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Exercise Oscillatory Ventilation*:

Instability of Breathing Control Associated With Advanced Heart Failure

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Abstract

Background—Instability of breathing control due to heart failure (HF) manifests as exercise oscillatory ventilation (EOV). Prior descriptions of patients with EOV have not been controlled and have been limited to subjects with left ventricular ejection fraction (LVEF) of ≤ 0.40. The aim of this study was to compare clinical characteristics including ventilatory responses of subjects with EOV to those of control subjects with HF matched for LVEF.

Methods—Subjects (n = 47) were retrospectively identified from 1,340 consecutive patients referred for cardiopulmonary exercise testing. Study inclusion required EOV without consideration of LVEF while control subjects (n = 47) were composed of HF patients with no EOV matched for LVEF. Characteristics for each group were summarized and compared.

Results—For EOV subjects, the mean LVEF was 0.37 (range, 0.11 to 0.70), and 19 subjects (41%) had an LVEF of ≥ 0.40. Compared to control subjects, EOV subjects had increased left atrial dimension, mitral E-wave velocity, and right heart pressures as well as decreased exercise tidal volume response, functional capacity, rest and exercise end-tidal carbon dioxide, and increased ventilatory equivalent for carbon dioxide and dead space ventilation (all $p < 0.05$). Multivariate analysis demonstrated atrial fibrillation (odds ratio, 6.7; $p = 0.006$), digitalis therapy (odds ratio, 0.27; $p = 0.02$), New York Heart Association class (odds ratio, 3.5; $p = 0.0006$), rest end-tidal carbon dioxide (odds ratio, 0.87; $p = 0.005$), and peak heart rate (odds ratio, 0.98; $p = 0.02$) were independently associated with EOV.

Conclusions—Patients with EOV have clinical characteristics and exercise ventilatory responses consistent with more advanced HF than patients with comparable LV systolic function; EOV may occur in HF patients with an LVEF of ≥ 0.40.

Keywords

exercise; heart failure; ventilation

Instability of ventilatory control is frequent in patients with heart failure (HF) and may manifest as exercise oscillatory ventilation (EOV).[1–3] EOV detected by cardiopulmonary exercise testing is characterized by the regular alteration of tidal volume (V_T) with a crescendo-decrescendo pattern without interposed apnea, which distinguishes it from other forms of

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periodic breathing observed in HF patients including Cheyne-Stokes respiration[4–6] and central sleep apnea.[1,7–10] The frequency of EOV has been reported to range from 12 to 30% of ambulatory HF patients managed at tertiary centers.[2,3] While EOV may be common in patients with advanced HF, it is seldom recognized or reported. Moreover, routine detection may be a worthwhile goal as EOV is associated with advanced HF and may resolve with therapeutic intervention.[11–15]

Prior reports[1–3,6,16,17] of EOV have been limited to descriptions of patients with left ventricular ejection fraction (LVEF) of ≤ 0.40 with associated findings that included severely decreased LVEF, advanced New York Heart Association (NYHA) class, decreased functional capacity, and adverse prognosis. However, these prior studies did not utilize control subjects matched for LVEF in order to facilitate the identification of other clinical characteristics that might discriminate individuals with EOV from HF patients with stable ventilatory control. Accordingly, the aim of this study was to evaluate clinical characteristics, including ventilatory responses of consecutive, unselected ambulatory patients with EOV for comparison with control subjects with HF and no EOV matched for LVEF.

Materials and Methods

The study was approved by the Mayo Clinic College of Medicine Institutional Review Board. All subjects provided informed consent.

Subject Selection

Subjects were retrospectively identified from 1,340 consecutive ambulatory patients without inducible ischemia who had been referred for the evaluation of dyspnea, exertional fatigue, or functional capacity by cardiopulmonary exercise testing and included 626 patients with a diagnosis of HF. Study inclusion required EOV detected by cardiopulmonary exercise testing, defined as a ≥ 25% variation of the amplitude of minute ventilation ($\dot{V}_E$)[18] persisting for ≥ 60% of exercise duration (Fig 1).[3] The amplitude of oscillatory ventilation was defined as (peak $\dot{V}_E$ – nadir $\dot{V}_E$/mean $\dot{V}_E$) × 100 and evaluated within single oscillatory cycles at 50% peak and peak exercise.[18] Control subjects included HF patients from the same referral cohort with no EOV matched for LVEF.

