CO₂ does not affect passive exercise ventilatory decline

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Bell, Harold J., and James Duffin. CO₂ does not affect passive exercise ventilatory decline. J Appl Physiol 95: 322–329, 2003. First published March 7, 2003; 10.1152/japplphysiol.01176.2002.—Breathing increases abruptly at the start of passive exercise, stimulated by afferent feedback from the moving limbs, and declines toward a steady-state hyperpnea as exercise continues. This decline has been attributed to decreased arterial CO₂ levels and adaptation in afferent feedback; however, the relative importance of these two mechanisms is unknown. To address this issue, we compared ventilatory responses to 5 min of passive leg extension exercise performed on 10 awake human subjects (6 men and 4 women) in isocapnic and poikilocapnic conditions. End-tidal PCO₂ decreased significantly during poikilocapnic (∆ = −1.5 ± 0.5 Torr, P < 0.001), but not isocapnic, passive exercise. Despite this difference, the ventilatory responses to passive exercise were not different between the two conditions. Using the fast changes in ventilation at the start (5.46 ± 0.40 l/min, P < 0.001) and end (3.72 ± 0.33 l/min, P < 0.001) of passive exercise as measures of the drive to breathe from afferent feedback, we found a decline of 68%. We conclude that the decline in ventilation during passive exercise is due to an adaptation in the afferent feedback from the moving limbs, not a decline in CO₂ levels.

Afferent feedback; ventilation; tidal volume; breathing frequency

The onset of exercise is accompanied by a rapid increase in minute ventilation (V˙E), which has been referred to as the “phase I” response (41) or the “fast neural drive” (8). Two mechanisms are widely accepted as being involved in this rapid ventilatory response: 1) central command and 2) peripheral (afferent) feedback. Central command is believed to involve a parallel stimulation of respiratory neurons in the medulla by motor command via the hypothalamus (10, 40). Afferent feedback, on the other hand, involves stimulation of respiratory neurons in the medulla by ascending signals originating in mechanically sensitive group III and IV afferents in the working muscles (16, 18, 37). It is believed that central command and afferent feedback interact or are integrated, such that a “fast exercise drive to breathe,” which represents both mechanisms, is observed at the onset of active exercise (6, 39).

Passive exercise is a valuable tool in the study of ventilatory control during exercise, because it enables an investigator to study the effects of afferent feedback mechanisms without a central command mechanism.

THE ONSET OF EXERCISE is accompanied by a rapid increase in minute ventilation (V˙E), which has been referred to as the “phase I” response (41) or the “fast neural drive” (8). Two mechanisms are widely accepted as being involved in this rapid ventilatory response: 1) central command and 2) peripheral (afferent) feedback. Central command is believed to involve a parallel stimulation of respiratory neurons in the medulla by motor command via the hypothalamus (10, 40). Afferent feedback, on the other hand, involves stimulation of respiratory neurons in the medulla by ascending signals originating in mechanically sensitive group III and IV afferents in the working muscles (16, 18, 37). It is believed that central command and afferent feedback interact or are integrated, such that a “fast exercise drive to breathe,” which represents both mechanisms, is observed at the onset of active exercise (6, 39).

Passive exercise is a valuable tool in the study of ventilatory control during exercise, because it enables an investigator to study the effects of afferent feedback mechanisms without a central command mechanism.

In other words, passive exercise provides a means of effectively isolating peripheral feedback during exercise. Passive exercise is achieved by having an experimenter move an individual’s limbs in a rhythmic, “exercise-like” pattern. The passive movement mimics exercise; yet volitional control is absent, and minimal metabolic changes are observed. The exercise-like limb movement during passive exercise does cause changes in limb muscles that stimulate mechanically sensitive afferents (17, 20, 22). The output from these afferents, in turn, stimulates breathing, and so an abrupt increase in V˙E is observed (14, 26). Because this reflex hyperpnea occurs with a minimal increase in CO₂ production in the tissues, a relative hyperventilation results. Decreased arterial CO₂ levels are therefore included in the classical descriptions of the respiratory consequences of passive exercise (7).

Also included in this description is the trend that occurs in ventilation. Specifically, after the abrupt increase in ventilation that occurs at the onset of passive exercise, there is a decline toward steady-state ventilation. This steady-state ventilation remains higher than at rest but lower than immediately after the onset of exercise. We refer to this phase of ventilatory response as passive exercise ventilatory decline (PEVD).

