Peak exercise			
VO_2 (ml/kg/min)	18.6 ± 3.3	12.7 ± 3.2	<0.001
Q (l/min)	13.2 ± 3.7	9.2 ± 2.5	0.004
SV (ml/beat)	91.6 ± 22.1	80.0 ± 25.1	0.11
HR (beats/min)	144 ± 20	119 ± 22	<0.001
V_E (l/min)	56.7 ± 14.3	42.9 ± 12.4	0.002
fb (breaths/min)	37 ± 6	36 ± 9	0.9
V_T (ml)	1,570 ± 433	1,206 ± 344	0.005
V_E/VCO_2 (ratio)	34.5 ± 3.6	37.1 ± 4.7	0.05
V_T/T_I (ratio)	2,273 ± 560	1,864 ± 452	0.01
DL_{CO} (ml/mm Hg/min)	24.7 ± 7.1	17.3 ± 4.2	<0.001
D_M (ml/mm Hg/min)	39.6 ± 12.9	27.2 ± 6.3	0.001
V_C (ml)	86.1 ± 24.3	66.4 ± 24.9	0.01

Values are mean ± SD. Final column reflects 2-tailed unpaired *t*-test.

DL_{CO} = diffusing capacity of the lungs for carbon monoxide; D_M = alveolar-capillary membrane conductance; fb = breathing frequency; HR = heart rate; Q = cardiac output; SV = stroke volume; V_C = pulmonary capillary blood volume; V_T = tidal volume; other abbreviations as in Table 2.

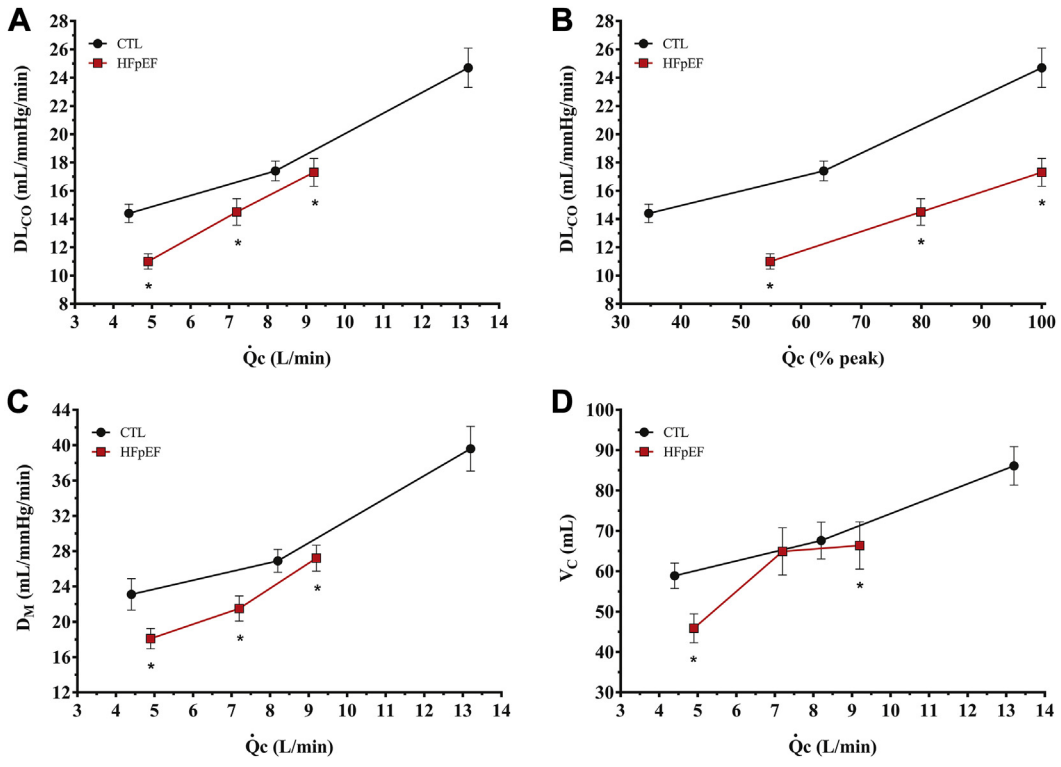
burden of pulmonary vascular disease, worse ventilatory inefficiency, greater HF severity, lower exercise capacity, and increased mortality (13–16). The present results show that these limitations in resting gas diffusion are also present in patients with HFpEF, and that the extent of these limitations is associated with impaired exercise capacity, hyperpnea, and symptoms of dyspnea.