Exercise Testing

Subjects underwent treadmill exercise testing to volitional fatigue following instrumentation for the measurement of heart rate, metabolic gas exchange, and oxygen saturation. The protocol used an initial treadmill speed and grade of 2.0 miles per hour and 0%, respectively, with speed and grade increased every 2 min to yield an approximate 2 metabolic equivalent increase per work level to a rating of perceived exertion of 18 to 20 on the Borg scale.[19]

Gas Exchange Measures and Physiologic Monitoring

Breath-by-breath measurements were obtained by a metabolic cart (Medical Graphics; St. Paul, MN). Measures included peak oxygen consumption ($\dot{V}_{O_2}$), carbon dioxide output ($\dot{V}_{CO_2}$), partial pressure of end-tidal carbon dioxide (P_{ETCO_2}), V_T, V_E, and breathing frequency. The data were collected continuously and reported as averages obtained over the final 30 s of each workload. Derived measures included the respiratory exchange ratio, defined as the ratio of $\dot{V}_{CO_2}/\dot{V}_{O_2}$ and the ventilatory equivalent for CO_2 ($\dot{V}_E/\dot{V}_{CO_2}$).[20]

Echocardiography

Chamber dimensions, right heart pressures, stroke volume, cardiac output, diastolic hemodynamics, and LVEF were assessed by echocardiography.[21–24]

Statistical Analysis

Characteristics, including ventilatory responses, were summarized with continuous data expressed as the mean ± SD or frequency expressed as a percentage. Characteristics of the study groups were compared by an unpaired two-tailed Student *t* test or Wilcoxon rank-sum test for continuous variables or χ^2 test for categoric variables. A Student paired *t* test was used for the comparison of ventilatory responses within groups.

Linear regression was performed to evaluate the relationship between P_{ETCO_2} and the $\dot{V}_E/\dot{V}_{CO_2}$. Multivariate regression using a backward selection procedure was used to identify characteristics independently associated with EOV; candidate variables for the multivariate model included those with $p \leq 0.2$ by univariate analysis. For all analyses, p values ≤ 0.05 were considered to be significant.

Results

Subject Characteristics

The frequency of EOV for all ambulatory patients without ischemia who had been referred for cardiopulmonary exercise testing was 47 of 1,340 (3.5%) compared to 45 of 646 (7.0%) for those with a referral diagnosis of HF ($p < 0.001$). The study group ($n = 47$) and control group ($n = 47$) were not different with regard to LVEF, body mass index, gender, or therapy with β-blockers, digitalis, and diuretics. On univariate analysis, characteristics that discriminated EOV subjects from control subjects included older age, more advanced NYHA class, and increased frequency of atrial fibrillation. Subjects with EOV were also less likely to be receiving treatment with an angiotensin-converting enzyme inhibitor or angiotensin-II receptor blocker and were more likely to have had a history of hypertension (Table 1).

Echocardiography

Cardiac output, index, and stroke volume were not different for subjects and control subjects, and values were within normal limits. For EOV subjects, the mean LVEF was 0.37 (range, 0.11 to 0.70), and 19 subjects (41%) had an LVEF of ≥ 0.40. Left atrial volume was significantly greater in subjects compared to control subjects as were estimates of right atrial and peak right ventricular systolic pressure. Mitral inflow peak E-wave velocity and peak velocity of pulmonary vein diastolic flow were also higher in subjects consistent with higher left atrial and pulmonary venous diastolic pressures (Table 2).[22]

Exercise and Ventilatory Responses

Subjects with EOV had significantly shorter exercise duration and lower peak heart rate compared to control subjects (Table 3). The breathing pattern of EOV subjects was also more rapid and shallower with significantly attenuated V_T response (Fig 2, top, A) and more limited functional capacity (Table 4). For EOV subjects, P_{ETCO_2} was significantly lower compared to control subjects both at rest and during exercise, while breathing frequency and $\dot{V}_E/\dot{V}_{CO_2}$ were significantly higher at rest and at 50% peak exercise, which is consistent with greater hyperventilation due to increased ventilatory drive. In addition, for EOV subjects there was a significant further decrease of P_{ETCO_2} during exercise consistent with increasing hyperventilation, which was not observed for control subjects (Table 4).

Resolution of Oscillatory Ventilation

In 18 subjects (38%), oscillatory ventilation resolved during the final stage of exercise (Fig 1). For this subgroup, exercise duration and peak $\dot{V}_{O_2}$ were not different from those values in control subjects; however, their exercise duration was significantly greater compared to the subgroup of subjects for whom EOV persisted ($p = 0.01$).

Subjects in whom EOV resolved were also compared to subjects in whom EOV persisted and control subjects with respect to changes in V_T and heart rate. For subjects in whom EOV resolved, V_T at peak exercise was similar to that in control subjects and was significantly higher than that for subjects in whom EOV persisted (Fig 2, bottom, B). The increase in V_T from rest to peak exercise and from 50% peak to peak exercise were also comparable to that in control subjects and was significantly higher than that for subjects in whom EOV persisted (Fig 2, bottom, B). For the subgroup in whom EOV resolved, there was also significantly greater increase of heart rate from 50% peak to peak exercise compared to that in the subgroup in whom EOV persisted (Δ heart rate, 29 vs 19 beats/min, respectively; p = 0.04).