Some four decades ago, Dejours (7) noted that PEVD may be the result of 1) a withdrawal of chemoreflex drive to breathe due to hyperventilation or 2) a decline in the amount of the drive to breathe resulting from the limb movement itself. The role of these two factors in PEVD has not been properly assessed. In a recent study where we compared two modes of passive exercise, we observed adaptation in the fast exercise drive to breathe from afferent feedback (3). However, our recent study was not designed to resolve the contribution of CO₂ withdrawal and adaptation of afferent feedback in PEVD. Passive exercise in that study was poikilocapnic, and we were therefore unable to assess any role of CO₂ in PEVD. So, although we have established that an adaptation in the fast exercise drive to breathe contributes to PEVD, whether changes in the end-tidal Pco₂ (PetCO₂) might also contribute to PEVD remains unknown. We hypothesize that they do not and that PEVD is due to adaptation in the afferent feedback from the moving limbs. The first aim of this study was therefore to determine whether the hypocapnia normally associated with passive exercise...
would influence PEVD. We did this by performing passive exercise on subjects using poikilocapnic and isocapnic breathing circuits and then comparing the ventilatory responses in these two background CO₂ conditions.

Adaptation in the fast exercise drive to breathe has previously been measured as the difference in rapid changes in 𝑉E at the end vs. the start of exercise. However, 𝑉E is the product of tidal volume (𝑉T) and respiratory rate (fR). It is important to include observations on these parameters when describing any changes in 𝑉E. To our knowledge, however, there is no information regarding how adaptation in the fast exercise drive to breathe is manifested in 𝑉T and fR, and to determine whether and how adaptation in the afferent feedback affects these parameters during passive exercise.

**MATERIALS AND METHODS**

All procedures involved in this study received ethical approval from the University of Toronto’s Office of Research Services before recruitment of subjects. Male and female subjects, 18–40 yr of age, were recruited from the general population at the University of Toronto. Volunteers first participated in the informed consent process in conformation with the Declaration of Helsinki; then they visited our laboratory on two separate occasions. Their first visit was a familiarization session, where the subjects were introduced to the equipment and procedures involved, and they were able to experience passive leg extension movements while breathing through a facemask connected to a low-resistance breathing circuit. Their second visit to the laboratory, ≤1 wk later, was to complete the experimental protocol as follows.

**General outline.** The protocol involved monitoring subjects at rest and during 5–6 min of passive leg extension exercise under two background conditions, isocapnia and poikilocapnia, separated by ∼20 min, during which the subject moved freely about the laboratory. The order of completion of the isocapnic and poikilocapnic passive exercise was pseudorandomized on the basis of the order of entry of the subject into the study.

**Isocapnic background.** Isocapnia was maintained through the use of a partial-rebreathing circuit, as described by Fahlman et al. (11), with large-bore tubing used to minimize resistance during breathing (Fig. 1). Briefly, fresh gas flow was set to equal resting alveolar ventilation (VA) so that any increase in the subject’s ventilation is satisfied by rebreathing expired air from a reservoir tube on the expired side of the circuit. Because 𝑃𝐶O₂ of mixed expired air approximates that of mixed venous blood, the extra ventilation does not provide any increase in CO₂ elimination. For our purposes in this study, the hyperpnea of passive exercise could therefore occur in the absence of the hypocapnia normally associated with this condition.

**Poikilocapnic background.** Poikilocapnia was maintained through use of a different circuit: a flow-by manifold made of the same large-bore tubing (Fig. 1). Fresh gas flow to the subject was supplied at a rate of ∼20% in excess of the ventilatory demand that would occur during the hyperpneic phase of the experiment. In this background condition, arterial 𝑃𝐶O₂ levels were not controlled and were free to achieve any steady-state levels that would normally be observed for the subject at a given level of 𝑉E.

**Fresh air composition.** In isocapnic and poikilocapnic background conditions, the fresh gas flow to the circuit was hyperoxic, a mixture of medical room air and medical O₂, such that end-tidal 𝑃𝑂₂ was maintained between 160 and 170 Torr. Hyperoxia was used to reduce the contribution of the carotid body chemoreceptors to the chemoreflex drive to breathe during both background conditions.

