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Respiratory symptom perception during exercise in patients with heart failure with preserved ejection fraction

Josh T. Goh[a,b,1], **Bryce N. Balmain**[a,b,1], **Andrew R. Tomlinson**[a,b], **James P. MacNamara**[a,b], **Satyam Sarma**[a,b], **Thomas Ritz**[c], **Denis J. Wakeham**[a,b], **Tiffany L. Brazile**[a,b], **Linda S. Hynan**[d], **Benjamin D. Levine**[a,b], **Tony G. Babb**[a,b,*]

[a]Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital Dallas, Dallas, TX, USA

[b]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA

[c]Department of Psychology, Southern Methodist University, Dallas, TX, USA

[d]The O'Donnell School of Public Health and Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX, USA

Abstract

We investigated whether central or peripheral limitations to oxygen uptake elicit different respiratory sensations and whether dyspnea on exertion (DOE) provokes unpleasantness and negative emotions in patients with heart failure with preserved ejection fraction (HFpEF). 48 patients were categorized based on their cardiac output ($\dot{Q}c$)/oxygen uptake ($\dot{V}O_2$) slope and stroke volume (SV) reserve during an incremental cycling test. 15 were classified as centrally limited and 33 were classified as peripherally limited. Ratings of perceived breathlessness (RPB) and unpleasantness (RPU) were assessed (Borg 0–10 scale) during a 20 W cycling test. 15 respiratory sensations statements (1–10 scale) and 5 negative emotions statements (1–10) were subsequently rated. RPB (Central: 3.5±2.0 vs. Peripheral: 3.4±2.0, p=0.86), respiratory sensations, or negative emotions were not different between groups (p>0.05). RPB correlated (p<0.05) with RPU (r=0.925), "anxious" (r=0.610), and "afraid" (r=0.383). While DOE provokes elevated levels

*Correspondence to: Institute for Exercise and Environmental Medicine, 7232 Greenville Ave, Dallas, TX 75231, USA. DrTonyBabb@TexasHealth.org (T.G. Babb).

[1]These authors contributed equally and are co-first authors.

CRediT authorship contribution statement

James P MacNamara: Writing – review & editing, Visualization, Validation, Supervision, Project administration. **Satyam Sarma:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Funding acquisition. **Thomas Ritz:** Writing – review & editing, Validation, Methodology, Formal analysis. **Denis J Wakeham:** Writing – review & editing, Validation, Project administration. **Tiffany L Brazile:** Writing – review & editing, Project administration. **Linda S Hynan:** Writing – review & editing, Software, Resources, Formal analysis, Data curation. **Benjamin D Levine:** Writing – review & editing, Validation, Software, Resources, Project administration, Investigation, Funding acquisition. **Tony G Babb:** Writing – review & editing, Validation, Supervision, Software, Resources, Project administration, Investigation, Funding acquisition, Formal analysis, Data curation. **Josh T Goh:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Bryce N Balmain:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Andrew R Tomlinson:** Writing – review & editing, Visualization, Validation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

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of negative emotions, DOE and respiratory sensations seem more related to a common mechanism rather than central and/or peripheral limitations in HFpEF.

Keywords

HFpEF; Dyspnea; Respiratory sensations; Exercise

1. Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) is the fastest growing form of HF and has become a major public health concern (Shah et al., 2020). The pathophysiology of HFpEF is complex, and several efforts have been made to identify specific phenotypes of patients with HFpEF based on clinical symptoms/markers (Rucker and Joseph, 2022). However, fewer studies have attempted to define distinct HFpEF phenotypes based on physiological limitations to exercise (Houstis et al., 2018; Shah et al., 2016). While we have previously characterized the relative contribution of central (e.g., cardiopulmonary) and peripheral (e.g., vascular and/or skeletal muscle) determinants of oxygen uptake to exercise limitation in these patients, currently it is unclear how central and/or peripheral limitations to oxygen uptake contribute to dyspnea on exertion (DOE), which is the primary chronic symptom of all patients with HFpEF (Obokata et al., 2018; Balmain et al., 2023).

DOE can be described as a subjective experience of breathing discomfort that varies in intensity (Parshall et al., 2012). In addition to intensity, DOE also encompasses qualitatively distinct respiratory sensations that are the result of a series of processes including neural activation, integration, and interpretation (Banzett et al., 2000; Davenport and Vovk, 2009; Bernhardt and Babb, 2016; Burki and Lee, 2010). Previous work has shown that healthy individuals and patients with chronic conditions (e.g., HF, COPD, neuromuscular weakness) who experience DOE can be distinguished based on their qualitative respiratory sensations of dyspnea (Mahler et al., 1996; Simon et al., 1990), regardless of the intensity of the sensation. Related, others have also used the multidimensional dyspnea assessment during cardiopulmonary exercise testing in various populations (e.g., healthy younger and older individuals, patients with COPD, patients with unexplained dyspnea) to provide further insight into whether certain exertional symptom perceptions can be explained by specific disease-related or physiological processes (Lewthwaite and Jensen, 2021; Lewthwaite et al., 2021; Phillips et al., 2021; Zhang et al., 2020; Balmain et al., 2020). Moreover, DOE can also be described in terms of affective distress, which reflects the unpleasantness and negative emotions associated with the intensity of the stimulus (Mahler and O'Donnell, 2015). An increased perception of unpleasantness or negative emotions provoked by DOE could be an important factor contributing to physical activity avoidance (Mahler and O'Donnell, 2015; Marines-Price et al., 2019), which may negatively impact patients' daily living, functional independence, and quality of life.

To date, DOE has been poorly evaluated and quantified in patients with HFpEF. While the intensity of DOE may be increased in patients with HFpEF, it is unknown if central or peripheral limitations that are prevalent in these patients elicit different qualitative

respiratory sensations during exercise. It is also unknown whether the intensity of DOE is associated with any perceived unpleasantness or negative emotions in these patients. Since HFpEF can be comprised of multiple pathophysiological abnormalities that could provoke DOE (Balmain et al., 2023, 2022a, 2022b, 2022c; Hearon et al., 2019; Olson et al., 2016; Melenovsky et al., 2014; Sarma et al., 2020a), such information on whether respiratory sensations differ between HFpEF patients with a central vs. peripheral limitation, and whether DOE is associated with any unpleasantness or negative emotions, could provide insight into the origin of DOE and inform effective management of dyspneic symptoms in these patients.

Therefore, the purpose of the present study was to investigate whether differences exist in the quantitative and qualitative respiratory sensations of dyspnea during constant-load exercise between HFpEF patients with primarily a central limitation vs. HFpEF patients with primarily a peripheral limitation and investigate the relationship(s) between DOE and unpleasantness and negative emotions (i.e., depression, anxiety, frustration, anger, and afraid) during constant-load exercise.