$\dot{V}e/\dot{V}co_2$ and End-Tidal CO_2

The relationship of $\dot{V}_E/\dot{V}_{CO_2}$ to P_{ETCO_2} may be summarized by the following modified alveolar gas equation[25] in which P_{ETCO_2} measured by cardiopulmonary exercise testing has been substituted for Pa_{CO_2}:

$$\dot{V}_E/\dot{V}_{CO_2} = 863/P_{ETCO_2}(1 - V_D/V_T)^{25}$$

A strong inverse correlation between $\dot{V}_E/\dot{V}_{CO_2}$ and P_{ETCO_2} for subjects and control subjects was observed, consistent with tight regulatory control of the Pa_{CO_2} by ventilation (Fig 3).[25] Though the slopes of the regression lines for the two study groups were not statistically different, the intercept for EOV subjects was shifted significantly upward, indicating that, at comparable P_{ETCO_2} values, EOV subjects had higher $\dot{V}_E/\dot{V}_{CO_2}$, which is consistent with greater physiologic dead space ventilation (V_D/V_T) [p = 0.002].

Multivariate Analysis

Subject characteristics independently associated with EOV included atrial fibrillation (odds ratio, 6.7; p = 0.006), digitalis therapy (odds ratio, 0.27; p = 0.02), NYHA class (odds ratio, 3.5 per one class change; p = 0.0006), resting P_{ETCO_2} (odds ratio, 0.87 per one unit; p = 0.05), and peak exercise heart rate (odds ratio, 0.98 per one unit; p = 0.02).

Discussion

A unique and noteworthy finding of this study was that a substantial proportion of EOV subjects (41%) had an LVEF of ≥ 0.40. Indeed, on average, EOV subjects had normal stroke volume and cardiac index that were not different from control subjects, indicating that severe LV systolic dysfunction is not a prerequisite for EOV. Additional novel observations were that EOV subjects had larger left atrial volume, findings that are consistent with higher estimated left atrial, pulmonary venous and right heart pressures, attenuated V_T response to exercise, and increased V_D/V_T compared to control subjects. This study also demonstrated EOV subjects had greater hyperventilation as well as increased $\dot{V}_E/\dot{V}_{CO_2}$. The tachypneic and shallow breathing pattern, increased V_D/V_T, lower P_{ETCO_2}, more abnormal hemodynamics, increased $\dot{V}_E/\dot{V}_{CO_2}$, more limited exercise capacity, and higher NYHA class are each consistent with more advanced HF in subjects with EOV despite LVEF matched to control subjects.

For this study, oscillatory ventilation was defined as a ≥ 25% variation of V_E amplitude[18] persisting for ≥ 60% of exercise duration,[3] whereas previous studies used less restrictive criteria, including a V_E amplitude threshold of ≥ 15%[1] or oscillations present for two or more consecutive cycles.[18] Furthermore, subject selection required only EOV without consideration of LVEF or prior diagnosis of HF, whereas prior studies[1–3,6,16–18] limited study enrollment to subjects with known HF and LVEF of ≤ 0.40. In addition, 70% of our subjects were treated with β-blockers compared to previous reports[2,3] in which such therapy was less frequently used, which may be relevant as β-blocker therapy may reduce hyperventilation and thereby

decrease the predisposition to EOV.[26] Hence, the lower frequency of EOV observed in our study compared to that in prior reports[1–3] may be related to differences in referral population, selection criteria, or therapy.

Other relevant methodological considerations were the use of control subjects matched for LVEF and multivariate analysis. Controlling for LVEF enabled the identification of characteristics other than LV systolic dysfunction, which distinguished EOV subjects from control subjects. One prior study[1] of EOV used multivariate analysis and demonstrated that only an apnea-hypopnea index of > 30 events per hour, as determined by polysomnography, was independently associated with EOV. In contrast, we report the novel observations that factors independently associated with EOV also include the presence of atrial fibrillation, lack of digitalis therapy, lower resting P_{ETCO_2}, and lower peak exercise heart rate.

The mechanisms that account for EOV have not been fully elucidated.[27–29] However, the breathing pattern of EOV is reminiscent of central sleep apnea, suggesting similar pathophysiology.[9,30] Indeed, EOV and central sleep apnea frequently coexist.[1] Increased cardiac-filling pressures with pulmonary congestion have been implicated as a primary factor in the genesis of periodic breathing due to central sleep apnea.[9,30] Our findings of increased left atrial volume, mitral peak E flow velocity, pulmonary venous diastolic flow velocity, and right heart pressures by echocardiography are consistent with higher left atrial, pulmonary venous, and pulmonary arterial pressure in EOV subjects compared to those in control subjects. Hence, the observations reported herein also support a possible role for increased cardiac filling pressures with pulmonary congestion in the genesis of EOV.