**Equipment.** In both CO₂ conditions, subjects were seated in a previously described (3) tandem chair apparatus that allows the experimenter to perform passive leg extension movements on the subject. The breathing circuits were interfaced using a facemask (8920/30/40 series, Hans Rudolph, Kansas City, MO) and seal (Ultimate Seal, Hans Rudolph) connected to a wide-bore turbine (model 17125, Universal Ventilation Meter, Vacu-Med, Ventura, CA) that monitored 𝑉E. A port on the turbine close to the mouth allowed sampling for measurement of end-tidal 𝑃𝑂₂ and 𝑃𝐶O₂ (models S-3A1 and CD-3A, respectively, AEI Technologies, Pittsburgh, PA). Leg muscle electromyogram (EMG) was monitored constantly throughout rest and passive exercise following recommended procedures for the use of passive surface electromyography (38). Surface electrodes (Grass electrodes and Grass EC2 electrode cream, Astro-Med, West Warwick, RI) were placed 20 cm apart over the vastus lateralis of the left leg, with the patella as a ground site. The raw EMG signal was passed through a Neurolog system containing a two-stage preamplifier (models NL 100 and NL 104 in series, Digitimer, Hertfordshire, UK) and a custom-built down-stream high-pass alternating-current filter.

**Data collection.** The continuous analog output from all monitoring devices was passed through a pulse code modulation recording adapter (model 4000A, Vetter, Rebersburg, PA), allowing backup of data on VHS tape (model HR D940U 500C Hi-Fi stereo video cassette recorder, JVC Americas). Custom-written computer software (Labview 6.1, National Instruments, Austin, TX; source code available on request) monitored the continuous analog output with the use of a 16-bit data acquisition card (model DAQCard-AI-16XE-50, National Instruments) installed in a Pentium III-based notebook computer. Data were displayed, analyzed, and collected on a breath-by-breath basis and were written to a text array file for further analysis in a specially written spreadsheet (Microsoft Excel, 2017).

**Passive exercise protocol.** In the isocapnic condition, subjects were monitored at rest while fresh gas flow was adjusted to approximate VA. This was done by slowly decreasing flow from an initial level approximating their resting 𝑉E to a level where their PETCO₂ levels began to rise. Once PETCO₂ began to rise, we reasoned that fresh gas flow had been decreased below VA. Further fine adjustments in fresh gas flow were made, and the subject was asked to take a series of three deep breaths to confirm that the isocapnic circuit was functioning and that fresh gas flow approximated VA. If PETCO₂ did not fall >1 Torr by the end of those three deep breaths, we proceeded to commence data collection; otherwise, further adjustments in fresh gas flow were made.

Once data collection began, subjects were monitored for ≥3 min of rest. At a randomly chosen time after 3 min had passed, passive exercise started abruptly by having the experimenter move the subject’s legs in an alternating fashion (phase angle 180°) at a frequency of 71 cycles per minute per leg. The experimenter maintained movement frequency by following a visual, but not audible, signal on a digital metronome (model DM55, Sanyo). Passive exercise was maintained for 5–6 min, when, at a randomly chosen point in the
Fig. 1. Breathing circuits. A: facemask with turbine and sampling catheter used to interface the subject to both breathing circuits. B: independent controls for O₂ and room air, allowing a hyperoxic fresh gas mixture to be provided at desired levels as indicated on a flowmeter. C: isocapnic breathing circuit designed to minimize influence of increased minute ventilation (Ve) on end-tidal P[CO₂] (PetCO₂). D: poikilocapnic breathing circuit designed to allow PetCO₂ to change in accordance with chemoreflex feedback mechanisms. V, airflow; V̇A, alveolar ventilation; PEEP, positive end-expiratory pressure.
5th min, movement of the subject’s legs was abruptly stopped. The subject was monitored for a further 3 min of rest; then data collection was stopped, and the data were saved to a file for analysis.

The poikilocapnic condition involved the same procedure, except the poikilocapnic breathing circuit was used, and fresh gas flow was set to a level in excess of the VE expected to occur during passive exercise.

Data analysis. Spreadsheet database functions were used to convert the breath-by-breath data collected during the described protocol to average 30-s binned values. The onset of passive exercise was taken as the reference point for binning, with the 5 min of passive exercise as bins 0–9 and rest before exercise as bins −1 to −6. The bins of rest after passive exercise were labeled A, B, and so on.

