

# Exercise Ventilatory Efficiency in Older and Younger Heart Failure Patients With Preserved Ejection Fraction

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## ABSTRACT

**Background:** Patients with heart failure with preserved ejection fraction (HFpEF) exhibit pulmonary abnormalities, but the studies to date have reported wide variability in the ventilatory equivalent for carbon dioxide ( $\dot{V}_E/\dot{V}_{CO_2}$ ) slope. It is possible that aging may contribute to that variability. We sought to compare ventilatory efficiency and its components in older and younger HFpEF patients during exercise.

**Methods and Results:** Eighteen older (O;  $80 \pm 4$  y) and 19 younger (Y;  $59 \pm 7$  y) HFpEF patients performed cardiopulmonary exercise testing to volitional fatigue. Measurements of arterial blood gases were used to derive  $V_D/V_T$ , dead space ventilation, and alveolar ventilation.  $\dot{V}_E/\dot{V}_{CO_2}$  slope was greater in older compared with younger HFpEF patients (O  $36 \pm 7$  vs Y  $31 \pm 7$ ;  $P = .04$ ). At peak exercise, older HFpEF exhibited greater  $V_D/V_T$  compared with younger HFpEF (O  $0.37 \pm 0.10$  vs Y  $0.28 \pm 0.10$ ;  $P < .01$ ), whereas  $PaCO_2$  was not different between groups ( $P = .58$ ).  $\dot{V}_E$  and alveolar ventilation were similar ( $P > .23$ ), but dead space ventilation was greater in older compared with younger HFpEF at peak exercise ( $P = .04$ ).

**Conclusions:** Older HFpEF patients exhibit greater ventilatory inefficiency resulting from elevated physiologic dead space during peak exercise compared with younger HFpEF patients. These results suggest that aging can worsen the pathophysiologic mechanisms underlying ventilatory efficiency during exercise in HFpEF. (*J Cardiac Fail* 2019;25:278–285)

**Key Words:** Breathing strategy, aging, physiologic dead space, hyperventilation.

Patients with heart failure (HF) with preserved ejection fraction (HFpEF) exhibit elevated pulmonary pressures, reduced lung diffusion capacity, and pulmonary gas exchange abnormalities.<sup>1–6</sup> The ventilatory equivalent for carbon dioxide ( $\dot{V}_E/\dot{V}_{CO_2}$ ) slope is an important prognostic tool for predicting hospitalizations and mortality in HFpEF.<sup>7–10</sup> The primary contributors to  $\dot{V}_E/\dot{V}_{CO_2}$  slope are the fraction of tidal volume comprised of dead space ( $V_D/V_T$ ) and mechanisms regulating arterial carbon dioxide tension ( $PaCO_2$ ), with  $V_D/V_T$  contributing to a greater extent on average in HFpEF.<sup>6</sup>

Mean  $\dot{V}_E/\dot{V}_{CO_2}$  slopes reported in the literature have been widely variable in HFpEF patients (ie, 30–39).<sup>2,5–19</sup> Some studies have reported that  $\dot{V}_E/\dot{V}_{CO_2}$  slope is significantly higher in HFpEF than control populations, whereas others have detected minimal or no difference between these groups. Although HFpEF was formerly considered to be a disease exclusive to aging,<sup>20</sup> recent studies have shown that HFpEF in the current era is being diagnosed much earlier in life, especially in the setting of obesity,<sup>21,22</sup> and it may be that age is an important contributor to the diversity in the ventilatory response to exercise.

Older HF patients display greater comorbidity burden, reduced quality of life, and diminished peak exercise capacity.<sup>20,23,24</sup> Aging also affects pulmonary function, lung diffusion capacity, respiratory mechanics, pulmonary pressures, and ventilation-perfusion matching.<sup>25–27</sup> However, no study has evaluated how age affects ventilatory control or its mechanisms (ie,  $V_D/V_T$  and  $PaCO_2$  regulation) in HFpEF. Accordingly, the purpose of the present study was to comprehensively examine ventilatory efficiency and the components of the alveolar gas equation in older versus younger HFpEF patients during peak exercise. We hypothesized that older HFpEF patients would exhibit greater

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$\dot{V}_E/\dot{V}_{CO_2}$  slope, resulting from elevated  $V_D/V_T$ , during exercise compared with younger HFpEF patients.