Pulmonary congestion imposes reduced lung compliance, which may limit the increase of V_T with exercise, making increased breathing frequency necessary to maintain $\dot{V}_E$.[31] The stretching of lung J-receptors by vascular congestion and interstitial edema also stimulates medullary respiratory centers via vagal afferents, which promotes rapid, shallow breathing[32–35] and heightens chemosensitivity with consequent hyperventilation with hypocapnia.[32,33] Oscillatory ventilation may then ensue as Pa_{CO_2} is driven to values near or below the apnea threshold[9,30,36,37]; as Pa_{CO_2} falls, hypoventilation occurs; as Pa_{CO_2} subsequently rises, hyperventilation resumes, thereby completing an oscillatory cycle.

In contrast, a mechanism for the resolution of oscillatory ventilation during exercise has not been previously proposed.[1–3] It is perhaps noteworthy that interventions that increase the difference between the ambient Pa_{CO_2} and the apnea threshold may resolve the periodic breathing of central sleep apnea, and are achieved by administration of CO_2[38] or acetazolamide, which increase the ambient Pa_{CO_2}.[13] Alternatively, this same difference may be made greater by lowering of the Pa_{CO_2} required to produce apnea (*ie*, the apnea threshold) by an increase of chemosensitivity such as achieved by treatment with phosphodiesterase inhibitors.[39,40] In this regard, β-adrenergic agonists increase $\dot{V}_E$[41] and may also lower the apnea threshold in patients with HF.[42] In our study, EOV subjects had significantly lower P_{ETCO_2} than control subjects at rest and with exercise. Furthermore, with exercise P_{ETCO_2} decreased further in EOV subjects, while remaining stable in control subjects. As ventilatory responses may be enhanced by increased β-adrenergic stimulation, acting either centrally[43] or via the influence of venous norepinephrine on peripheral chemoreceptors,[41] our observations suggest further that the enhancement of chemosensitivity during exercise may have decreased the ambient Pa_{CO_2} while also sufficiently lowering the apnea threshold such that EOV resolved (*ie*, because the apnea threshold was not approached, thereby preventing the initiation or maintenance of periodic breathing). In addition, the observation of a significantly greater increase in exercise heart rate for subjects in whom EOV resolved compared to that in subjects in whom it persisted is consistent with greater preservation of postsynaptic β-adrenergic function[44] in the former

subgroup, suggesting that superior exercise capacity may have been mediated by β-adrenergic effects on both heart rate and chemosensitivity.

The resolution of EOV with the stabilization of ventilatory control was associated with a nearly twofold increase of V_T from 50% peak to peak exercise compared to subjects in whom EOV persisted, which likely contributed to the greater functional capacity in the former subgroup. The magnitude of this difference seems unlikely to have been due to bronchodilation, though some role for this mechanism cannot be excluded. It seems more likely that the restoration of stable ventilatory control led to increased V_T by the resolution of episodic hypoventilation.

Clinical Implications

As diuretics,[12,13] inotropes,[11] cardiac resynchronization,[14] and cardiac surgery[11,15] may reduce or abolish periodic breathing, the presence of EOV suggests that an intensification of therapy be considered to optimize cardiac hemodynamics, improve symptoms, and increase functional capacity. The detection of EOV may also be useful for the assessment of patients with well-preserved LVEF in whom the diagnosis of HF is not certain. Hence, the recognition of EOV by cardiopulmonary exercise testing may be useful for the diagnosis and surveillance of HF while also identifying a high-risk patient subgroup and therapeutic target.

Study Limitations

The main limitation of this study was its retrospective design. Nevertheless, the validity of the observations is strengthened by the large study group size, the use of control subjects matched for LVEF, and the magnitude of differences between subjects and control subjects. There was a statistically significant difference in age between the subject and control groups, but it seems unlikely that this difference influenced ventilatory responses, as might be expected from the higher V_D/V_T associated with more advanced age, as age-associated increases have been estimated at < 0.1%/year.[45]

Conclusions

Patients with EOV have clinical characteristics and exercise ventilatory responses that are consistent with more advanced HF than control subjects with comparable left ventricular systolic function; EOV may occur in HF patients with an LVEF of ≥ 0.40.