The fast changes in VE, VT, and fb that accompanied exercise transitions were measured as described elsewhere (16) and were used as a measure of the fast exercise drive to breathe resulting fromafferent feedback mechanisms. Briefly, the fast exercise drive to breathe at the start of exercise (ΔVEStart) was calculated as the difference between the third breath after the onset of passive exercise and the previous 30-s bin of rest. The fast exercise drive to breathe at the end of passive exercise (ΔVEEnd) was calculated as the difference between the last 30-s bin of passive exercise and the first breath after the return to restful breathing. The same procedures were used to determine fast changes in the components of VE, VT, and fb, at four times, chosen to delineate the transitions between rest and exercise: 1) the last bin of rest before the start of passive exercise, 2) the third breath of passive exercise, 3) the last bin of passive exercise, and 4) the first breath of the return to rest after passive exercise. EMG data were analyzed in a similar manner, including the bins immediately before and after the transitions from rest to exercise and from exercise to rest (bins −1, 0, 9, and A). The two-way repeated-measures ANOVA also tested PETCO2 at three times, chosen to delineate the PETCO2 trajectories: 1) the last bin of rest before the onset of passive exercise, 2) the fourth bin of passive exercise, and 3) the last bin of passive exercise. In the event that ANOVA revealed significant differences in the data (P ≤ 0.05), further analysis (post hoc testing) was performed using Bonferroni’s pairwise comparison procedure, a relatively conservative method of analyzing such differences. Values are means ± SE.

RESULTS

Subject population. Ten subjects (6 men and 4 women) volunteered and completed all procedures. The subjects’ age, height, and weight were 22.0 ± 1.1 yr, 168.1 ± 4.1 cm, and 58.7 ± 3.7 kg, respectively. All were nonsmokers and reported no history of cardiopulmonary pathology.

Ventilation. The time of measurement of VE was a significant factor (P ≤ 0.001), as was the CO2 condition to a lesser degree (P = 0.037), with no significant interaction between the two factors (P = 0.420). ΔVEStart and ΔVEEnd were not significantly affected by CO2 condition. The values at the chosen times of measurement for both CO2 conditions are shown in Table 1.

During passive exercise, VE was significantly higher in isocapnia than in poikilocapnia (P = 0.037) and decreased significantly (P < 0.001) from the start to the end of passive exercise for both CO2 conditions. However, the decrease in VE was not significantly different between the CO2 conditions. Passive exercise caused a significant increase in VE at the start of exercise (ΔVEStart = 5.46 ± 0.40 l/min, P < 0.001) and a significant decrease in VE at the end of exercise (ΔVEEnd = 3.72 ± 0.33 l/min, P < 0.001). If these changes are taken as measures of the fast exercise drive to breathe, after 5 min of passive leg extension movements, the fast exercise drive to breathe declined to 68% of that at the start of the exercise (P < 0.01) (Fig. 2).

VT. The time of measurement of VT was a significant factor (P ≤ 0.001), as was the CO2 condition to a lesser degree (P = 0.023), with no significant interaction between the two factors (P = 0.198). The values at the chosen times of measurement for both CO2 conditions are shown in Table 1. ΔVTStart and ΔVTEnd were not significantly affected by CO2 condition (P = 0.198).

VT decreased significantly (P < 0.001) from the start to the end of passive exercise for both CO2 conditions, and passive exercise caused a significant increase in VT at the start of exercise (ΔVTStart = 227 ± 26 ml, P < 0.001) and a significant decrease in VT at the end of exercise (ΔVTEnd = 354 ± 32 ml, P < 0.001). If these changes are taken as estimates of the fast exercise drive to breathe, after 5 min of passive leg extension movements, the VT component of the fast exercise drive to breathe declined to 53% of that at the start of exercise (P = 0.002).

fb. The fb was significantly affected only by the time of measurement (P ≤ 0.001). The independent effect of CO2 condition was not significant (P = 0.757), and there was no interaction effect between the factors (P = 0.306). The values at the chosen times of measurement for both CO2 conditions are shown in Table 1.

