Coupling of dyspnea perception and occurrence of tachypnea during exercise

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Abstract During exercise, tidal volume initially contributes to ventilatory responses more than respiratory frequency, and respiratory frequency then increases rapidly while tidal volume stabilizes. Dyspnea intensity is also known to increase in a threshold-like manner. We tested the possibility that the threshold of tachypneic breathing is equal to that of dyspnea perception during cycle ergometer exercise (n = 27). Dyspnea intensity was scored by a visual analog scale. Thresholds were expressed as values of pulmonary O₂ uptake at each breakpoint. Dyspnea intensity and respiratory frequency started increasing rapidly once the intensity of stimuli exceeded a threshold level. The thresholds for dyspnea intensity and for occurrence of tachypnea were significantly correlated. An intraclass correlation coefficient of 0.71 and narrow limits of agreement on the Bland–Altman plot indicated a good agreement between these thresholds. These results suggest that the start of tachypneic breathing coincides with the threshold for dyspnea intensity during cycle ergometer exercise.

Keywords Dyspnea · Exercise hyperpnea · Pulmonary O₂ uptake · Respiratory frequency · Tachypnea

Introduction

Respiratory output is primarily regulated by an autonomic metabolic control system in the brainstem to maintain blood gas homeostasis via reflex feedback pathways from chemoreceptors. The ventilatory responses to experimental challenges such as hypercapnia and exercise have been investigated to evaluate the capability of metabolic control to cope with an increased demand for pulmonary gas exchange. As a result, participants’ overall ventilation increases, depending on an individual’s unique responsiveness to the demand [1–3].

The mechanisms that control ventilation seem more complex during exercise than during hypercapnia. Although the primary driver of exercise hyperpnea is still controversial [4, 5], a feed-forward control mechanism [6] and reflex responses to afferent feedback from the periphery to the respiratory centers [7] are likely involved. Nevertheless, the depth and rhythm of breathing show a similar and stereotypical pattern in response to both increases in the level of hypercapnia and exercise intensity [3, 8, 9]. During both hypercapnia and exercise, breathing patterns comprise an initial increase in tidal volume (VT) and a subsequent rapid increase in respiratory frequency (fR) at the VT plateau. This tachypneic breathing occurs once the intensity of stimuli exceed a threshold level [8, 10]. Duffin et al. [3] referred to this as the breathing patterning threshold. This tachypneic pattern may result from reflexes mediated by pulmonary stretch receptors and chest wall receptors [11]. However, particularly in humans, mechanisms underlying this tachypneic pattern are still unclear [3, 12].

Exercise and hypercapnia increase overall ventilation with changes in breathing patterns, accompanied by differing levels of dyspnea [13, 14]. Dyspnea increases in a threshold-like manner against pulmonary O₂ uptake (VO₂)
during exercise and against the end-tidal CO$_2$ fraction during hypercapnia [15–18]. We have previously reported that the thresholds for dyspnea and $f_R$ are significantly correlated, and show a good agreement during gradual hypercapnia in healthy human participants [19]. In the previous paper, the intensity of dyspnea and $f_R$ both showed rapid increases that were virtually simultaneous at a similar level of CO$_2$. That is, changes in the subjective measure of dyspnea coincide with those in the objective measure of respiration, particularly the onset of tachypneic breathing during hypercapnia. Therefore, to extend our previous investigation [19], here we ask: does this subjective–objective coupling of respiratory variables reside in exercise hyperpnea?

In a series of recent human and animal research under conscious conditions, we have attempted to show that nonmetabolic factors play a part in alteration in the rhythm of breathing [19–21]. The $f_R$, rather than the $V_T$, is susceptible to the influence of nonmetabolic factors such as negative emotions [22]. Because dyspnea causes negative emotions [23], the rhythm of breathing is likely to be affected by dyspnea. Therefore, in the present study, we tested the possibility that the threshold of tachypneic breathing is equal to that of dyspnea perception during cycle ergometer exercise, as previously shown by hypercapnic stimuli [19]. We measured the ventilatory and dyspnea responses to increases in exercise intensity and compared the thresholds for dyspnea and objective respiratory variables. This straightforward approach succeeded in demonstrating a subjective–objective coupling of respiratory variables during exercise, by seeing the results from a new perspective concerning whether or not nonmetabolic factors contribute to alteration in the rhythm of breathing.