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Abbreviations

EOV

exercise oscillatory ventilation

HF

heart failure

LVEF
: left ventricular ejection fraction

NYHA
: New York Heart Association

P_{ETCO_2}
: end-tidal carbon dioxide

$\dot{V}_{CO_2}$
: carbon dioxide output

V_D/V_T
: physiologic dead space ventilation

$\dot{V}_E$
: minute ventilation

$\dot{V}_E/\dot{V}_{CO_2}$
: ventilatory equivalent for CO_2

$\dot{V}_{O_2}$
: oxygen consumption

V_T
: tidal volume

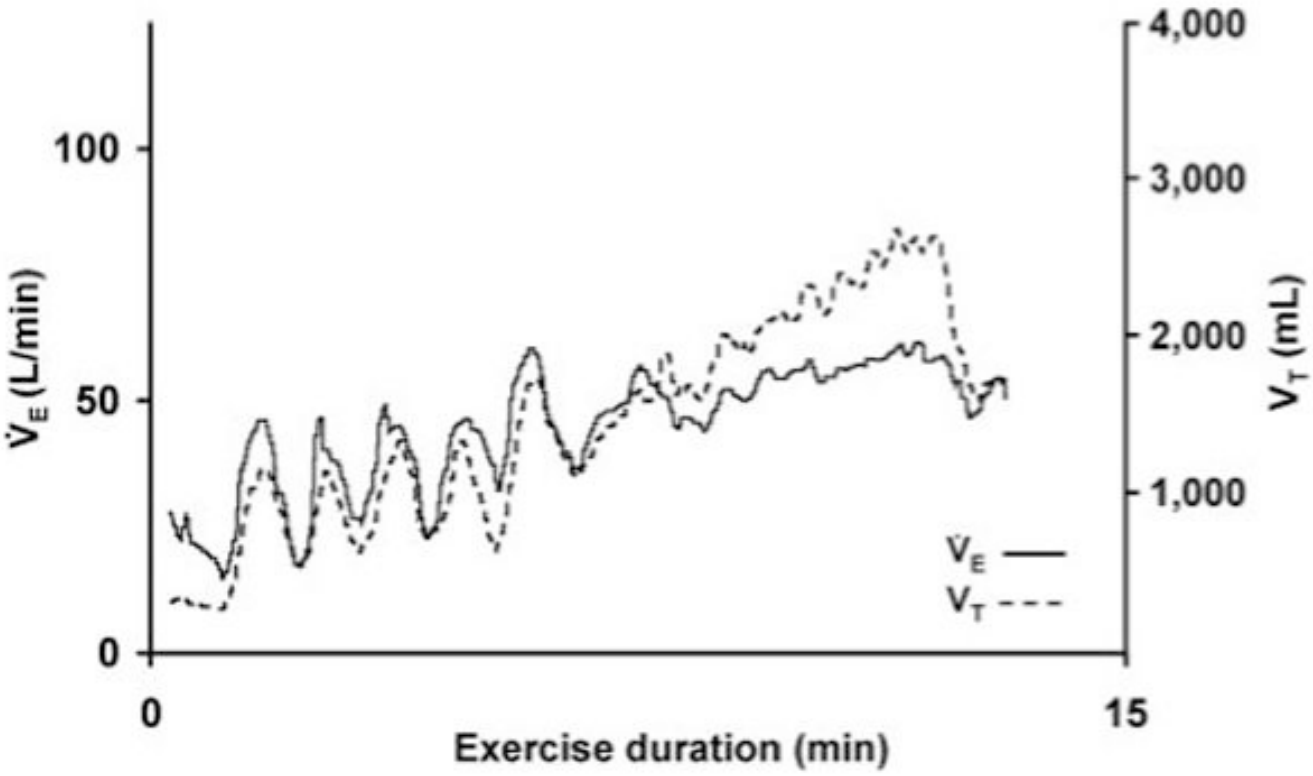

Figure 1.
Oscillation of $\dot{V}_E$ during exercise in a subject with chronic, stable NYHA class III HF. Ventilatory oscillation resolved during the final phase of exercise. Oscillation of V_T is also shown; in this individual the magnitude of breath-to-breath V_T oscillation varied by > 250% during a single oscillatory cycle.