## Methods

### Patients

Thirty-seven patients diagnosed with HFpEF were referred to our study by their primary cardiologists for cardiopulmonary exercise testing (CPET) as part of a comprehensive HF evaluation at the Mayo Clinic, Rochester, Minnesota. The HFpEF patients exhibited typical clinical symptoms (ie, dyspnea and fatigue), left ventricular ejection fraction (LVEF)  $\geq 50\%$ , and elevated left heart filling pressures at rest or with exercise.<sup>1</sup> Patients were excluded for the following: pulmonary hypertension, significant coronary artery disease (stenosis  $\geq 50\%$ ), clinically significant pulmonary disease, cor pulmonale, primary renal or hepatic disease, valvular heart disease (any stenosis, more than mild regurgitation, etc), hypertrophic or infiltrative cardiomyopathy, constrictive pericarditis, and deep vein thrombosis. All of the authors have full access to the data in the study and take full responsibility for its integrity and the analysis. All aspects of this study were approved by the Mayo Clinic

Institutional Review Board and conformed with the Declaration of Helsinki.

### Echocardiography

Resting 2-dimensional and tissue Doppler echocardiography according to guidelines of the American Society of Echocardiography were used to assess LVEF morphology and function, ie, early transmitral flow velocity (E), late transmitral flow velocity (A), E/A ratio, early diastolic mitral annular velocity ( $e'$ ), and peak E/ $e'$  ratio.<sup>28</sup>

### CPET protocol

HFpEF patients performed the CPET while remaining on standard pharmacologic therapy. All participants performed cycling exercise at an initial workload of 20 W while pedaling at 60 rpm. The workload was increased by 10 W every 3 minutes until volitional exhaustion. Heart rate and rhythm were continuously monitored during the CPET with the use of 12-lead electrocardiography. Breath-by-breath open-circuit spirometry (Medgraphics, St Paul, Minnesota) was used to continuously measure ventilatory and metabolic data throughout the CPET. The final 30 seconds of ventilatory and metabolic

**Table 1.** Patient Characteristics

Characteristic	Younger Patients With HFpEF	Older Patients With HFpEF	P Value
n	19	18	
Age (y)	59 $\pm$ 7	80 $\pm$ 4*	<.01
Sex (men/women)	8/11	9/9	.88
Height (cm)	170 $\pm$ 9	168 $\pm$ 11	.54
Weight (kg)	107 $\pm$ 22	89 $\pm$ 22*	.02
Body mass index (kg/m <sup>2</sup> )	37 $\pm$ 7	31 $\pm$ 6*	.01
LV ejection fraction (%)	60 $\pm$ 12	61 $\pm$ 12	.79
Hemoglobin (g/dL)	12.1 $\pm$ 1.3	12.9 $\pm$ 1.3	.08
Creatinine (mg/dL)	1.4 $\pm$ 0.4	1.3 $\pm$ 0.5	.34
Coronary artery disease, n (%)	4 (21)	4 (22)	.75
Diabetes mellitus, n (%)	8 (42)	3 (16)	.18
Hypertension, n (%)	18 (95)	18 (100)	.98
NYHA functional class, n (%)			.93
II	5 (26)	4 (22)	
III	14 (74)	14 (78)	
<b>Drug therapy, n (%)</b>			
ACE inhibitor or ARB	12 (63)	12 (67)	.90
Antiarrhythmic	4 (21)	2 (11)	.71
$\beta$ -Blocker	14 (74)	11 (61)	.64
Ca <sup>2+</sup> -channel blocker	6 (32)	4 (22)	.79
Digoxin	3 (16)	1 (6)	.64
Nitrate (oral, sublingual, or topical)	4 (21)	3 (17)	.94
Aspirin	13 (69)	13 (72)	.92
Diuretics	15 (79)	16 (89)	.71
<b>Echocardiography</b>			
LA volume (mL)	86 $\pm$ 35	83 $\pm$ 31	.84
LA volume index (mL/m <sup>2</sup> )	41 $\pm$ 15	40 $\pm$ 11	.81
Mitral E-wave velocity (cm/s)	89 $\pm$ 27	97 $\pm$ 42	.76
Mitral A-wave velocity (cm/s)	73 $\pm$ 23	83 $\pm$ 38	.41
Mitral E/A	1.4 $\pm$ 0.6	1.4 $\pm$ 0.9	.54
Mitral septal tissue Doppler velocity ( $e'$ ) (cm/s)	7 $\pm$ 2	6 $\pm$ 2	.32
Mitral E/ $e'$	15 $\pm$ 6	15 $\pm$ 5	.96