**Methods**

**Participants**

A total of 27 young adult males (mean age, 21.9 years) participated in this study. Participants gave written informed consent before participating in the experiments, which were approved by the Showa University Committee for Human Experimentation. The study conformed to the principles of the Declaration of Helsinki.

Of the 27 participants, 22 exercised at least once a week. We checked before the start of exercise to see whether the participant was healthy enough to pedal a cycle ergometer.

**Measurement of pulmonary gas exchange and ventilation**

The participants each wore a facemask. Ventilation and pulmonary gas exchange was measured with a respiratory monitor (Aeromonitor AE300, Minato Medical Science, Osaka, Japan). This monitor measured flow rate at the mouth with a hot-wire flow meter, and continuously calculated minute ventilation ($V_E$, l/min), $V_T$ (l), and $f_R$ (breaths/min). The monitor also measured (breath-by-breath) the fractions of O$_2$ and CO$_2$ in expired gas to determine VO$_2$ and pulmonary CO$_2$ output (VCO$_2$). The monitor was calibrated before each test.

**Measurement of dyspnea intensity**

The intensity of dyspnea was measured using a 100-mm horizontal visual analog scale (VAS) with the maximum feeling of dyspnea on the right side and the feeling of no dyspnea on the left side of the scale [19]. A piece of paper displaying the VAS was presented to the participants every 2 min (Fig. 1). This means that dyspnea intensity was measured immediately before the start of exercise (3 min), in the middle of each level of exercise (5, 9, and 13 min), immediately before the time of change in exercise intensity (7 and 11 min), and immediately before the cessation of exercise (15 min) (Fig. 1). The participants made a mark on the scale at each time point using a pen, and were not allowed to see their previous scores during each test.

**Exercise**

The intensity of dyspnea and the breathing pattern were measured during cycle ergometer exercise (Fig. 1). Exercise testing was performed on an electrically braked bicycle ergometer. The participants sat on the seat of the ergometer and kept their feet on the pedals for a 3-min rest.
period, during which we measured baseline values of the respiratory parameters. After the 3-min rest period, the participants started exercise at an initial work rate of 50 W, which was increased in a stepwise manner by 50 W every 4 min to 150 W. All participants completed the testing.

Breath-by-breath VCO₂, VE, fr, and VT were plotted against VO₂ during offline analysis. However, dyspnea VAS was not measured in a breath-by-breath way because it was scored at 2-min intervals. Therefore, individual VAS scores were plotted against VO₂ at the corresponding time, which was predicted by regression analysis between time and VO₂ in each participant (Fig. 1). The baseline VAS score was plotted against mean VO₂ at rest for offline analysis.

**Thresholds for dyspnea and respiratory variables**

Commercial software was used for analyses (SigmaPlot 12, SYSTAT, Chicago, IL, USA). Each plot was fitted with a segmented linear regression model composed of two segments connected by a breakpoint to predict the thresholds for dyspnea (Tvias), VCO₂ (Tvc02), VE (Tve), fr (Tr), and VT (Tvt) [19]. Dyspnea VAS, VCO₂, VE, and fr began to increase rapidly at the breakpoint. However, Tvt was determined separately where the regression slope started to decrease. The thresholds were taken as VO₂ values at the breakpoint.

**Assessment of agreement**

We used intraclass correlation coefficients (ICC) and Bland–Altman plots to measure the agreement between the thresholds of the subjective (Tvias) and objective variables (Tvc02, Tve, Tr, and Tvt). The agreement between the thresholds was tested by the ICC using two-way random single measures with absolute agreement [24] (IBM SPSS Statistics 23; IBM Corp., Armonk, NY, USA). The level of clinical significance is considered poor agreement, fair agreement, good agreement, and excellent agreement when ICC < 0.40, 0.40 < ICC < 0.59, 0.60 < ICC < 0.74, and 0.75 < ICC < 1.00, respectively [25]. In addition to the agreement, Pearson correlation analyses were performed (Prism 6; GraphPad software Inc., La Jolla, CA, USA). The Bland–Altman plot is typically used to assess the level of agreement between measurements derived from two different methods [26]. In this plot, the within-participant differences between the two methods (Y-axis) are plotted against the mean of both methods (X-axis). This plot provides “95 % limits of agreement” as the mean value for the within-participant difference ±2 standard deviations. The 95 % limits of agreement indicate graphically how well the two methods agree. The 95 % confidence interval (CI) of the mean within-participant difference is calculated to detect systematic bias, and linear regression analysis between the within-participant differences and the mean of both methods is used to show proportional bias (Prism 6; GraphPad software Inc.). A study exploring the relationship between the threshold for dyspnea and the ventilatory threshold during exercise used this plot and showed similarities between these thresholds [17].