2. Methods

This was a retrospective analysis of previously collected data. Although some of these data have been published elsewhere (Balmain et al., 2023, 2022a, 2022b, 2022c; Babb et al., 2023), we repeat only the methods and data essential to the new findings presented herein.

2.1. Participants

We evaluated 48 patients with HFpEF who were enrolled in our larger ongoing study (NCT04068844). Patients with HFpEF were included if they were over the age of 55 years, had signs and symptoms of heart failure based on Framingham criteria (Lofstrom et al., 2019), an ejection fraction ≥50%, and evidence of pulmonary congestion confirmed by hospitalization requiring intravenous diuretics, pulmonary edema by chest x-ray, elevated NT-proBNP (>900 pg/mL), or a PCWP of ≥25 mmHg at peak exercise or an increase in PCWP ≥15 mmHg from rest to peak exercise. Participants were excluded if they had severe valvular heart disease, congenital heart disease, left bundle branch block, known restrictive or infiltrative cardiomyopathy, acute myocarditis, NYHA Class IV chronic heart failure or chronic heart failure that cannot be stabilized on medical therapy, a prior ejection fraction <50%, manifest/provocable ischemic heart disease, chronic kidney disease stage IV or greater, significant obstructive lung disease (i.e., forced expiratory volume in 1 second [FEV_1] <40% predicted), or regularly used phosphodiesterase inhibitors (e.g., sildenafil or tadalafil). Prior to all testing, written and informed consent was obtained. The experimental procedures were reviewed and approved by the UT Southwestern Medical Center Institutional Review Board (Reference no: STU2019–0617).

2.2. Study design

Participants visited the laboratory on two separate occasions. During the first visit, participants underwent preparticipation health screening (i.e., medical Hx), which included completing the modified Medical Research Council (mMRC) questionnaire to

characterize symptom burden, body composition scans (dual x-ray absorptiometry, GE), pulmonary function testing according to ATS/ERS guidelines (Graham et al., 2019) (i.e., spirometry, lung volumes, DLCO, and maximal voluntary ventilation manoeuvres), and a maximal exercise-echocardiography cardiopulmonary exercise test to exclude provocable ischemia. During the second visit, patients underwent pulmonary artery and radial artery catheterizations, and performed a six-minute constant-load cycling test (at 20 W) and a maximal incremental cycling test (data not shown) on an upright cycle ergometer (Lode BV, Groningen, the Netherlands), as described previously (Balmain et al., 2023).

2.3. Catheterization protocol

Catheterizations were performed as described previously (Balmain et al., 2023, 2022a, 2022b, 2022c). Briefly, all patients had a 6 French Swan-Ganz catheter placed in the pulmonary artery via brachial or antecubital vein access under fluoroscopic guidance. Pulmonary artery pressure (PAP) and PCWP were measured at the end of expiration at rest and during the final minute of constant-load exercise. PCWP position was verified by observation of typical waveforms. All participants also underwent radial artery catheterization using a modified Seldinger technique. Arterial and mixed venous blood samples were collected at rest and during constant-load cycling. The samples were directly placed in an ice bath and immediately analyzed specifically for partial pressure of O_2 (P_aO_2) and CO_2 (P_aCO_2), arterial and venous O_2 content (vol%), hemoglobin O_2 saturation (HbO_2%), lactate, and pH (ABL90 FLEX blood gas analyzer, Radiometer). All blood samples were corrected for central blood temperature and reference gases and commercial standards were used to calibrate the blood gas analyzer before all testing.

2.4. Cardiorespiratory responses

Heart rate (HR) and rhythm were monitored continuously using a 12-lead electrocardiogram. Blood pressure was monitored via arterial waveform tracings. Gas exchange, including ventilation ($\dot{V}_E$), oxygen uptake ($\dot{V}O_2$), and carbon dioxide elimination ($\dot{V}CO_2$), was measured using a customized breath-by-breath measurement system (Beck Integrative Physiological System, BIPS; KCBeck, Physiological Consulting, Liberty, UT, USA) integrated with a mass spectrometer (Perkin-Elmer, model 1100). These measurements were made at rest, during the final minute of constant-load cycling, and at peak exercise (data not shown).

2.5. Measurement of exertional symptoms, respiratory sensations, and negative emotions

Before the constant-load cycling test, participants were given detailed written instructions for rating the intensity of perceived breathlessness (RPB, 0–10 Borg scale), unpleasantness of breathlessness (RPU, 0–10 Borg scale), and exertion (RPE, 6–20 Borg scale). These instructions were followed up with a verbal confirmation of their understanding of the rating process. These measurements were made at rest (except for RPE) and during the final minute of constant-load cycling. Following the constant-load cycling test, patients completed a dyspnea questionnaire to examine the quality of their respiratory sensations if their RPB >0. Subjects rated 15 respiratory sensations statements (1–10 scale), which

were adapted from Mahler et al (Mahler et al., 1996). Subjects also rated another 5 negative emotions statements (1–10 scale), which permitted the investigation of potential relationships between RPB and unpleasantness and negative emotions (i.e., depression, anxiety, frustration, anger, and afraid) during constant-load exercise.

2.6. Derived parameters

Cardiac output ($\dot{Q}c$) was determined by the direct Fick method (i.e., $\dot{Q}c=\dot{V}O_2/a\text{-}vO_2$ difference), where a-vO_2 difference was calculated as the difference between arterial and venous O_2 content. Stroke volume (SV) was determined as the quotient of $\dot{Q}c$ and HR. Pulmonary vascular resistance (PVR) was calculated as: (mean PAP-PCWP)/$\dot{Q}c$. We also calculated the dead space to tidal volume ratio (V_D/V_T) using the Enghoff modification of the Bohr equation as previously described (Balmain et al., 2022a). The $\dot{V}_E/\dot{V}CO_2$ slope was calculated as the slope of the relation between the rest-to-20 W change in $\dot{V}_E$ and the rest-to-20 W change in $\dot{V}CO_2$ (Balmain et al., 2022a).

2.7. Categorization of HFpEF patients

After the exercise test, all patients were categorized based on their $\dot{Q}c/\dot{V}O_2$ slope and SV reserve. The $\dot{Q}c/\dot{V}O_2$ slope was calculated as the slope of the relation between $\dot{Q}c$ and $\dot{V}O_2$ measured at rest, constant-load cycling, and peak exercise. SV reserve was calculated as: $([SV_{\text{constant-load cycling}} - SV_{rest}]/SV_{rest}) \times 100$. Patients with a $\dot{Q}c/\dot{V}O_2$ slope <5 (i.e., indicating insufficient cardiac reserve (Chomsky et al., 1996), or a $\dot{Q}c/\dot{V}O_2$ slope between 5 and 6 and a SV reserve <50%, were classified as having primarily a central limitation. Patients with a $\dot{Q}c/\dot{V}O_2$ slope >6 (i.e., indicating sufficient cardiac reserve (Chomsky et al., 1996), or a $\dot{Q}c/\dot{V}O_2$ slope between 5 and 6 and a SV reserve >50%, were classified as having primarily a peripheral limitation.