PULMONARY DIFFUSION RESERVE IN HEART FAILURE. In the normal alveolar-capillary interface, DL_{CO} increases linearly with cardiac output during exercise. This is typically attributed to increased D_M and V_C due to capillary and alveolar distention and recruitment, which results in increased surface area available for gas exchange, along with more homogenous distribution of red cells within and among the pulmonary capillaries (17). Previous studies in HFrEF patients have evaluated changes in global gas diffusion (DL_{CO}) during exercise. Smith et al. (18) found that the increase in DL_{CO} relative to cardiac output was impaired in patients with HFrEF during low-level exercise (30 W). Olson et al. (19) later confirmed and extended this observation, showing reduced DL_{CO} both at low level and peak exercise in patients with HFrEF. The present results in HFpEF reveal a similar picture, with impaired recruitment of pulmonary gas diffusion reserve during exercise in patients with HFpEF compared with that in control subjects.

The primary novel finding in the present study is the evaluation of the individual determinants of lung diffusion during exercise, which has not been studied to date in any HF population. Agostoni et al. (15) examined DL_{CO}, D_M, and V_C at baseline and then 2 min following exercise in patients with HFrEF and control subjects. The investigators observed that although V_C increased after exercise in patients with HFrEF, D_M decreased, which was consistent with the development of interstitial pulmonary edema. Similar reductions in D_M have been observed following acute saline infusion in patients with HFrEF (13,14).

In contrast, the present study did not observe a reduction in D_M during exercise, although absolute values of D_M were lower in patients with HFpEF compared with control subjects for any given workload. The reason for the discrepant results may relate to the timing of D_M assessment, which was during exercise in the present study, as opposed to after exercise had been completed in the study of Agostoni et al. (15). Following cessation of exercise, many of the factors that dictate recruitment of D_M (e.g., distention of alveolar septae from increased ventilation, opening of capillaries with increased cardiac output) are no longer present. The slope of increase in D_M relative to cardiac output was similar in cases and control subjects (**Figure 2**), which argues against the development of interstitial pulmonary edema during exercise in in patients with HFpEF, despite a greater increase in V_C with submaximal exercise (**Figures 2 and 3**). It may be that chronic remodeling of the alveolar-capillary membrane protects against

FIGURE 2 DL_{CO}, DL_{CO}/Q Ratio, D_M, and V_C as a Function of Cardiac Output During Exercise

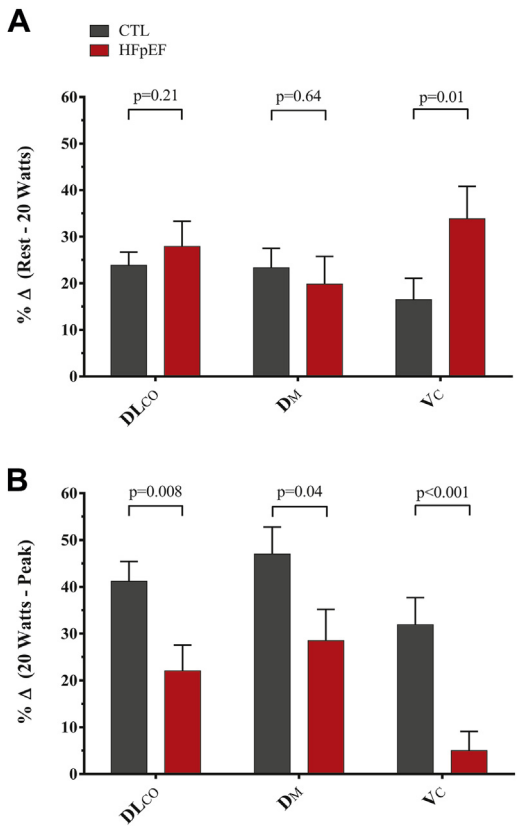


(A) Diffusing capacity of the lungs for carbon monoxide (DL_{CO}), **(B)** DL_{CO}/cardiac output (Q) ratio, **(C)** alveolar-capillary membrane conductance (D_M), and **(D)** pulmonary capillary blood volume (V_C) as a function of cardiac output during exercise. *$p < 0.05$ versus control subjects.

the development of interstitial edema during transient increases in pulmonary venous pressure during exercise in patients with HFpEF, but at the cost of impediment to gas transfer at the membrane (i.e., lower D_M) (20,21). Cardiac output reserve was depressed in patients with HFpEF, and it cannot be determined from these data whether D_M and V_C responses to exercise might have differed if cardiac output were closer to normal.