**Statistics**

The mean values of the threshold were compared with one-way repeated measures analysis of variance. Post hoc comparisons were performed using Dunnett’s test (Prism 6; GraphPad software Inc.). For all analyses, significance was recorded at P < 0.05. All values are presented as mean ± SE.

**Results**

**Predicted VO₂ at the time of dyspnea measurement**

Participants performed incremental exercise starting at a work rate of 50 W, which was increased by 50 W every 4 min to 150 W. Breath-by-breath VO₂ values before and during exercise in a representative participant are shown in Fig. 1. After the onset of exercise, VO₂ increased stepwise at the beginning and then almost linearly with time, even though the work rate increased in a stepwise manner. In the present study, we planned to present the thresholds as the VO₂. However, we measured dyspnea intensity in a time-based manner. Linear trends of VO₂ with time, as shown in this representative participant, were confirmed in all participants. Therefore, VO₂ at each time predicted by the regression analysis between time and breath-by-breath VO₂ was sufficient to estimate Tvias, which was taken as the VO₂.

**Excluded participants**

This experiment was performed in 27 participants, but five participants were excluded from the final analysis because their responses differed from the typical breathing patterns, which comprise an initial increase in V'r and a subsequent increase in fr. One participant was excluded because fr started to increase immediately after the onset of exercise. In four participants, the segmented linear regression could not detect a breakpoint in any of the five variables, primarily because of data scattering. Accordingly, data from 22 participants were included in the statistical analyses.
Single participant

Typical examples from one participant are shown in Fig. 2a. The participant is the same person for whom results are shown in Fig. 1. In this participant, the intensity of dyspnea started to increase rapidly at a VO$_2$ of 13.4 ml/min/kg ($T_{\text{VAS}}$), as estimated by the segmental linear regression model. $T_{\text{VCO}_2}$, which is comparable to the ventilatory threshold, determined by plotting VO$_2$ and VCO$_2$, was 12.0 ml/min/kg. For $T_{\text{VE}}$, the slope was steeper after than before the threshold in all of the 22 participants eligible for the statistical analyses. The $T_{\text{VE}}$ of this participant was 14.7 ml/min/kg. The $f_R$ increased bifphasically, similar to the intensity of dyspnea. During the initial phase, $f_R$ increased gradually and then rapidly after reaching the threshold. $T_{\text{IR}}$ was a VO$_2$ of 16.9 ml/min/kg in this participant. Although $V_T$ changed in a biphasic manner, the response showed an initial rapid increase and subsequently reached a plateau. $T_{\text{VT}}$, where the slope became less steep, was estimated to be 17.9 ml/min/kg.

Comparison of mean values of the thresholds

The mean regression lines and breakpoints for the 22 participants showed a similar trend to the results for a typical participant (Fig. 2b). Two regression lines were constructed for each variable in each participant, and they lay on either side of the threshold. For dyspnea VAS, $f_R$, $V_E$, and VCO$_2$, the regression slope was smaller before the threshold than after the threshold in all 22 participants. For $V_T$, the regression slope was larger before $T_{VT}$ than after $T_{VT}$ in 21 of the 22 participants. The remaining participant showed a small increase in the slope after $T_{VT}$ (before: 0.037 l/VO$_2$, after: 0.040 l/VO$_2$), but his dyspnea VAS, $f_R$, $V_E$, and VCO$_2$ showed common responses to those found in the other 21 participants. Therefore, we included this participant in the analysis.