LV, left ventricular; NYHA, New York Heart Association; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; LA, left atrial.

\* $P < .05$  vs younger patients with HFpEF.

data at rest and peak exercise were used for data analysis. The ventilatory efficiency response was expressed as a linear regression by plotting  $\dot{V}_E$  (ordinate) and  $\dot{V}CO_2$  (abscissa) with the use of data at rest and  $\dot{V}O_{2peak}$ , and the slope was determined for each patient. Using all exercise data to derive  $\dot{V}_E/\dot{V}CO_2$  slope is clinically relevant and prognostically superior to determining  $\dot{V}_E/\dot{V}CO_2$  slope with exercise data before the respiratory compensation threshold in HF patients.<sup>29</sup> Sampling of arterial blood gases occurred at the end of each stage from the radial artery for measurement of partial pressures of carbon dioxide (PaCO<sub>2</sub>) and oxygen (PaO<sub>2</sub>) as well as pH (pHa) and oxygen saturation (SaO<sub>2</sub>). Metabolic, ventilatory, and blood gas measurements were used to calculate  $V_D/V_T$  ( $V_D/V_T = 1 - [863 \times \dot{V}CO_2]/[\dot{V}_E \times PaCO_2]$ ), alveolar ventilation ( $\dot{V}_A$ ;  $\dot{V}_A = \dot{V}_E \times [1 - V_D/V_T]$ ), dead space ventilation ( $\dot{V}_D$ ), alveolar volume ( $V_A$ ), and dead space volume ( $V_D$ ).<sup>2,6</sup>

### Statistical Analyses

Values are reported as mean  $\pm$  SD. Statistical analyses were performed with the use of Sigmasat 2.0 (Jandel Scientific, San Rafael, California). Participant

characteristics were compared with the use of unpaired *t* test or chi-square test of association (for categorical data) when appropriate. Normality was assessed with the use of the Shapiro-Wilk test, and nonparametric tests were used when appropriate. Metabolic, ventilatory, and components of the alveolar gas equation were compared via 2-way analysis of covariance (ANCOVA; intensity [ie, rest versus peak exercise]  $\times$  age) with body mass index (BMI) entered into the ANCOVA model as a covariate. Statistical significance was set at  $P < .05$ .

## Results

### Patient Characteristics

Younger HFpEF patients were heavier and had a greater BMI compared with older HFpEF patients (Table 1). No significant differences were present in comorbidities, drug therapies, or echocardiographic indices between the groups. Resting echocardiography measurements indicated that there were increased filling pressures in the older and younger HFpEF patients. All participants completed the study without adverse events.