2.8. Statistical analysis

Data were analyzed using SPSS 22.0 (SPSS, Chicago, IL). Between group differences (central limitation vs. peripheral limitation) in outcome variables were analyzed by independent t-tests at rest and during constant-load cycling. Comparisons were not made between conditions (i.e., rest vs. 20 W). Assumptions of normality were assessed using the Shapiro-Wilk test (in addition to an examination of Q-Q plots). The Shapiro-Wilk test was nonsignificant for independent t tests, indicating that the data did not deviate significantly from a normal distribution. Relationships between variables were assessed with Pearson Correlation Coefficients. Statistical significance was defined as $p<0.05$. Regarding reference equations, we used Hankinson et al., 1999 for spirometry, Goldman and Becklake 1959 for lung volumes, Burrows et al., 1961 for diffusing capacity, and Jones 1988 for predicted peak $\dot{V}O_2$. All data are presented as mean±SD.

3. Results

3.1. Patient characteristics

48 patients with HFpEF were evaluated. Patient characteristics, including comorbidities and medications are displayed in Table 1. By design, the $\dot{Q}c/\dot{V}O_2$ slope was lower in patients

with a central limitation compared with those with a peripheral limitation (5.31±0.50 vs. 7.02±1.23, p<0.001). All patients were not smoking at the time of the study. 17 patients had a history of smoking (~26 pack-year history on average) and one patient had a prior lobectomy. 15 patients were classified as having primarily a central limitation (6 female and 9 male) and 33 patients were classified as having primarily a peripheral limitation (24 female and 9 male). Patients were similar in age, BMI, %body fat, and peak exercise capacity (i.e., $\dot{V}O_{2peak}$ in L/min, mL/min/kg, and as a percent of predicted value). Pulmonary function was also similar between groups. Cardiorespiratory, hemodynamic, and arterial blood gas (and derived parameters) responses at rest and during 20 W cycling are shown in Table 2. Briefly, and other than RER at 20 W cycling, no between-group differences were observed in cardiorespiratory, hemodynamic, or arterial blood gas (and derived parameters) responses at rest or 20 W.

3.2. Respiratory symptom perception

While all patients experienced moderate levels of DOE (i.e., an RPB of ~3–4 units on average) during upright cycling exercise at 20 W, RPB (Fig. 1, Panel A) and RPU (Fig. 1, Panel B) were not different between groups (both p>0.05). Nor were there any differences in the qualitative respiratory sensations of dyspnea experienced during exercise between the two groups (Table 3, all p>0.05). Lastly, there were also no differences in the negative emotions experienced as a result of the intensity of dyspnea during exercise between the two groups (Table 3, all p>0.05).

3.3. Correlations

To investigate the relationships between DOE and the affective distress due to DOE in these patients, we correlated RPB with RPU and negative emotions experienced during constant-load exercise. We found that RPB correlated with RPU (Fig. 2, Panel A), and feelings of anxiety (Fig. 2, Panel C) and being afraid (Fig. 2, Panel F). Furthermore, considering that obesity and gas exchange abnormalities (both of which can contribute to DOE) are common in HFpEF (Balmain et al., 2022a, 2022b; Sarma et al., 2020b; Obokata et al., 2017), we also investigated the relationships between the magnitude of obesity, pulmonary function, gas exchange, and DOE in these patients. Indeed, we found that % body fat correlated with FVC (Fig. 3, Panel A) and $\dot{V}_E$ as a percent of their maximum value (Fig. 3, Panel B), both of which correlated with RPB (Fig. 3, Panels C and D, respectively). As expected, V_D/V_T correlated with the $\dot{V}_E/\dot{V}CO_2$ slope (Fig. 4, Panel A), which also correlated with RPB (Fig. 4, Panel B). Lastly, we also found that DLCO (as a %predicted value) did not correlate with V_D/V_T (Fig. 5, Panel A), but correlated with the $\dot{V}_E/\dot{V}CO_2$ slope (Fig. 5, Panel B)

4. Discussion

The major findings of this study were: 1) though patients experienced moderate levels of DOE, there were no differences in RPB, RPU, or qualitative respiratory sensations of dyspnea between HFpEF patients with a central vs. peripheral limitation; 2) there were no between-group differences in the negative emotions experienced as a result of DOE; 3) RPB correlated with RPU, and emotions of anxiety and being afraid; 4) % body fat correlated with FVC and $\dot{V}_E$, which were also correlated with RPB; and 5) V_D/V_T correlated with the

$\dot{V}_E/\dot{V}CO_2$ slope, which also correlated with RPB. Our findings suggest that while DOE can provoke elevated levels of negative emotions, DOE and respiratory sensations appear more related to pulmonary limitations, such as obesity-related changes in pulmonary function and/or underlying gas exchange abnormalities, than central and/or peripheral limitations in patients with HFpEF.

We demonstrated that patients with HFpEF experienced moderate levels of DOE (i.e., an RPB of ~3–4 units on average) during upright cycling exercise at 20 W, which is considered to be higher than the upper limit of normal for a given work rate (Ekstrom et al., 2024). These findings are consistent with previous studies that also reported moderate levels of DOE (i.e., RPB of ~4.5 units on average) in patients with HFpEF, albeit during cycling at 20 W in the supine position (Obokata et al., 2018; Fermoyle et al., 2021). However, we did not observe a difference in DOE (i.e., RPB or RPU) between those patients with primarily a central limitation vs. those with primarily a peripheral limitation to oxygen uptake. Nor did we find any differences in the qualitative respiratory sensations of dyspnea experienced during exercise between these two HFpEF groups. Given that previous work has shown that healthy individuals and patients with chronic conditions who experience DOE can be distinguished based on their qualitative respiratory sensations of dyspnea (Mahler et al., 1996; Simon et al., 1990), our findings would, therefore, indicate that the mechanism of DOE could be from a common origin among the two HFpEF groups. Taken together, the findings of the present study suggest that the intensity of DOE and respiratory sensations experienced during exercise may not be related or specific to central and/or peripheral limitations to oxygen uptake in patients with HFpEF.