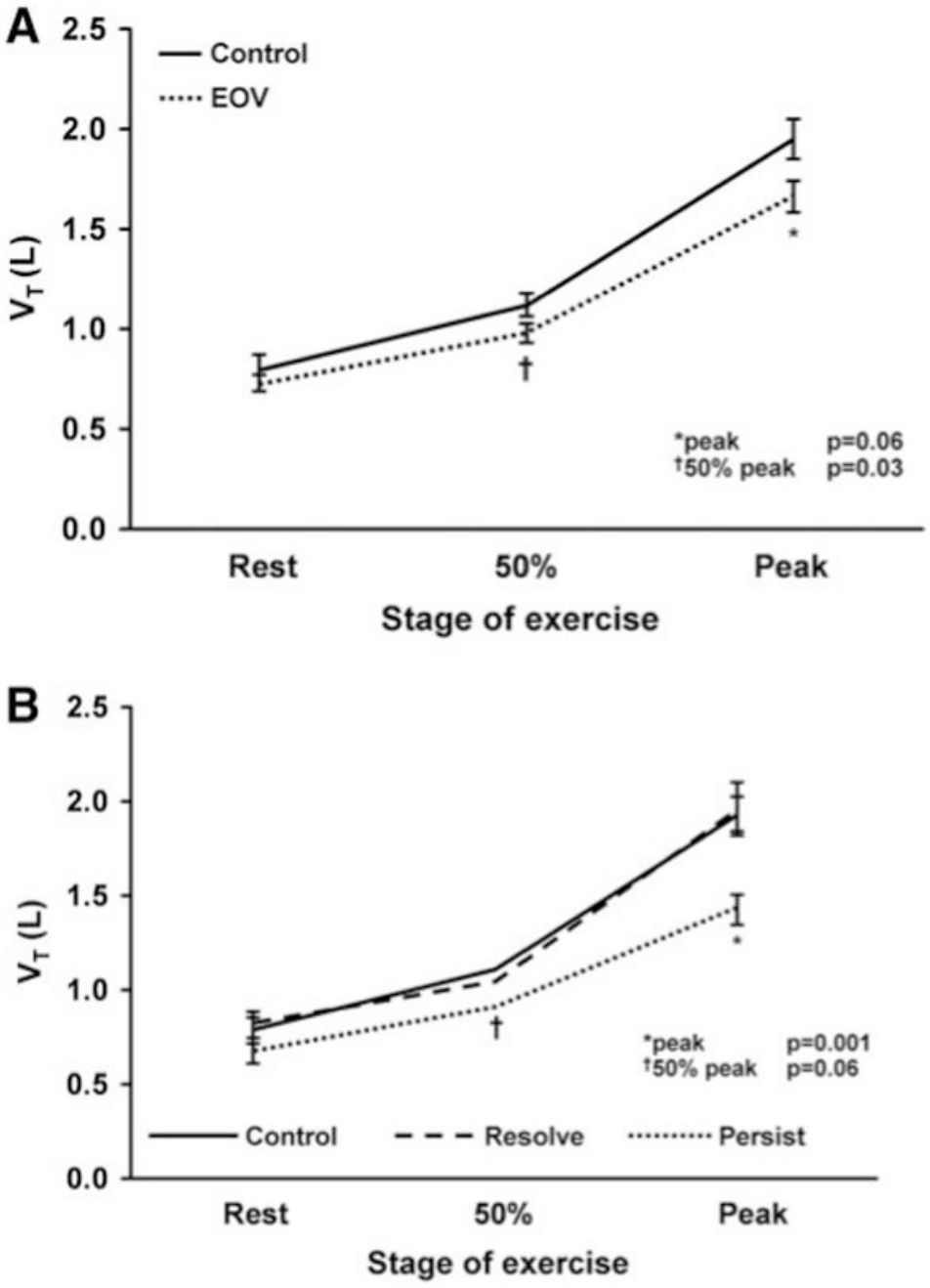

Figure 2.

Top, *A*: V_T from rest through peak exercise in control subjects and subjects with EOV; bars represent SEs at each stage. The difference of V_T between groups was significant at 50% peak ($p = 0.03$); however, at peak exercise the difference was not significant ($p = 0.06$). *Bottom*, *B*: subjects with EOV are portrayed in the following two subgroups: subjects in whom EOV resolved; and subjects in whom EOV persisted and compared to control subjects; bars represent SEs at each stage. In subjects in whom EOV persisted, V_T at 50% peak ($p = 0.06$) and peak exercise ($p = 0.001$) was lower than in subjects in whom EOV resolved. The mean increase in V_T from 50% to peak exercise in subjects for whom EOV resolved was also significantly greater

(0.9 ± 0.4 vs 0.5 ± 0.2, respectively; $p < 0.001$) than that observed for the subgroup in whom EOV persisted.