Table 1. VE, VT, and fb at times chosen to delineate transitions between rest and exercise

<table>
<thead>
<tr>
<th></th>
<th>LBOR</th>
<th>3rd BOE</th>
<th>LBOE</th>
<th>1st BOE</th>
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<tbody>
<tr>
<td>VE, l/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iso</td>
<td>9.01 ± 1.09</td>
<td>14.70 ± 1.43</td>
<td>11.44 ± 1.24</td>
<td>7.94 ± 0.92</td>
</tr>
<tr>
<td>Poik</td>
<td>8.39 ± 0.79</td>
<td>13.61 ± 1.13</td>
<td>10.63 ± 1.00</td>
<td>6.70 ± 0.73</td>
</tr>
<tr>
<td>VT, ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iso</td>
<td>622 ± 58</td>
<td>829 ± 72</td>
<td>695 ± 54</td>
<td>574 ± 45</td>
</tr>
<tr>
<td>Poik</td>
<td>587 ± 60</td>
<td>834 ± 65</td>
<td>613 ± 37</td>
<td>494 ± 43</td>
</tr>
<tr>
<td>fb, breaths/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iso</td>
<td>14.5 ± 1.1</td>
<td>17.5 ± 0.9</td>
<td>16.7 ± 1.4</td>
<td>14.1 ± 1.3</td>
</tr>
<tr>
<td>Poik</td>
<td>14.6 ± 0.9</td>
<td>16.6 ± 1.0</td>
<td>17.3 ± 1.0</td>
<td>13.6 ± 1.1</td>
</tr>
</tbody>
</table>

Values are means ± SE. VE, expired ventilation; VT, tidal volume; fb, breathing frequency; LBOR, last bin of rest before start of passive exercise; BOE, breath of passive exercise; LBOE, last bin of passive exercise; BOR, breath of return to rest after passive exercise; Iso, isocapnia; Poik, poikilocapnia.
The \( f_b \), averaged for both CO\(_2\) conditions, was 14.6 ± 0.7 breaths/min during the last 30 s before passive exercise and rapidly increased to 17.1 ± 0.7 breaths/min as a result of the onset of leg movement (\( P = 0.002 \)). In contrast to the adaptation observed in \( V_t \) as passive exercise progressed, \( f_b \) remained constant throughout the exercise session (\( P = 1.000, 1 - \beta = 1.000 \)). At the end of passive exercise, \( f_b \), averaged for both CO\(_2\) conditions, immediately declined from 17.0 ± 0.8 to 13.9 ± 0.8 breaths/min (\( P < 0.001 \)). Thus \( \Delta f_b \text{Start} \) and \( \Delta f_b \text{End} \), averaged for both CO\(_2\) conditions, were 2.5 ± 0.5 and 3.1 ± 0.6 breaths/min, respectively.

\( \text{PETCO}_2 \). The \( \text{PETCO}_2 \) trajectories (Fig. 3) in isocapnic passive exercise differed significantly from those observed in poikilocapnic passive exercise (Table 2). Resting \( \text{PETCO}_2 \), during the last bin before the start of passive exercise was not different between isocapnic and poikilocapnic conditions (40.8 ± 0.6 and 40.1 ± 0.5 Torr, respectively, \( P = 0.137, 1 - \beta = 0.947 \)). However, \( \text{PETCO}_2 \) was different between poikilocapnic and isocapnic passive exercise for the fourth and last bins (\( P \leq 0.001 \)). Moreover, there was a significant interaction effect between time of measurement and CO\(_2\) condition (\( P \leq 0.001 \)). \( \text{PETCO}_2 \) remained significantly decreased throughout the 5 min of passive exercise in the poikilocapnic condition, as evidenced by the significant difference between rest and the last bin of passive exercise (\( P = 0.017 \)), a decline of 1.5 ± 0.5 Torr. By contrast, in the isocapnic protocol, \( \text{PETCO}_2 \) had demonstrated a small nonsignificant (\( P = 0.961 \)) increase during passive exercise averaging 0.5 Torr (Table 2).