For the mean regression lines, we averaged the slope and intercept of 22 (<threshold) and another 22 (>threshold) regression lines for each variable. The mean threshold values, with the threshold values of each individual (open circles), are shown in Fig. 3. Statistical analysis showed that the thresholds were significantly different between the five parameters ($P < 0.0001$, one-way analysis of variance). Dunnett’s multiple-comparison post hoc tests, where $T_{\text{VAS}}$ served as a control, showed that $T_{\text{VT}}$ (22.3 ± 1.2 ml/min/kg) was higher than $T_{\text{VAS}}$ (18.1 ± 1.2 ml/min/kg, $P < 0.01$). There were no significant differences between $T_{\text{VAS}}$ and $T_{\text{VCO}_2}$, $T_{\text{VE}}$, or $T_{\text{IR}}$.

Agreement between the thresholds assessed by ICC

We analyzed the agreement between $T_{\text{VAS}}$ and any of the other thresholds using the ICC and the Bland–Altman plot (Fig. 4). $T_{\text{VAS}}$ and all other thresholds were significantly correlated (Fig. 4, left panels). The calculated ICC values between $T_{\text{VAS}}$ and any of the other thresholds were also significant. The data plots are close to the identical line (dotted line) in Fig. 4b, c, and a good agreement of ICC values was found between $T_{\text{VAS}}$ and $T_{\text{VE}}$ (0.65) and between $T_{\text{VAS}}$ and $T_{\text{IR}}$ (0.71).
There were no significant differences between $T_{VT}$ values of each individual (open circles). The threshold for $V_T$ ($T_{VT}$) was significantly higher than that for dyspnea VAS ($T_{VAS}$) ($P < 0.01$, Dunnett’s multiple-comparison post hoc test with $T_{VAS}$ serving as a control). There were no significant differences between $T_{VAS}$ and $T_{VCO2}$, $T_{VAS}$ and $T_{VE}$, or $T_{VAS}$ and $T_{IR}$. Values are mean ± SE ($n = 22$).

**Agreement between the thresholds assessed by the Bland–Altman plot**

We further assessed the level of agreement between $T_{VAS}$ and any of the other thresholds (Fig. 4, right panels) using Bland–Altman plots. The widths of the 95% limits of agreement (gray color area) were 18.5 ml/min/kg of VO$_2$ for $T_{VCO2}$ and $T_{VAS}$ (Fig. 4a, right panel), 17.0 ml/min/kg for $T_{VE}$ and $T_{VAS}$ (Fig. 4b, right panel), 15.5 ml/min/kg for $T_{IR}$ and $T_{VAS}$ (Fig. 4c, right panel), and 20.4 ml/min/kg for $T_{VT}$ and $T_{VAS}$ (Fig. 4d, right panel). Therefore, the smaller width of the 95% limits of agreement suggests better agreement between $T_{IR}$ and $T_{VAS}$ than other combinations. A negative correlation was found between the mean value and the difference value (Fig. 4a, right panel), suggestive of proportional bias between $T_{VCO2}$ and $T_{VAS}$. This implies that the difference between $T_{VCO2}$ and $T_{VAS}$ (i.e., $T_{VCO2} - T_{VAS}$) varies depending on their mean.