At present, the reason as to why RPB (and RPU) did not differ between the two HFpEF groups remains unclear. However, these findings could be related to the high prevalence of obesity in both patient groups in the present study (Table 1). Notably, more than 80% of patients with HFpEF have obesity, and obesity is an independent risk factor and a primary comorbidity for HFpEF (Kitzman et al., 2016; Ratchford et al., 2022). We have (Balmain et al., 2020) previously demonstrated that patients with obesity have similar, or even higher levels of DOE, compared with patients who are nonobese but have significant cardiovascular or respiratory limitations. Even in the absence of dyspnea-inducing comorbidities, obesity increases the risk of having a dyspnea diagnosis (Goh et al., 2023). We have also identified numerous obesity-related factors that could influence DOE in healthy adults and patients with HFpEF with obesity; these factors pertain to obesity-related breathing limitations and include decreased pulmonary function (Babb et al., 2023; Lazarus et al., 1998; Ray et al., 1983), altered respiratory mechanics (Babb et al., 2023; DeLorey et al., 2005), increased work of breathing (Babb et al., 2008; Sharp et al., 1964), altered ventilatory efficiency (Babb et al., 2023; Balmain et al., 2021), and increased metabolic demand of exercise (Babb, 1999). Thus, it is certainly possible that factors associated with obesity could be a potential cause of DOE in both HFpEF groups in the present study. The fact that %body fat correlated with FVC and $\dot{V}_E$, and that FVC and $\dot{V}_E$ correlated with RPB in the present study, supports this suggestion.

Moreover, there is a growing body of evidence showing that patients with HFpEF exhibit increased $\dot{V}/\dot{Q}$ mismatch and ventilatory inefficiency when compared with control

participants (Balmain et al., 2023, 2022a; Van Iterson et al., 2017). Indeed, we observed an increased V_D/V_T and an increased $\dot{V}_E/\dot{V}CO_2$ slope relative to what we (Balmain et al., 2022a), and others (Sun et al., 2002), have previously reported in healthy older individuals. However, no differences were observed in these parameters between those with primarily a central limitation vs. those with primarily a peripheral limitation in the present study, suggesting that ventilatory demand during exercise was similar between groups. We also demonstrated that V_D/V_T correlated with the $\dot{V}_E/\dot{V}CO_2$ slope, which also correlated with RPB. Although the association between the $\dot{V}_E/\dot{V}CO_2$ slope and RPB was relatively weak, we cannot rule out the possibility that the magnitude of $\dot{V}/\dot{Q}$ mismatch and ventilatory inefficiency (and thus, ventilatory demand) played a role in provoking DOE in these patients. Similar findings have been reported in patients with pulmonary hypertension and patients with COPD and HF (Rocha et al., 2017; Neder et al., 2022). Further support for the hypothesis that a gas exchange impairment could explain, in part, the intensity of DOE is that DLCO (as a %predicted value) correlated with the magnitude of ventilatory demand (i.e., the $\dot{V}_E/\dot{V}CO_2$ slope) in our patients.

We also found that the intensity of DOE was associated with increased levels of affective distress. This was evidenced by the fact that RPB correlated with feelings of unpleasantness, anxiety, and being afraid. These negative emotions are consistent with our previous work (Balmain et al., 2020) and others (Lewthwaite et al., 2021) who reported that DOE in patients with obesity and COPD induced greater feelings of unpleasantness, anxiety, and frustration. We have (Marines-Price et al., 2019) also previously demonstrated that DOE was associated with feelings of unpleasantness, anxiety, and fear in otherwise healthy adults with obesity. As such, these findings highlight that measurements of the affective distress associated with DOE are essential to obtain since the unpleasantness/negative emotions provoked by DOE are, indeed, not reflected simply by obtaining a single measurement of RPB.

Previous reports have suggested that in addition to physiological mechanisms that could explain an increased DOE, the origin of the perception of DOE could be, in part, related to psychophysiological mechanisms (Bernhardt and Babb, 2016). Indeed, the perception of dyspnea involves processes including neural activation, integration, and interpretation (Banzett et al., 2000; Davenport and Vovk, 2009; Bernhardt and Babb, 2016; Burki and Lee, 2010). It has been proposed that a gating system, known as affective processing, regulates how afferent respiratory information is associated with negative emotions (O'Donnell et al., 2007). This is an integral component for determining the emotional response to DOE, which can be largely related to individuals' past experiences/expectations (Gerlach et al., 2013). Notably, these neural mechanisms deserve further study in patients with HFpEF, particularly since the affective distress component of DOE could negatively affect patients' willingness to engage in physical activity (Lansing et al., 2009). Such behaviour could significantly impact a patient's daily living, functional independence, and health-related quality of life.

5. Methodological considerations

One of the major strengths of the present study is that all testing was performed on a cycle ergometer in the upright position, which contrasts with the other HFpEF studies that have

measured dyspnea during exercise in the supine position (Obokata et al., 2018; Fermoyle et al., 2021). We must emphasize that the latter is not typical of how individuals perform physical activity and thus, supine exercise may not be an appropriate methodology to inform why patients become symptomatic when they are performing activities of daily living (in the upright position). Moreover, DOE was not quantified during an incremental exercise test. Rather, DOE was quantified during a submaximal constant-load cycling test that was performed for six minutes to account for the time delay between physiological adjustments to exercise load and the stabilization in perception (Bernhardt and Babb, 2016). This is an important consideration given that the temporal dynamics of respiratory sensations are slower to establish than those for physiological responses (Moosavi et al., 2004). Not only does a constant-load exercise test provide an adequate amount of time to ensure that the respiratory sensation(s) reach a temporal steady-state, a constant-load exercise test is also more reflective of the patient's symptom provoking activities of daily living. To that point, the exercise work rate was set at 20 W to represent the metabolic demands of activities of daily living. Performing the cycling test at 20 W also facilitates direct comparison with other HFpEF studies in the literature. Indeed, this representation of DOE, respiratory sensations, or negative emotions associated with DOE, cannot be achieved if the duration of the exercise stage is too short, the exercise intensity is too high, or if the intensity of the exercise stage is changed too often (e.g., incremental exercise test. Lastly, we acknowledge that dynamic operating lung volumes and critical inspiratory constraints were not assessed as part of this study.

6. Conclusion

Though patients experienced a moderate level of DOE, we demonstrated that RPB, RPU, qualitative respiratory sensations, and feelings of unpleasantness and negative emotions associated with the intensity of DOE did not differ between patients with primarily a central limitation vs. patients with primarily a peripheral limitation. We also demonstrated that %body fat correlated with FVC and $\dot{V}_E$, which were also correlated with RPB, and that V_D/V_T correlated with the $\dot{V}_E/\dot{V}CO_2$ slope, which was also correlated with RPB. These data have important clinical implications and suggest that while DOE can provoke elevated levels of negative emotions, DOE and respiratory sensations appear more related to pulmonary limitations, such as obesity-related breathing limitations and/or underlying gas exchange abnormalities, rather than central and/or peripheral limitations to oxygen uptake in patients with HFpEF. Overall, we suggest that health care providers should consider not only an assessment of the intensity of DOE, but also an assessment of the patient's "perception" of DOE, as these assessments together could provide insight into the origin of DOE and inform effective management of dyspneic symptoms in these patients.