**Table 2.** Metabolic and Ventilatory Data

Variable	Younger Patients With HFpEF	Older Patients With HFpEF	P Value
<b>Rest</b>			
n	19	18	
$\dot{V}O_2$ (mL·kg <sup>-1</sup> ·min <sup>-1</sup> )	2.3 $\pm$ 0.6	2.8 $\pm$ 0.6	.17
$\dot{V}O_2$ (L/min)	0.2 $\pm$ 0.1	0.3 $\pm$ 0.1	.47
$\dot{V}CO_2$ (L/min)	0.2 $\pm$ 0.1	0.2 $\pm$ 0.1	.81
RER	0.87 $\pm$ 0.12	0.84 $\pm$ 0.10	.22
HR (beats/min)	69 $\pm$ 13	69 $\pm$ 8	.75
SBP (mm Hg)	149 $\pm$ 22	142 $\pm$ 21	.47
DBP (mm Hg)	71 $\pm$ 12	64 $\pm$ 11	.07
MAP (mm Hg)	97 $\pm$ 14	90 $\pm$ 13	.19
$\dot{V}_E$ (L/min)	8 $\pm$ 3	9 $\pm$ 3	.18
$V_T$ (L)	0.5 $\pm$ 0.2	0.5 $\pm$ 0.2	.94
$f_B$ (breaths/min)	15 $\pm$ 4	18 $\pm$ 5	.09
$V_D/V_T$	0.39 $\pm$ 0.09	0.47 $\pm$ 0.10	.08
PaCO <sub>2</sub> (mm Hg)	42 $\pm$ 4	41 $\pm$ 3	.54
PaO <sub>2</sub> (mm Hg)	74 $\pm$ 11	69 $\pm$ 10	.08
SaO <sub>2</sub> (%)	96 $\pm$ 2	94 $\pm$ 4*	.03
pHa	7.39 $\pm$ 0.04	7.39 $\pm$ 0.04	.77
<b>Peak exercise</b>			
Workload	39 $\pm$ 12	31 $\pm$ 9*	.02
$\dot{V}O_2$ (mL·kg <sup>-1</sup> ·min <sup>-1</sup> ) <sup>†</sup>	8.7 $\pm$ 2.0	7.9 $\pm$ 2.0	.18
$\dot{V}O_2$ (L/min) <sup>†</sup>	0.9 $\pm$ 0.3	0.7 $\pm$ 0.1	.10
$\dot{V}CO_2$ (L/min) <sup>†</sup>	0.9 $\pm$ 0.3	0.8 $\pm$ 0.2	.14
RER <sup>†</sup>	1.04 $\pm$ 0.11	1.07 $\pm$ 0.09	.62
HR (beats/min) <sup>†</sup>	100 $\pm$ 15	97 $\pm$ 16	.94
SBP (mm Hg) <sup>†</sup>	182 $\pm$ 37	181 $\pm$ 28	.97
DBP (mm Hg) <sup>†</sup>	77 $\pm$ 13	71 $\pm$ 7	.12
MAP (mm Hg) <sup>†</sup>	112 $\pm$ 20	108 $\pm$ 13	.43
$\dot{V}_E$ (L/min) <sup>†</sup>	30 $\pm$ 11	28 $\pm$ 7	.92
PaO <sub>2</sub> (mm Hg)	74 $\pm$ 15	72 $\pm$ 15	.87
SaO <sub>2</sub> (%)	95 $\pm$ 4	93 $\pm$ 6	.36
pHa	7.38 $\pm$ 0.04	7.38 $\pm$ 0.06	.70

$\dot{V}O_2$ , oxygen uptake;  $\dot{V}CO_2$ , carbon dioxide production; RER, respiratory exchange ratio; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure;  $\dot{V}_E$ , ventilation;  $V_T$ , tidal volume;  $f_B$ , breathing frequency;  $V_D/V_T$ , fraction of dead space to  $V_T$ ; PaCO<sub>2</sub>, arterial carbon dioxide tension; PaO<sub>2</sub>, arterial oxygen tension; SaO<sub>2</sub>, arterial oxygen saturation; pHa, arterial pH.

\* $P < .05$  vs younger patients with HFpEF;

<sup>†</sup> $P < .05$  vs rest.