**Discussion**

In the present study, we tested the possibility that the threshold of tachypneic breathing is equal to that of dyspnea perception during cycle ergometer exercise. This possibility was supported by the results of this study. We found that the mean value of $T_{VAS}$ was similar to those of $T_{VCO2}$, $T_{VE}$, and $T_{IR}$, while it was significantly lower than that of $T_{VT}$. Correlation analyses showed significant correlations between $T_{VAS}$ and any of the other thresholds ($T_{VCO2}$, $T_{VE}$, $T_{IR}$, and $T_{VT}$), indicating that a subjective respiratory parameter (dyspnea) is linked with objective respiratory parameters. Furthermore, a good agreement between $T_{VAS}$ and $T_{IR}$, supported by both the ICC and the Bland–Altman plot, suggests that $T_{VAS}$ coincides most with $T_{IR}$ in exercise hyperpnea. This meant that dyspnea VAS and $f_R$ both showed rapid increases that were virtually simultaneous during incremental exercise.
We found that changes in the subjective measure of dyspnea coincided with those in the objective measure of respiration, particularly the onset of tachypneic breathing. Dyspnea VAS increased gradually before reaching its threshold, and then increased more rapidly thereafter. Thus, we detected a breakpoint in dyspnea. Our results showed that $T_{\text{VAS}}$, $T_{\text{VCO2}}$, $T_{\text{VE}}$, and $T_{\text{fR}}$ occurred nearly simultaneously during incremental exercise. Evidence supporting this finding was reported by Martin and Weil [10], who showed that $T_{\text{fR}}$ and $T_{\text{IR}}$ occur simultaneously at the ventilatory threshold. Similarly, Scheuermann and Kowalchuk [27] reported that $fR$ showed a sudden increase at the ventilatory threshold. Furthermore, Amiard et al. [17] reported that $T_{\text{VAS}}$ and $T_{\text{VCO2}}$ were significantly correlated and showed a good agreement. We confirmed these previously reported relationships, and we further demonstrated that $T_{\text{VAS}}$ agreed most with $T_{\text{IR}}$, which is consistent with our previous paper showing a good agreement between $T_{\text{VAS}}$ and $T_{\text{IR}}$ during increasing hypercapnia [19]. Therefore, we can say that tachypneic breathing is associated with the perception of dyspnea during exposure to the two leading physical ventilatory stimuli, exercise and hypercapnia.

We found that $T_{\text{IR}}$ is more agreeable to $T_{\text{VAS}}$ than $T_{\text{VE}}$ is, and also that $T_{\text{IR}}$ is more agreeable to $T_{\text{VAS}}$ than $T_{\text{VT}}$ is. This is consistent with our previous observation during hypercapnia [19]. Amiard et al. attributed the similarity between the threshold for dyspnea and the ventilatory threshold to a nonlinear increase in overall ventilation resulting from an increase in $\text{VCO2}$ caused by the accumulation of blood lactate. This may be true, but we need to consider overall ventilation as a product of $fR$ and $V_T$ when discussing mechanisms that control ventilation. Dejours [1] stressed the importance of considering the combination of $fR$ and $V_T$ when studying ventilation. Otherwise, one may neglect the other features of ventilatory control.

$T_{\text{VT}}$ occurred in a delayed fashion, and it showed less coincidence with $T_{\text{VAS}}$ than $T_{\text{IR}}$ did. The interpretation of this result needs some considerations of measuring dyspnea intensity. It is generally accepted that the quality of dyspnea is grouped into three principal types: air hunger, respiratory work/effort, and chest tightness [28]. Smith et al. [14] reported the dominance of air hunger at the end of exercise in healthy participants. Air hunger is derived from increased central respiratory drive that is not matched by adequate ventilatory responses, while respiratory work/effort derives from corolla discharge [29]. In fact, air hunger has been shown experimentally to be caused by reduced $V_T$ combined with chemical respiratory stimuli such as hypercapnia or hypoxia [23, 30, 31]. In a pathological state of the lung, lung expansion is mechanically restricted during exercise by lung hyperinflation in patients with chronic obstructive pulmonary disease, and the restriction of lung expansion is linked with air hunger [32, 33]. If the trend toward the leveling off of $V_T$ were a cause of dyspnea in the present study, $T_{\text{VT}}$ should precede or coincide with $T_{\text{VAS}}$. However, $T_{\text{VAS}}$ significantly preceded $T_{\text{VT}}$. Our possible explanation for the preceding appearance of $T_{\text{VAS}}$ is that the dyspnea we measured included both air hunger and respiratory work/effort. In patients with stable asthma, Laveneziana et al. [34] reported the dominance of respiratory work/effort among dyspnea descriptors during exercise before the inflection of $V_T$, and they also reported that difficult/unsatisfied inspiration, which is similar to air hunger [32], was markedly increased at peak exercise. Thus, in the present study, the dyspnea of respiratory work/effort may have increased as ventilation increased before exercise intensity reached $T_{\text{VT}}$, which could explain the preceding appearance of $T_{\text{VAS}}$. $T_{\text{VT}}$ may be associated with the threshold for air hunger, but we did not specifically measure the threshold for air hunger. We should have distinguished between air hunger and respiratory work/effort in the present study. In this regard, there is still some ambiguity in the meaning of $T_{\text{VAS}}$. We measured dyspnea VAS at 2-min intervals, but the thresholds for air hunger and respiratory work/effort may be determined by measuring dyspnea VAS more frequently if these thresholds occur separately.