**Leg muscle EMG.** No independent effect of CO\(_2\) condition with respect to the amount of leg muscle EMG activity during passive exercise could be resolved (\( P = 0.528 \)). However, the time of measurement was a significant factor (\( P < 0.001 \)). Leg muscle activity increased from 2.4 ± 0.4 \( \mu \)V during bin 1 to 4.6 ± 0.7 \( \mu \)V during bin 4 (\( P = 0.01 \)). At the cessation of passive exercise, EMG decreased from 5.1 ± 0.9 \( \mu \)V during bin 9 to 2.7 ± 0.5 \( \mu \)V during bin A (\( P = 0.004 \)). There was no interaction effect between the two factors. Therefore, there were no apparent differences between the isocapnic and poikilocapnic protocols with regard to increases in EMG activity during passive movement (\( P = 0.532 \)).

**DISCUSSION.**

Effectiveness of passive exercise. To attribute the changes we observed to an afferent feedback mechanism, it is important that the passive exercise was truly passive. We observed that the root-mean-square EMG signal showed a significant increase from rest during passive exercise, which could be attributed to 1) an increase in vastus lateralis activity or 2) a movement noise artifact. We previously assessed the efficacy of passive exercise using our tandem exercise chair and compared the device with an upright tandem bicycle (3), and we found no increase in metabolic gas exchange over rest for the chair but an increase for the bicycle. In that study as well, using the chair apparatus, we observed increases in EMG during passive exercise comparable to those we observed here and much smaller than the increase on the bicycle, which was 500% larger.

We are therefore confident that our data presented here result from passive movements that were truly passive, and we attribute the physiological adjustments we observed to afferent feedback mechanisms. Moreover, with respect to differences between isocapnic and poikilocapnic conditions, the analysis of EMG data showed no significant difference in EMG measures, so differences in ventilatory responses cannot be attributed to differences in passive exercise characteristics.

**\( \text{PETCO}_2 \) trajectories.** Our methods sufficed to establish significantly different \( \text{PETCO}_2 \) trajectories for isocapnic and poikilocapnic conditions throughout passive exer-
Fig. 3. Histogram plots for PETCO₂, ventilation, Vt, and breathing frequency in isocapnic (thick lines) and poikilocapnic (thin lines) conditions. Bin width is 30 s. Values are means ± SE.
cise. During poikilocapnic passive exercise, $\text{PETCO}_2$ was significantly less than at rest throughout the exercise session, whereas in isocapnia, $\text{PETCO}_2$ did not decline but, rather, showed a small nonsignificant increase from rest during passive exercise. Indeed, isocapnic $\text{PETCO}_2$ was higher than poikilocapnic $\text{PETCO}_2$ throughout the isocapnic protocol as a consequence of our method of establishing isocapnia; to match fresh gas flow to $\dot{V}_A$, it was gradually reduced until $\text{PETCO}_2$ just increased above resting levels.

The small nonsignificant increase in $\text{PETCO}_2$ from rest during passive isocapnic exercise was likely due to the return of a pool of venous blood in the stationary lower limbs to the central circulation when the leg extension movements were commenced (28). During poikilocapnic passive exercise, this effect was offset by the initial hyperventilation. Our use of hyperoxia markedly reduced the peripheral chemoreflex sensitivity to differences in within-breath arterial $\text{CO}_2$ changes between the two $\text{CO}_2$ conditions (12, 27, 29).

**Ventilation and the fast exercise drive.** Ventilation was generally higher throughout the isocapnic protocol, because $\text{PETCO}_2$ was also higher, but PEVD was the same for both $\text{CO}_2$ conditions. It might be expected that the fall in $\text{PETCO}_2$ during poikilocapnic passive exercise would have led to a significantly larger PEVD, but we suggest that the fall in $\text{PETCO}_2$ did not withdraw a significant chemoreflex drive to breathe. This is a result of our observation that at rest our subjects were at or near their chemoreflex threshold for chemoreflex response, ~40 Torr (9, 24). This threshold corresponds to the level of $\text{PETCO}_2$ where a ramp increase in this parameter first begins to elicit an increase in observed ventilation and below which ventilation is driven mainly by other drives to breathe such as wakefulness (24, 35). Therefore, only adaptation in afferent feedback would contribute significantly to PEVD, consistent with our observations.

Despite different $\text{PETCO}_2$ trajectories during isocapnic and poikilocapnic passive exercise, we found no differences in the degree of adaptation in the fast exercise drive to breathe. The adaptation of 68% found in these experiments agrees well with previously reported values for passive (3) and active (21, 25) exercise. The lack of interaction between the factors of $\text{CO}_2$ condition and time of measurement for ventilation supports our contention that PEVD is the result of adaptation in afferent feedback, and not $\text{CO}_2$-mediated chemoreflex withdrawal of ventilatory drive, during passive exercise.