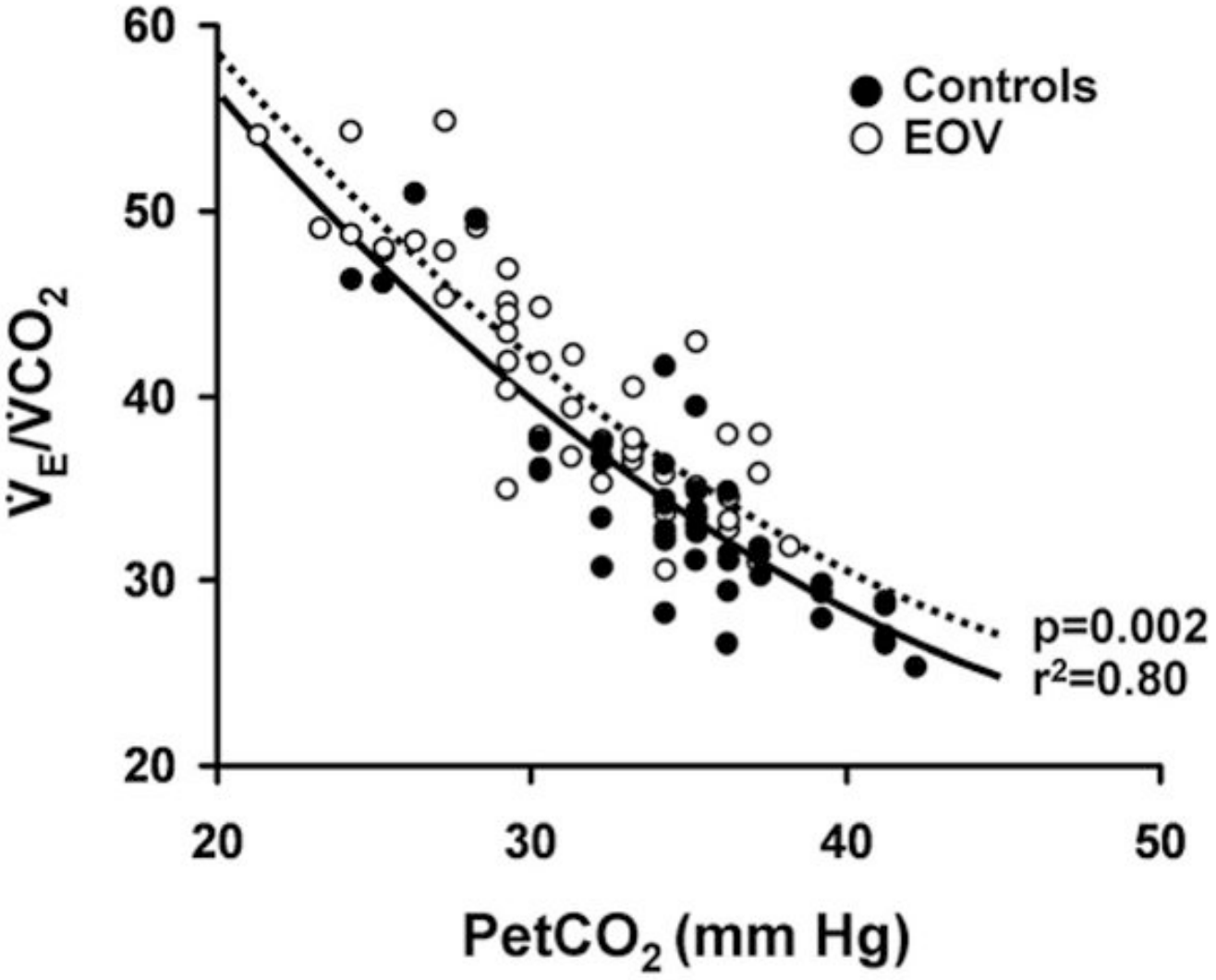

Figure 3.

Relationship of P_{ETCO_2} to $\dot{V}_E/\dot{V}_{CO_2}$ at 50% peak exercise in control subjects and subjects with EOV. The slopes of the regression lines for each group are similar; however, the significant upward shift of the intercept for EOV subjects is consistent with significantly increased V_D/V_T per the modified alveolar gas equation at comparable $\dot{V}_E/\dot{V}_{CO_2}$.

Table 1
Characteristics of Patients and Control Subjects*

Characteristics	Control Subjects (n = 47	EOV Patients (n = 47)	p Value
Age, yr	55 ± 13	61 ± 14	0.03†
NYHA class	2.1 ± 0.9	2.6 ± 0.8	0.006†
BMI, kg/m^2	29 ± 5.0	29 ± 6.8	0.49†
LVEF	0.35 ± 0.14	0.37 ± 0.17	0.77†
Male gender	33 (70)	34 (72)	0.82‡
HF diagnosis	47 (100)	45 (96)	0.49‡
History of hypertension	11 (23)	21 (42)	0.03‡
Ischemic etiology	14 (30)	20 (49)	0.07‡
Atrial fibrillation	6 (13)	16 (35)	0.01‡
Pacemaker	13 (28)	11 (23)	0.64‡
Medications			
ACE-I or ARB	36 (78)	28 (60)	0.05‡
Digoxin	28 (60)	19 (42)	0.10‡
β-blockers	33 (70)	33 (70)	1.00‡
Diuretics	34 (72)	37 (79)	0.47‡
Calcium blockers	3 (6)	8 (16)	0.51‡
Nitrates	11 (22)	8 (16)	0.44‡

*Values are given as the mean ± SD or No. (%), unless otherwise indicated. ACE-I = ACE-inhibitor; ARB = angiotensin-II receptor blocker; BMI = body mass index.

†Determined by *t* test.

‡Determined by χ^2 test.