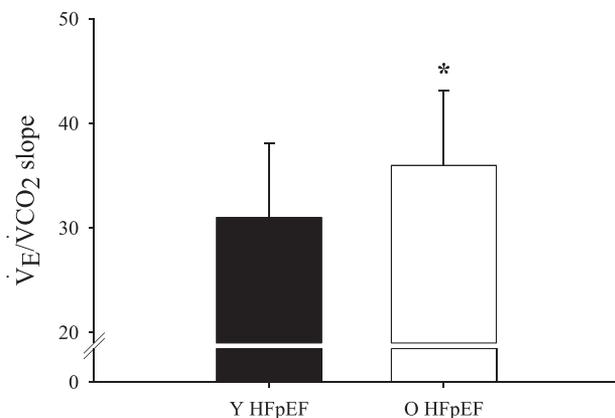
## Metabolic and Ventilatory Data

BMI was a significant covariate for resting absolute  $\dot{V}CO_2$  and  $\dot{V}O_2$ , as well as peak-exercise relative  $\dot{V}O_2$ . At rest, older HFpEF patients had lower  $SaO_2$  than younger HFpEF patients, but no other differences were present (Table 2). At peak exercise, older compared with younger HFpEF patients had a lower workload.  $\dot{V}_E/\dot{V}CO_2$  slope was greater in the older than in the younger HFpEF patients (Fig. 1;  $P = .04$ ). At peak exercise,  $PaCO_2$  was not different between the groups ( $P = .58$ ), whereas older HFpEF patients had greater  $V_D/V_T$  compared with younger HFpEF patients (Fig. 2;  $P < .01$ ). At peak exercise,  $\dot{V}_E$  and  $V_T$  were similar between the groups (all  $P > .19$ ). However, older HFpEF patients had lower  $V_A$  as well as greater  $f_B$  and  $V_D$  at peak exercise than younger HFpEF patients (Fig. 3) (all,  $P < .05$ ). As a result, older HFpEF patients had greater  $\dot{V}_D$  compared with younger HFpEF patients ( $P = .04$ ), whereas  $\dot{V}_A$  was not different between the groups at peak exercise ( $P = .23$ ).

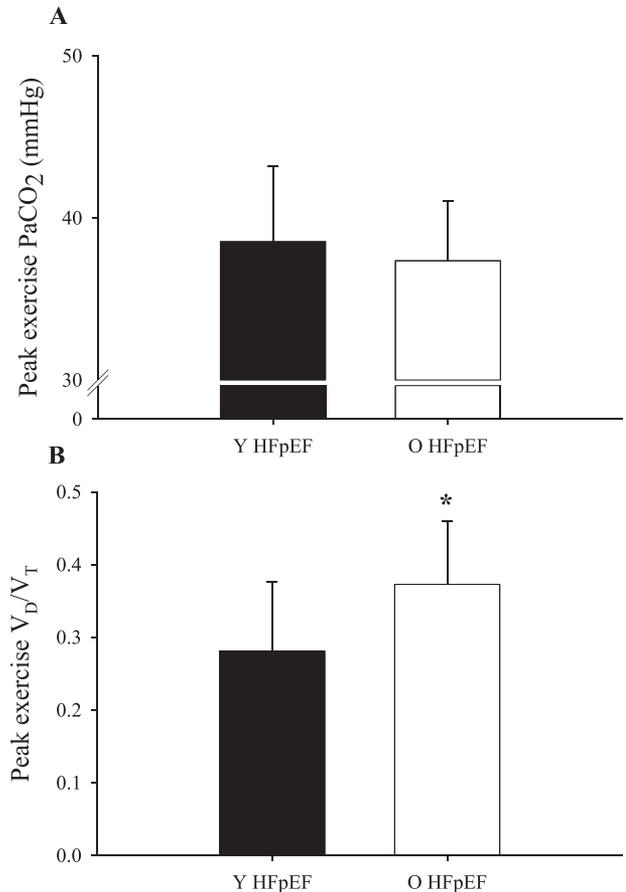
## Discussion

### Major Findings

This is the first study comparing ventilatory efficiency and the components of the alveolar gas equation in older and younger HFpEF patients during exercise. Consistent with our hypotheses, ventilatory inefficiency, as indicated by a higher  $\dot{V}_E/\dot{V}CO_2$  slope, was greater in older than in younger HFpEF patients during peak exercise. Furthermore,  $V_D/V_T$  was elevated in the older HFpEF patients compared with younger HFpEF patients, whereas  $PaCO_2$  was not different. Finally, at similar peak  $\dot{V}_E$ , older HFpEF patients had smaller  $V_A$  but greater  $f_B$  and  $V_D$  compared with younger HFpEF patients, resulting in exacerbated  $\dot{V}_D$  during exercise. Taken together, these findings are clinically important because they provide support for “aging” as a



**Fig. 1.**  $\dot{V}_E/\dot{V}CO_2$  slope in older (O, open bar; n = 18) and younger (Y, solid bar; n = 19) HFpEF patients. Older HFpEF patients had a greater  $\dot{V}_E/\dot{V}CO_2$  slope than younger HFpEF patients ( $P = .04$ ). \*Significantly different from younger HFpEF patients. Data are shown as mean and SD.