We also have a somewhat new perspective about the close relationship between $T_{\text{VAS}}$ and $T_{\text{IR}}$. Behavioral respiratory control that relies on inputs from the higher centers [22, 35] would be involved in the alteration of the respiratory rhythm during exercise. Gallagher et al. [12] proposed that tachypneic breathing during exercise is not based on the mechanical limitations of lung expansion in healthy humans. That is, whether the restriction of lung expansion plays a role in healthy humans is unclear. The similarity between $T_{\text{VAS}}$ and $T_{\text{IR}}$ we found could explain the tachypneic breathing pattern that emerges with a strong respiratory stimulus in terms of emotional respiratory behavior. Dyspnea incorporates affective dimensions that include unpleasantness [29]. During laboratory dyspnea challenges, unpleasantness was accompanied by both respiratory work/effort and air hunger [23]. Masaoka et al. [36] reported that unpleasantness at rest does not affect the metabolic rate, but it increases with a slight decrease in $V_T$. Therefore, one possible explanation for the onset of tachypneic breathing during exercise is that unpleasantness accompanied by dyspnea reaches a level that induces emotional respiratory reactions to induce a tachypneic breathing pattern. $T_{\text{VAS}}$ may be a clinical predictor of exercise tolerance. Akaishi et al. [37] reported that in heart disease patients, the more rapid and shallower that breathing patterns are during cardiopulmonary exercise testing, the lower exercise tolerance is. It is speculated that patients beginning to
show rapid and shallow breathing patterns at low exercise intensities have an early onset of dyspnea. Amiard et al. [17] stated that in children with congenital heart impairments, particularly those who cannot perform up to maximal exercise levels, dyspnea thresholds may be a good alternative to ventilatory gas exchange thresholds because these two thresholds occur concomitantly with each other. Thus, presumably, exercise tolerance is approximated by the inflection points of $f_T$, $V_r$, and dyspnea intensity.

We excluded five participants. Data scattering prevented the segmented linear regression analysis with SigmaPlot software in four participants. We acknowledge that the reason for the data scattering is unclear. It may be better to increase exercise intensity more slowly over time to increase the number of data points. The final participant was excluded because $f_T$ started to increase immediately after the onset of exercise. In our previous study, there were different types of breathing pattern responses during increasing hypercapnia. The most common response during increasing hypercapnia was similar to that found during exercise in the present study [19]; however, in two of the 21 participants in the previous study, $f_T$ started to increase at the beginning of hypercapnia and reached a plateau [19]. We succeeded in finding a good agreement between $T_{VAS}$ and $T_{IR}$ in most of the participants of the present study, but we have to remember that breathing pattern responses were not always uniform during physical stimuli.

A major shortcoming of this work is that we could not demonstrate a causal relationship between dyspnea perception and tachypneic breathing during exercise. Our straightforward approach showed a good agreement between $T_{VAS}$ and $T_{IR}$ during exercise, but our results do not give evidence that dyspnea-induced negative emotions change the respiratory rhythm. At least, we should have discerned the quality of dyspnea and scored affective components of dyspnea such as distress, simultaneously with the level of dyspnea [29, 33]. We have tried to identify where the rhythm of emotion-related respiration is generated in conscious humans using brain-imaging techniques such as functional magnetic resonance imaging and electroencephalogram dipole modeling [36, 38, 39]. These techniques may enable us to demonstrate whether or not there is a cause-and-effect relationship between dyspnea and tachypneic breathing. We also have to mention here that we increased exercise intensity by 50 W every 4 min to 150 W. Using a gradient increase might have been a better option to determine the thresholds. In particular, for $T_{VAS}$, dyspnea VAS should have been measured more frequently, with exercise intensity more gradually and slowly increased.

In conclusion, these results suggest that the start of tachypneic breathing coincides with the threshold for dyspnea perception during cycle ergometer exercise. Dyspnea seems to be a candidate for contributing to the sudden change in breathing patterns during exercise, but whether dyspnea is a cause of tachypneic breathing is a subject for further investigation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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