**Pattern of breathing.** We found that the fast exercise drive to breathe produced an immediate increase in $\dot{V}_T$ and $f_b$ at the onset of passive exercise that persisted throughout the session, with an immediate decrease in $\dot{V}_T$ and $f_b$ at the end of passive exercise. Although $\dot{V}_T$ declined during passive exercise, $f_b$ did not, suggesting to us that $f_b$ may therefore have been entrained to the exercise rhythm (1, 2, 4, 5, 29). In humans, the feature of entrainment is well established in many forms of locomotor activity, including walking (23), running (31), cycling (29), rowing (36), and arm-cranking (29) exercise. Suggested reasons for a mechanism that favors entrainment include mechanical efficiency (5), metabolic cost (23), and neural interaction between centers responsible for locomotor and respiratory rhythm generation (13, 32).

We used a limb movement frequency of 71 cycles per minute per leg, rather than 65 cycles per minute per leg in a previous study (16), to enhance the fast exercise drive, which it did. However, $f_b$ did not change significantly during passive exercise, and, as a result, PEVD was produced by a decline in $\dot{V}_T$, rather than in $f_b$. Although this observation may have resulted from an entrainment of breathing rhythm to exercise rhythm, we did not measure entrainment, and so we have no data to confirm or deny this possibility.

**Mechanism of adaptation.** The site where and the mechanism by which the respiratory-related afferent feedback signal adapts over time remain unclear. It seems unlikely that the adaptation occurs at the level of the peripheral receptor units. Group III afferents demonstrate burst activity in the initial stage of a maintained passive stretch stimulus and adapt rapidly within 3–8 s, whereas group IV afferents show a slower response with less tendency to adapt (17–19). Although it is true that group III afferents are believed to be more important in transducing the mechanical stimulus that increases ventilation during passive exercise (15), the time course of their adaptation is not compatible with the movement stimulus used in the present study. Therefore, afferent feedback may decline during a maintained stretch stimulus, but it is unlikely to adapt to a phasic stimulus such as the passive exercise used in this study.

A more likely possibility is a central adaptation to the afferent signal (33). This scenario is supported by our observations regarding the components of ventilation, $\dot{V}_T$, and $f_b$. If the afferent signal at the level of the receptors were to adapt, one would expect $\dot{V}_T$ and $f_b$ to decline over time, which is contrary to our observation. We therefore suggest that the adaptation in respiratory afferent drive takes place in a central neural structure that receives the signal. Although the precise central structure(s) involved has yet to be confirmed, the nucleus of the solitary tract may have importance (33, 34).

**Summary.** We conclude that PEVD can be attributed to adaptation in the fast exercise drive to breathe, and not to changes in $\text{PETCO}_2$. This fast drive to breathe from afferent feedback decreased to 68% of that at the start of exercise over 5 min. We also found that the fast

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**Table 2. End-tidal $\text{PCO}_2$ in isocapnia and poikilocapnia for the last bin of rest, bin containing maximum difference, and last bin of passive exercise**

<table>
<thead>
<tr>
<th></th>
<th>Bin –1</th>
<th>Bin 3</th>
<th>Bin 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iso</td>
<td>40.8 ± 0.5</td>
<td>41.3 ± 0.6</td>
<td>41.1 ± 0.6</td>
</tr>
<tr>
<td>Poik</td>
<td>40.1 ± 0.5</td>
<td>38.6 ± 0.6</td>
<td>39.0 ± 0.7</td>
</tr>
</tbody>
</table>

Values are means ± SE given in Torr. Bin –1, last bin of rest; bin 3, bin containing maximum difference; bin 9, last bin (steady state) of passive exercise.
exercise drive to breathe augments $V_t$ and $f_b$. Furthermore, we conclude that the adaptation observed in the fast exercise drive to breathe results from changes in $V_t$, and not from changes in $f_b$. $V_t$ of the fast exercise drive to breathe adapted to a value of 53% of that at the start of exercise after 5 min of passive leg extensions. The $f_b$ remained constant throughout 5 min of passive exercise, and we suggest that this is related to an entrainment mechanism.

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