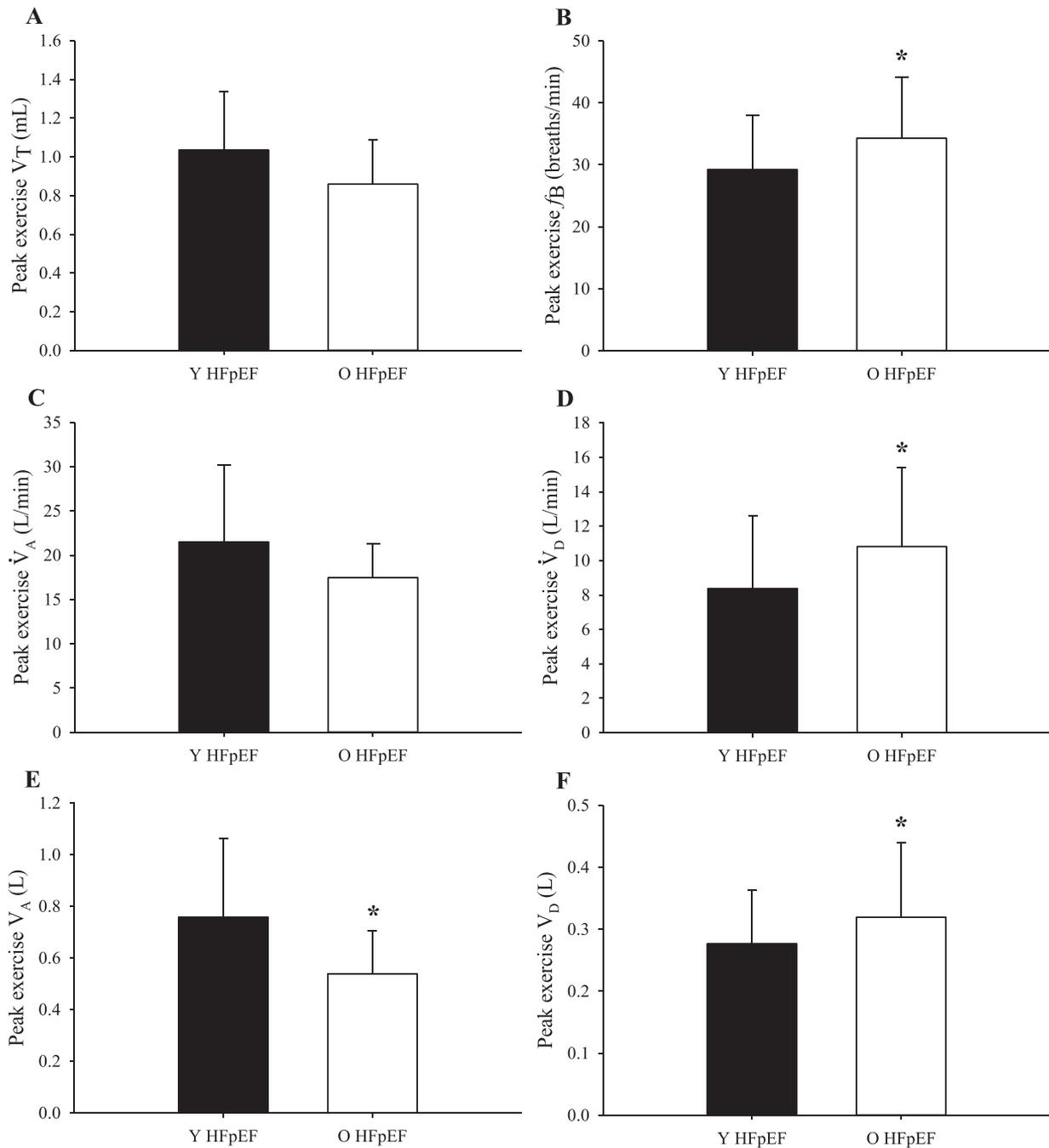


**Fig. 2.** (A) Peak-exercise partial pressure of arterial carbon dioxide ( $PaCO_2$ ) and (B) physiologic dead space ( $V_D/V_T$ ) in older (O, open bars; n = 18) and younger (Y, solid bars; n = 19) HFpEF patients. No differences were present in  $PaCO_2$  between groups ( $P = .58$ ).  $V_D/V_T$  was greater for older than for younger HFpEF patients ( $P < .01$ ). \*Significantly different from younger HFpEF patients. Data are shown as mean and SD.

contributor to the heterogeneous pathophysiologic mechanisms in HFpEF.