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Data Availability

Data will be made available on request.

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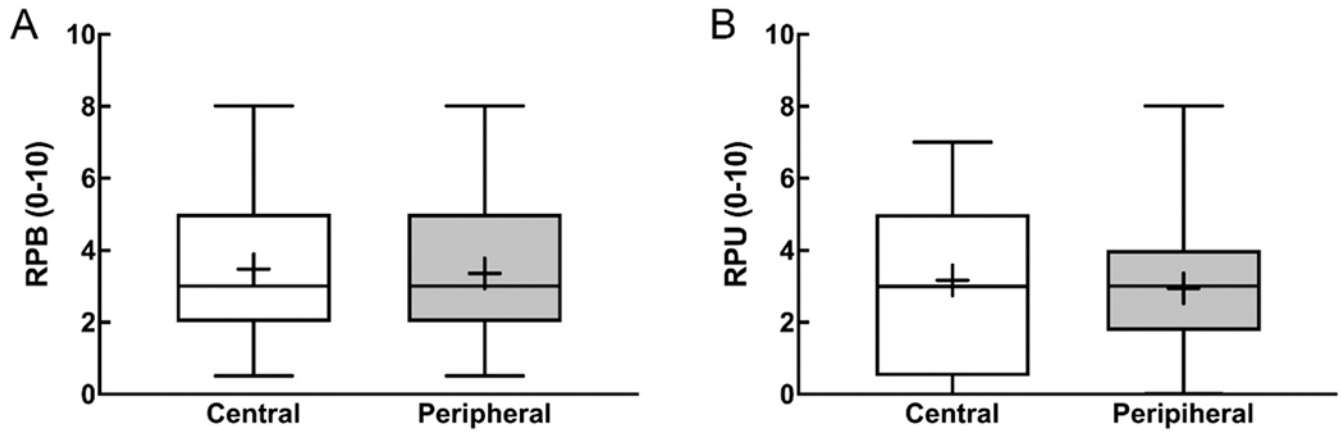

Fig. 1.

RPB (Panel A) and RPU (Panel B) measured at 20 W cycling in patients witH a primarily central limitation and patients with a primarily peripheral limitation. “+” = mean values.

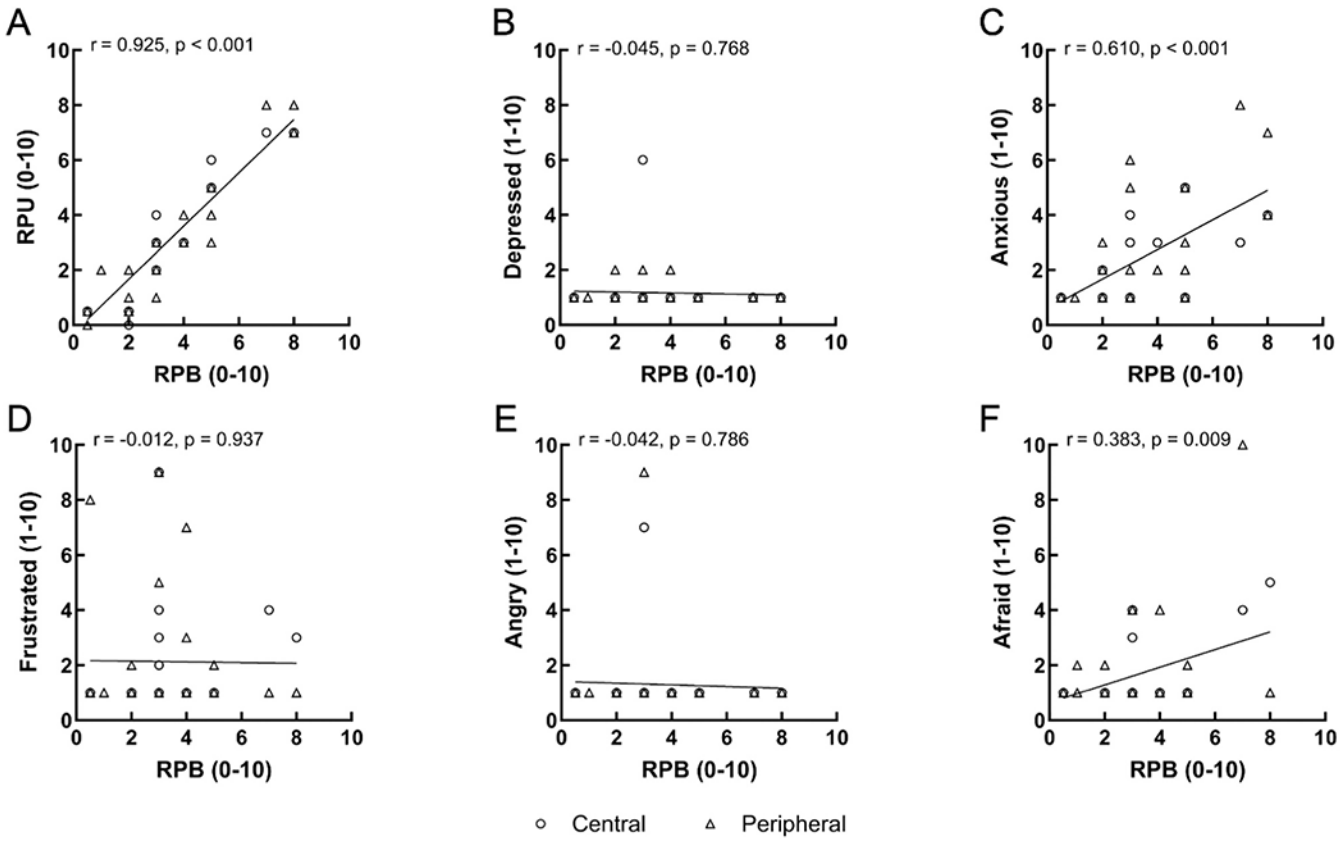

Fig. 2.

Correlation plots demonstrating the relationships between RPB and RPU (Panel A), and RPB and negative emotions (Panels B – F) during 20 W cycling in the total cohort of patients with HFpEF. Solid line indicates linear regression. Note that some data points are overlapping. Circles represent those patients with primarily a central limitation and triangles represent those patients with primarily a peripheral limitation.