Table 2

Echocardiographic Findings*

Variables	Control Subjects	No.	EOV Patients	No.	p Value
LVEF ≥ 0.40	19 (40)	47	19 (41)	46	0.93†
Stroke volume, mL/beat	80 ± 22	46	77 ± 29	45	0.36‡
Cardiac output, L/min	5.5 ± 1.5	46	5.5 ± 1.8	45	0.62‡
Cardiac index, L/min/m^2	2.7 ± 0.17	45	2.7 ± 0.8	44	0.41‡
LVEDd, mm	62 ± 11	47	60 ± 12	45	0.38‡
Left atrial volume, mL	71 ± 27	42	90 ± 38	43	0.01‡
Mitral E-wave velocity, m/s	0.8 ± 0.3	44	1.0 ± 0.4	44	0.02‡
Pulmonary vein diastolic velocity, m/s	0.5 ± 0.2	39	0.6 ± 0.2	34	0.009‡
Right atrial pressure, mm Hg	7.6 ± 3.7	36	9.9 ± 5.2	30	0.04‡
RV systolic pressure, mm Hg	38 ± 15	36	46 ± 17	40	0.02‡

*Values are given as No. (%) or the mean ± SD, unless otherwise indicated. LVEDd = left ventricular end-diastolic diameter; RV = right ventricular.

†Determined by χ^2 test.

‡Determined by *t* test.

Table 3
Rest and Exercise Heart Rate, BP, and Symptoms*

Variables	Control Subjects (n = 47)	EOV Patients (n = 47)	p Value†
Rest			
HR, beats/min	74 ± 13	73 ± 14	0.58
Systolic BP, mm Hg	105 ± 16	110 ± 21	0.32
Diastolic BP, mm Hg	67 ± 11	69 ± 11	0.22
Peak exercise			
HR, beats/min	131 ± 29	112 ± 25	0.002
Systolic BP, mm Hg	133 ± 34	130 ± 34	0.75
Diastolic BP, mm Hg	69 ± 15	64 ± 12	0.07
RPE, Borg scale	17 ± 2	18 ± 2	0.38
Duration, min	7.5 ± 2.9	5.9 ± 2.1	0.006

*Values are given as the mean ± SD, unless otherwise indicated. HR = heart rate; RPE = rating of perceived exertion.

†Determined by *t* test.

Table 4
Measured Parameters of Ventilation and Gas Exchange at Rest and Exercise*

Variables	Control Subjects (n = 47)	EOV Patients (n = 47)	p Value†
Rest			
$\dot{V}O_2$, mL/kg/min	3.9 ± 1.2	4.1 ± 1.1	0.34
$\dot{V}CO_2$, L/min	0.31 ± 0.11	0.31 ± 0.11	0.99
$\dot{V}_E$, L/min	12 ± 4.2	14 ± 5.1	0.23
V_T, L	0.79 ± 0.51	0.72 ± 0.29	0.84
fb, breaths/min	17 ± 4.7	20 ± 4.4	< 0.001
P_{ETCO_2}, mm Hg	33 ± 3.3	31 ± 4.3‡	0.02
$\dot{V}_E/\dot{V}CO_2$	40 ± 4.7	45 ± 7.5	0.002
50% peak exercise			
$\dot{V}O_2$, mL/kg/min	10 ± 2.9	8.6 ± 3.0	0.005
$\dot{V}CO_2$, L/min	0.71 ± 0.25	0.61 ± 0.22	0.04
$\dot{V}_E$, L/min	24 ± 7.5	25 ± 8.7	0.84
V_T, L	1.1 ± 0.4	1.0 ± 0.3	0.03
fb, breaths/min	21 ± 4.7	26 ± 5.8	< 0.001
P_{ETCO_2}, mm Hg	35 ± 4.0	31 ± 4.5	< 0.001
$\dot{V}_E/\dot{V}CO_2$	34 ± 5.6	41 ± 6.8	< 0.001
Peak exercise			
$\dot{V}O_2$, mL/kg/min	20 ± 7.5	16 ± 5.2	0.01
$\dot{V}CO_2$, L/min	1.9 ± 0.87	1.4 ± 0.56	0.01
$\dot{V}_E$, L/min	61 ± 25	57 ± 20	0.66
V_T, L	1.9 ± 0.7	1.7 ± 0.6	0.06
fb, breaths/min	32 ± 5.5	35 ± 7.1	0.08
P_{ETCO_2}, mm Hg	34 ± 5.3	30 ± 5.0‡	< 0.001
$\dot{V}_E/\dot{V}CO_2$	34 ± 6.6	40.2 ± 7.8	< 0.001
RER	1.1 ± 0.12	1.1 ± 0.13	0.08

*Values are given as the mean ± SD, unless otherwise indicated. fb = breathing frequency; RER = respiratory exchange ratio

†Determined by *t* test.

‡p = 0.03 for comparison of P_{ETCO_2} (within group) from rest to peak exercise.