### Aging and HFpEF

HFpEF has generally been considered to be a disease associated with aging;<sup>20</sup> however, recent studies have shown that HFpEF is being diagnosed earlier in life. For example, some recent studies investigating HFpEF have reported mean ages of 54–58 yrs,<sup>9,18</sup> which is consistent with the younger HFpEF group presented here. From the present study, the underlying mechanisms contributing to this younger HFpEF group are unclear. Exercise capacity was not different between groups; however, the younger HFpEF patients may likely have had a higher  $\dot{V}O_{2peak}$  if corrected for lean body mass.<sup>30</sup> Moreover, obesity and hypertension have been suggested to play a role;<sup>21,22</sup> however, the younger HFpEF patients were less obese than the older HFpEF patients and the incidences of comorbidities were similar between groups. Similarly, the echocardiographic



**Fig. 3.** Components of the alveolar gas equation at similar  $\dot{V}_E$  in older and younger HFpEF patients: (A) peak exercise tidal volume ( $V_T$ ), (B) breathing frequency ( $f_B$ ), (C) alveolar ventilation ( $\dot{V}_A$ ), (D) dead space ventilation ( $\dot{V}_D$ ), (E) alveolar volume ( $V_A$ ), and (F) dead space volume ( $V_D$ ) in older (*O*, open bars;  $n = 18$ ) and younger (*Y*, solid bars;  $n = 19$ ) HFpEF patients.  $\dot{V}_E$  and  $V_T$  were similar between groups (all  $P > .19$ ). Older HFpEF patients had lower  $V_A$  but greater  $f_B$ ,  $V_D$ , and  $\dot{V}_D$  than younger HFpEF patients (all  $P < .05$ ), whereas  $\dot{V}_A$  was not different between groups. \*Significantly different from younger HFpEF patients. Data are shown as mean and SD.

variables were not different between groups. It is important to note that the diastolic function present in the HFpEF groups was abnormal (as indicated by the large LA volume index [40–41 mL/m<sup>2</sup>] and high E/A and E/e' [1.4 and 15, respectively]) even when compared with healthy older adults (LA volume index  $\sim 30$  mL/m<sup>2</sup>, E/A 0.84–1.2, E/e' 11–11.7).<sup>31–35</sup>

#### Effect of Aging on $V_E/\dot{V}CO_2$ Slope in HFpEF

Ventilatory efficiency (ie,  $\dot{V}_E/\dot{V}CO_2$  slope) is a strong prognostic tool in predicting survival in HFpEF. However, the  $\dot{V}_E/\dot{V}CO_2$  slope and ratio values reported in HFpEF have been variable (ie, 30–39).<sup>6,8,9,13,15–18,36</sup> In the present study, we found that older HFpEF patients had a greater

$\dot{V}_E/\dot{V}CO_2$  slope than younger HFpEF patients at peak exercise. Our findings are consistent with studies suggesting higher  $\dot{V}_E/\dot{V}CO_2$  slopes and ratios in older compared with younger HFpEF patients (ie, 34–39 vs 30, respectively)<sup>6,8,9,13,15–18,36</sup> as well as higher  $\dot{V}_E/\dot{V}CO_2$  slopes in older compared with younger patients with HF and reduced ejection fraction.<sup>14</sup> These findings are clinically important for older HFpEF patients because a high  $\dot{V}_E/\dot{V}CO_2$  slope is associated with hospitalizations and mortality.<sup>7–10</sup> It is important to note that although the younger HFpEF patients had a lower  $\dot{V}_E/\dot{V}CO_2$  slope, they also exhibited the characteristic reduction in peak tolerance.