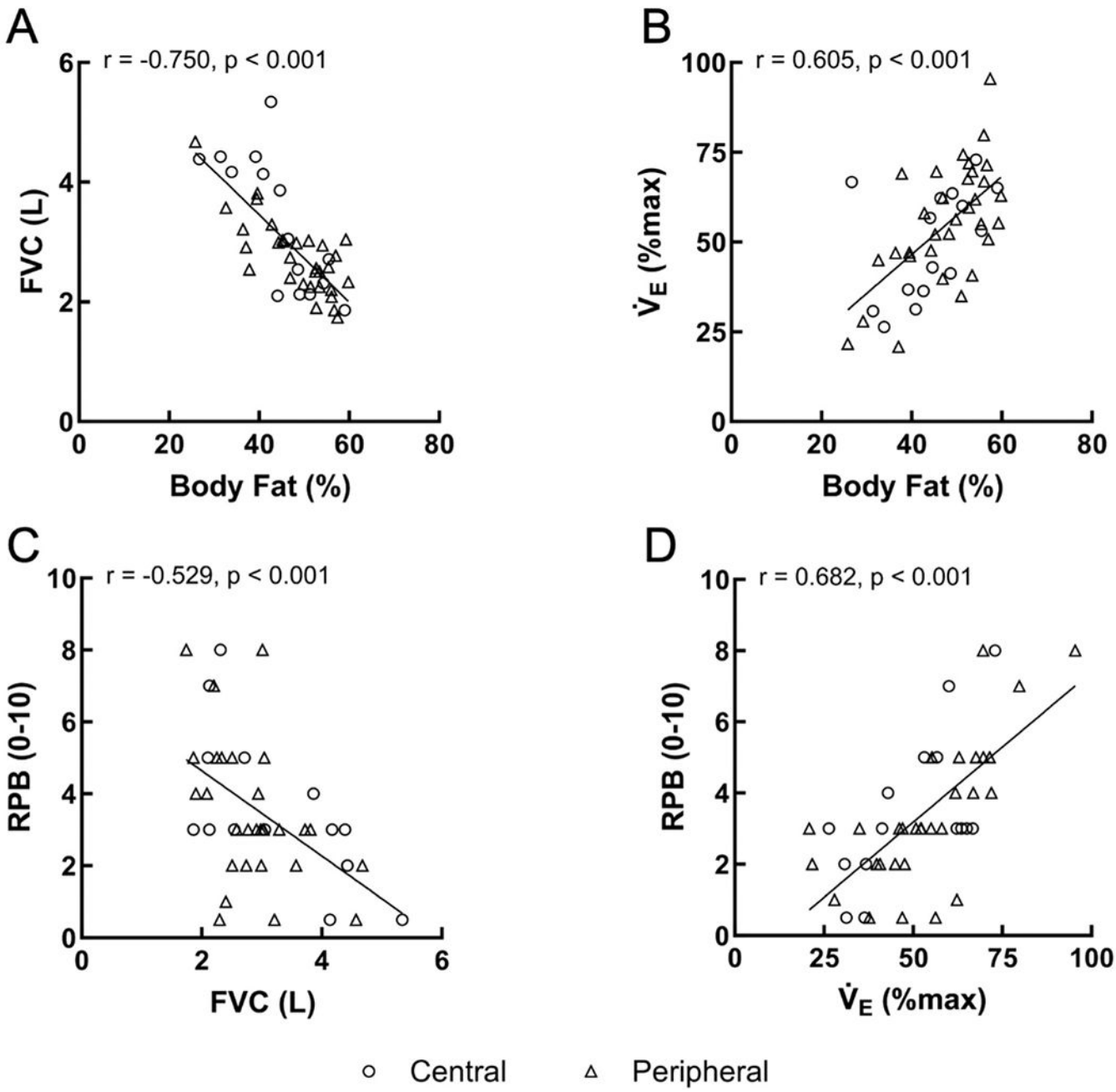

Fig. 3.

Correlation plots demonstrating the relationship between %body fat and FVC (Panel A), %body fat and $\dot{V}_E$ (Panel B), FVC and RPB (Panel C), and $\dot{V}_E$ and RPB (Panel D). Solid line indicates linear regression. Circles represent those patients with primarily a central limitation and triangles represent those patients with primarily a peripheral limitation.

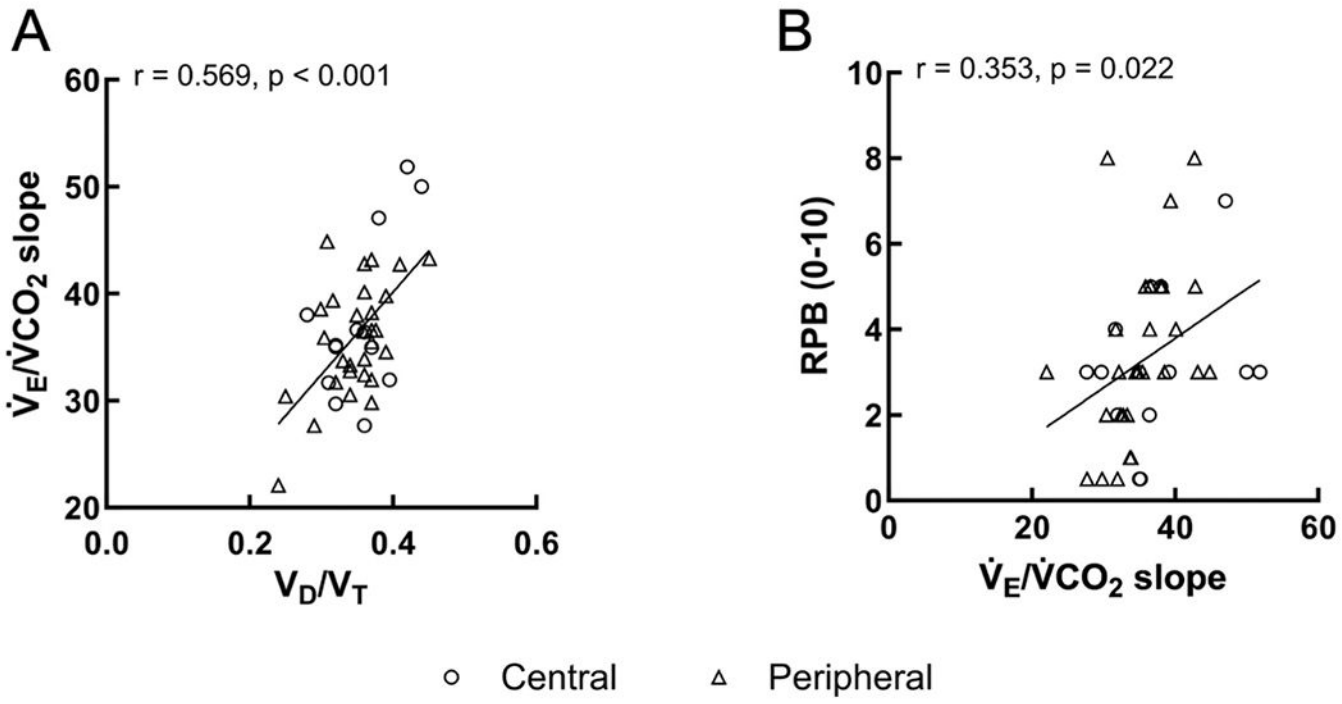

Fig. 4.