CHANGES IN PULMONARY CAPILLARY BLOOD VOLUME DURING EXERCISE IN HFpEF. Reduction in exercise capacity in many patients with HFpEF is determined largely by inadequate cardiac output reserve, which, when coupled with stress-induced elevations in pulmonary venous pressures, markedly limits exercise capacity (1,4,22). In this light, we can envision a setting where the decrements in cardiac reserve, coupled with elevated filling pressures, would exacerbate hemodynamic pooling in the pulmonary circulation. This theoretical construct is supported by the present study, which demonstrates a greater increase in V_C from rest to a low intensity workload (20 W) in patients with HFpEF. This rapid rise during the onset of exercise corresponds to the time when the largest increase in left heart filling pressures is observed in patients with HFpEF (1,23). Eighty percent of the total increase in pulmonary venous pressure that will occur during exercise in patients with HFpEF is observed in the first 1.5 min of exercise at 20 W (1). We speculate that increases in venous return in this early stage cannot be accommodated by the left ventricle in HFpEF because of diastolic reserve limitation (4), such that during onset of exercise, right ventricular output transiently exceeds left ventricular output, and thus, blood pools in the pulmonary circulation. This is consistent with the greater relative increase in V_C in the patients with HFpEF observed at 20 W. With higher levels of exercise, a new steady state may be reached in patients with HFpEF, where left- and right-sided cardiac outputs are matched, even as

FIGURE 3 Percent Change From Rest to Matched Submaximal Absolute Workload (20 W) and Percent Change From Matched Submaximal Absolute Workload (20 W) to Peak Exercise



(A) Percent change from rest to matched submaximal absolute workload (20 W) and **(B)** percent change from matched submaximal absolute workload (20 W) to peak exercise for DL_{CO}, D_M, and V_C during exercise. Abbreviations as in Figure 2.

they both remain lower than what is observed in control subjects, as in the present study and others (22). Alternatively, it may simply be that the ability to recruit greater pulmonary capillary volume becomes rapidly saturated in HFpEF during low-level exercise due to vascular remodeling.

STUDY LIMITATIONS. Body mass index was greater in the patients with HFpEF compared with control subjects, although this seems unlikely to influence gas diffusion in the lungs, because lung size does not vary with body composition. Invasive LV filling pressures were not assessed as part of this study, but are well known to increase dramatically during exercise in patients with HFpEF, and measures reflective of resting LV filling pressures (B-type natriuretic peptide, early mitral inflow velocity/medial mitral annular velocity, left atrial volume) were all increased in patients with HFpEF compared with control subjects. Future study is required to clarify how hemodynamic derangements relate to observed changes in gas diffusion in HFpEF. Control subjects in the present study displayed somewhat depressed exercise capacity and mild ventilatory inefficiency. However, all were recruited a priori based upon the absence of known cardiovascular disease, and the mildly abnormal exercise findings in this group would only bias any observed group differences toward the null. Right ventricular function is known to be abnormal in HFpEF, but it was not assessed in the present study (24).

CONCLUSIONS

The results of this study confirm our hypothesis that patients with HFpEF demonstrate significant reductions in pulmonary gas diffusion capacity during exercise compared with healthy control subjects. The impairment of DL_{CO} reserve is related to abnormalities in D_M and V_C, which vary as a function of exercise intensity with persistent depression in D_M throughout exercise. This is presumably related to alveolar-capillary remodeling, with a greater increase in V_C early during exercise, followed by a failure to increase V_C, which further reflects deficits in vascular recruitment reserve. These data provide important new insights into the pulmonary effects of hemodynamic abnormalities that develop during exercise in HFpEF, and demonstrate that patients with HFpEF have impaired lung diffusion both at rest and during graded exercise that is related to abnormalities in lung conductance and capillary blood volume. Further study is warranted to determine how these abnormalities in lung diffusion might be targeted therapeutically to improve exercise capacity and tolerance in patients with HFpEF.

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REPRINT REQUESTS AND CORRESPONDENCE: Dr. Thomas P. Olson, Division of Cardiovascular Diseases, Department of Medicine, Mayo Clinic, 200 1st Street NW, Joseph 4-225C, Rochester, Minnesota 55905. E-mail: olson.thomas2@mayo.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: Patients with HFpEF display abnormal pulmonary gas transfer at rest that is related to abnormalities in lung membrane conductance and pulmonary capillary oligemia, despite evidence of elevated filling pressures.

COMPETENCY IN MEDICAL KNOWLEDGE 2: With low-level exercise, when filling pressures increase dramatically, there is a greater increase in pulmonary capillary blood volume in HFpEF that is coupled to increased ventilatory drive and greater symptoms of dyspnea.

COMPETENCY IN MEDICAL KNOWLEDGE 3: Up to maximum exercise, there is persistently impaired gas transfer related to reduced membrane conductance and inability to further recruit the pulmonary capillary vasculature in HFpEF.

TRANSLATIONAL OUTLOOK 1: Novel therapies that target pulmonary gas transfer, through either hemodynamic or non-hemodynamic mechanisms, may help improve exercise tolerance in patients with HFpEF.

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