Ventilatory efficiency is determined by the level of hyperventilation and  $V_D/V_T$ . At peak exercise in HFpEF patients,  $V_D/V_T$  contributes to a greater extent to  $\dot{V}_E/\dot{V}CO_2$  slope than  $PaCO_2$ .<sup>6</sup> Our findings indicate that elevated  $V_D/V_T$  was responsible for the greater  $\dot{V}_E/\dot{V}CO_2$  slope in the older compared with younger HFpEF patients during exercise, whereas the degree of hyperventilation was not different between groups. These findings are consistent with previous studies reporting increased  $V_D/V_T$  in healthy older compared with younger adults during exercise,<sup>37–39</sup> suggesting that alterations associated with aging are partially responsible for the elevated  $V_D/V_T$  in HFpEF. From these data it is unclear if aging and the HFpEF syndrome interact synergistically to further elevate  $\dot{V}_E/\dot{V}CO_2$  slope and physiologic dead space in older HFpEF during exercise. Taken together, these data suggest that “aging” contributes to the increased  $V_D/V_T$  and thus worsens ventilatory inefficiency during exercise.

Physiologic dead space can be altered by breathing strategy and ventilation-perfusion mismatch during exercise. In the present study, older HFpEF patients likely had ventilation-perfusion heterogeneity that subsequently resulted in an alternate breathing strategy. Specifically, older HFpEF patients exhibited a greater  $f_B$  during peak exercise (with similar  $\dot{V}_E$ ) to offset the lower  $V_A$ . As a result of this breathing strategy,  $\dot{V}_A$  was similar between groups whereas  $\dot{V}_D$  was consequently greater in the older compared with younger HFpEF patients. It is likely that the constraint of  $V_A$  in the older HFpEF patients was compounded by the presentation of the HFpEF syndrome and aging. For example, HF patients often exhibit restrictive lung abnormalities likely due to cardiomegaly, pulmonary congestion, weakened inspiratory muscles, or increased elastic recoil pressure,<sup>40–42</sup> and as a result lung closing volume is generally above functional residual capacity.<sup>43</sup> This latter anomaly results in cyclic airway opening and closing during tidal breathing and consequent maldistribution of ventilation<sup>43</sup> that is likely further exaggerated with aging.<sup>44</sup> These aberrant pulmonary derangements and subsequent altered breathing strategy have important implications for ventilatory work and blood flow redistribution in older HFpEF patients.<sup>45,46</sup>

### Methodologic Considerations and Future Directions

There are several methodologic considerations that may have influenced our results. First, we acknowledge the

relatively small sample size, which may have limited our ability to determine differences in some measurements (eg, hemoglobin). Studies with larger sample sizes may be necessary to confirm our findings. Second, younger and older control groups were not incorporated in this study. Therefore, future studies are necessary to determine if aging and the HFpEF syndrome interact synergistically to worsen ventilatory efficiency during exercise. Third, ventilation-perfusion matching, pulmonary function (including closing volume), and respiratory mechanics were not assessed. Future studies using these techniques are warranted to determine the underlying pathophysiologic mechanisms specific to the pulmonary system responsible for the increased  $\dot{V}_E/\dot{V}CO_2$  slope and  $V_D/V_T$  in older HFpEF. Finally, this study did not incorporate an interventional experimental design. Future studies are required with the use of interventions such as inhibition of locomotor muscle neural feedback,<sup>47</sup> altering central-peripheral hemodynamics (eg, via inorganic nitrite supplementation<sup>16,17</sup>), and modifying dead space to better understand the underlying pathophysiology of ventilatory inefficiency in HFpEF.

### Conclusion

Compared with younger HFpEF patients, older HFpEF patients exhibit greater ventilatory inefficiency resulting from elevated physiologic dead space during peak exercise. These results suggest that aging can worsen the pathophysiologic mechanisms underlying ventilatory efficiency during exercise in HFpEF. Future studies are warranted to determine the pathophysiologic pulmonary mechanisms responsible for the increased  $\dot{V}_E/\dot{V}CO_2$  slope and  $V_D/V_T$  during exercise in older HFpEF patients.

### Disclosures

None.

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