Correlation plots demonstrating the relationship between V_D/V_T and the $\dot{V}_E/\dot{V}CO_2$ slope (Panel A) and the relationship between the $\dot{V}_E/\dot{V}CO_2$ slope and RPB (Panel B). Solid line indicates linear regression. Circles represent those patients with primarily a central limitation and triangles represent those patients with primarily a peripheral limitation.

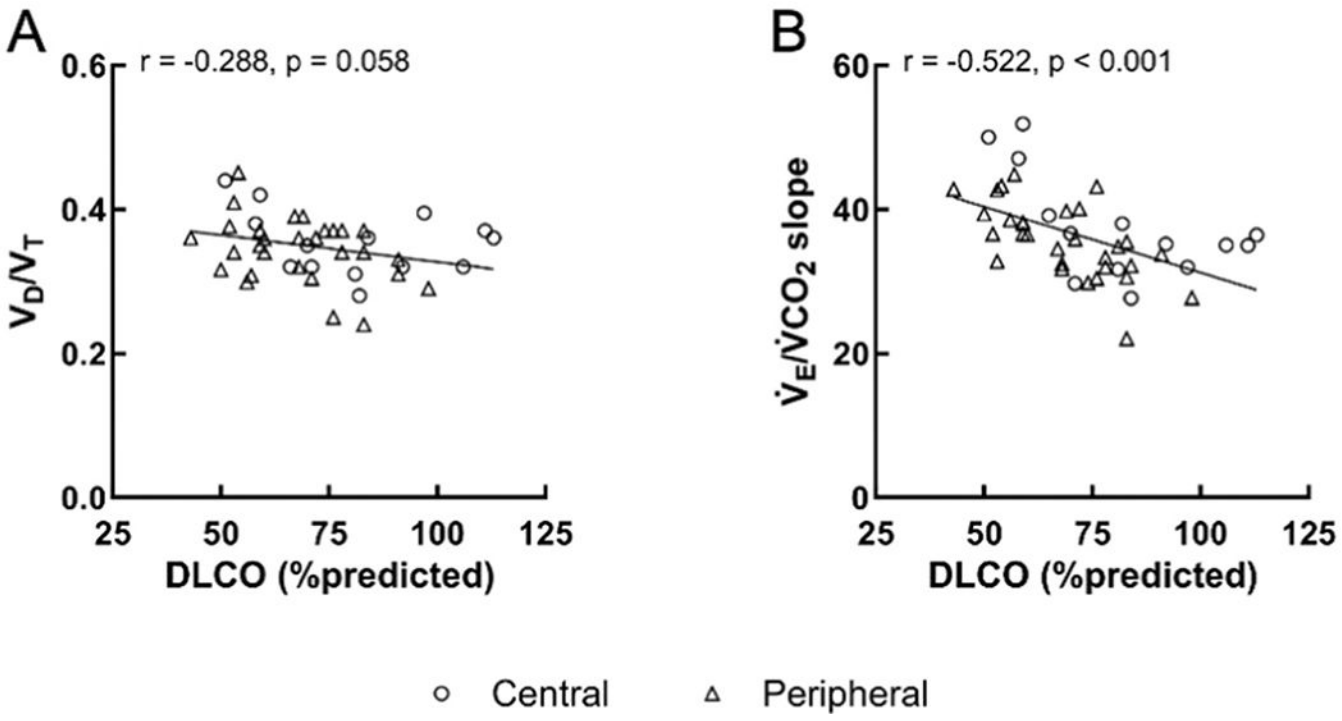

Fig. 5.

Correlation plots demonstrating the relationship between DLCO and V_D/V_T (Panel A) and DLCO and the $\dot{V}_E/\dot{V}CO_2$ slope (Panel B). Solid line indicates linear regression. Circles represent those patients with primarily a central limitation and triangles represent those patients with primarily a peripheral limitation.

Table 1

Patient characteristics.

	Central Limitation (n=15)	Peripheral Limitation (n=33)
Demographics and symptom burden		
Age (y)	70.9 ± 5.5	70.0 ± 7.0
Sex (female/male)	6/9	24/9
Height (cm)	171.4 ± 9.1	165.7 ± 9.2
Weight (kg)	103.7 ± 15.1	107.3 ± 19.1
BMI (kg/m^2)	35.5 ± 6.3	39.2 ± 7.1
mMRC score	1.7 ± 1.1	1.9 ± 0.9
$\dot{V}O_{2peak}$ (L/min)	1.5 ± 0.5	1.2 ± 0.3
$\dot{V}O_{2peak}$ (mL/min/kg)	14.0 ± 4.8	11.8 ± 2.8
$\dot{V}O_{2peak}$ (%predicted)	80.9 ± 20.5	73.1 ± 16.9
Peak Work Rate (W)	90 ± 40	72 ± 23
Body composition		
Body fat (%)	44.5 ± 8.8	47.7 ± 8.9
Total fat mass (kg)	45.6 ± 11.8	50.5 ± 15.0
Lean body mass (kg)	53.2 ± 9.5	50.8 ± 7.6
Visceral adipose tissue (kg)	3.2 ± 1.6	2.7 ± 1.1
Co-morbidities		
Hypertension (%)	93	100
Diabetes mellitus (%)	50	52
Atrial fibrillation (%)	50	24
Obstructive lung disease (%)	21	10
Obstructive sleep apnea (%)	79	69
Medications		
Beta blocker (%)	43	62
Calcium channel blocker (%)	14	21
Angiotensin converting enzyme inhibitor (%)	71	66
Loop diuretic (%)	79	79
Thiazide diuretic (%)	7	34
Aldosterone agonist (%)	29	28
Pulmonary function		
FVC (L)	3.3 ± 1.1	2.8 ± 0.7
FVC (%predicted)	86.0 ± 17.7	90.8 ± 15.4
FEV_1 (L)	2.3 ± 0.9	2.1 ± 0.6
FEV_1 (%predicted)	81.4 ± 21.3	90.0 ± 16.3
FEV_1/FVC (%)	70.6 ± 11.8	75.1 ± 7.6
MVV (L/min)	90.2 ± 35.1	78.1 ±21.6
MVV (%predicted)	84.6 ±23.1	84.3 ± 18.5
TLC (L)	5.6 ± 1.5	4.9 ± 1.0

	Central Limitation (n=15)	**Peripheral Limitation (n=33)**
TLC (%predicted)	96.6 ± 17.8	94.4 ± 12.6
FRC (L)	2.9 ± 1.0	2.4 ± 0.7
FRC (%predicted)	101.5 ± 29.2	103.6 ± 18.6
ERV (L)	0.6 ± 0.5	0.4 ± 0.4
RV (L)	2.2 ± 0.5	2.0 ± 0.5
RV (%predicted)	95.1 ± 22.4	90.8 ± 17.1
IC (L)	2.8 ± 0.8	2.4 ± 0.6
IC (%predicted)	93.1 ± 20.2	88.4 ± 20.6
DLCO (%predicted)	80.4 ± 19.2	68.9 ± 13.6
DLCO/V_A (%predicted)	106.1 ± 33.0	109.8 ± 23.3

Data are presented as mean ± SD, where appropriate. BMI = body mass index; DLCO = diffusing capacity of the lung for carbon monoxide; FEV_1 = forced expired volume in one second; FRC: functional residual capacity; IC: inspiratory capacity; FVC = forced vital capacity; MVV = maximal voluntary ventilation; mMRC: modified medical research council; RV: residual volume; TLC = total lung capacity; V_A = alveolar volume; $\dot{V}O_{2peak}$ = peak oxygen uptake.

Table 2

Cardiorespiratory, hemodynamic, and arterial blood gas measurements at rest and during exercise (20 W).

	Central Limitation (n=15)	Peripheral Limitation (n=33)
Rest		
$\dot{V}_E$ (L/min)	13.0 ± 2.6	11.9 ± 2.8
$\dot{V}O_2$ (L/min)	0.27 ± 0.06	0.24 ± 0.06
$\dot{V}CO_2$ (L/min)	0.22 ± 0.05	0.20 ± 0.06
$\dot{V}_E/\dot{V}CO_2$ ratio	61.5 ± 9.5	63.0 ± 12.2
RER	0.79 ± 0.04	0.80 ± 0.09
V_D/V_T	0.40 ± 0.05	0.38 ± 0.05
HR (beats/min)	77 ± 9	74 ± 17
$\dot{Q}c$ (L/min)	4.5 ± 1.1	4.4 ± 1.6
SV (mL/beat)	60 ± 19	60 ± 23
PCWP (mmHg)	7.3 ± 4.4	7.9 ± 3.6
Mean PAP (mmHg)	18.3 ± 6.7	17.4 ± 5.1
PVR (WU)	2.7 ± 1.5	2.3 ± 0.7
P_aO_2 (mmHg)	84.9 ± 8.3	85.7 ± 12.6
P_aCO_2 (mmHg)	39.0 ± 3.9	40.6 ± 5.1
a-vO_2 difference	6.3 ± 1.0	5.7 ± 1.0
HbO_2 (%)	95 ± 2	95 ± 2
pH	7.42 ± 0.02	7.42 ± 0.05
Lactate (mmol/L)	1.35 ± 0.74	1.15 ± 0.68
Exercise (20 W)		
W*R* (% peak)	27 ± 12	31 ± 11
$\dot{V}_E$ (L/min)	28.0 ± 3.5	28.3 ± 5.9
$\dot{V}O_2$ (L/min)	0.77 ± 0.14	0.78 ± 0.19
$\dot{V}CO_2$ (L/min)	0.63 ± 0.12	0.66 ± 0.16
$\dot{V}_E/\dot{V}CO_2$ ratio	45.6 ± 6.1	43.5 ± 5.6
$\dot{V}_E/\dot{V}CO_2$ slope (rest to 20 W)	37.5 ± 7.1	34.9 ± 6.5
RER	0.81 ± 0.04	0.84 ± 0.06 *
V_D/V_T	0.35 ± 0.04	0.35 ± 0.04
HR (beats/min)	91 ± 11	92 ± 16
$\dot{Q}c$ (L/min)	7.6 ± 1.8	8.5 ± 2.3
SV (mL/beat)	86 ± 27	93 ± 22
PCWP (mmHg)	18.2 ± 7.1	20.8 ± 8.6
Mean PAP (mmHg)	32.6 ± 9.2	34.6 ± 9.8
PVR (WU)	2.2 ± 1.2	1.7 ± 0.6
P_aO_2 (mmHg)	86.2 ± 10.1	84.6 ± 12.5

	Central Limitation (n=15)	**Peripheral Limitation (n=33)**
P_aCO_2 (mmHg)	39.8 ± 4.2	42.0 ± 4.1
a-vO_2 difference	10.5 ± 2.0	9.3 ± 1.1
HbO_2 (%)	95 ± 2	95 ± 3
pH	7.40 ± 0.02	7.40 ± 0.03
Lactate (mmol/L)	1.91 ± 0.72	2.01 ± 0.86

Data are presented as mean ± SD. 20 W = 20 watts; a-vO_2 difference = arteriovenous oxygen difference; HbO_2 = hemoglobin oxygen saturation; HR = heart rate; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; $\dot{Q}c$ = cardiac output; RER = respiratory exchange ratio; SV = stroke volume; V_D/V_T = physiologic dead space to tidal volume ratio; $\dot{V}_E$ = minute ventilation; $\dot{V}O_2$ = oxygen consumption; $\dot{V}CO_2$ = CO_2 elimination; WR = work rate.

* P<0.05.

Table 3

Respiratory descriptors and negative emotions.

	Central Limitation (n=15)	Peripheral Limitation (n=33)
Respiratory sensations (1–10)		
1. breath does not go in all the way	3.4 ± 1.9	3.0 ± 2.4
2. breathing requires effort	4.5 ± 2.1	4.4 ± 2.6
3. smothering	2.5 ± 2.2	2.2 ± 2.1
4. hunger for air	4.2 ± 3.1	3.2 ± 2.7
5. breathing is heavy	4.5 ± 2.7	3.7 ± 2.6
6. out of breath	4.8 ± 2.9	3.8 ± 3.0
7. chest feels tight	3.3 ± 2.6	1.9 ± 1.4
8. breathing requires work	4.1 ± 2.4	4.2 ± 2.6
9. suffocating	2.5 ± 2.4	2.1 ± 1.8
10. chest is constricted	3.3 ± 2.6	2.2 ± 2.4
11. breathing is rapid	3.6 ± 2.3	3.0 ± 2.7
12. breathing is shallow	2.9 ± 1.6	3.2 ± 2.6
13. breathing more	3.5 ± 2.0	4.2 ± 3.0
14. cannot get enough air	4.2 ± 3.2	3.8 ± 3.3
15. breath does not go out all the way	3.5 ± 2.5	2.3 ± 2.1
Negative emotions (1–10)		
Depressed	1.3 ± 1.2	1.2 ± 0.7
Anxious	2.6 ± 1.3	2.4 ± 1.9
Frustrated	2.3 ± 2.1	2.3 ± 2.5
Angry	1.4 ± 1.5	1.3 ± 1.4
Afraid	2.0 ± 1.5	1.5 ± 1.7

Data are presented mean ± SD.