

# Response of Tidal Volume to Inspiratory Time Ratio During Incremental Exercise

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**OBJECTIVE:** There is some debate about the participation of the Hering-Breuer reflex during exercise in human beings. This study aimed to investigate breathing pattern response during an incremental exercise test with a cycle ergometer. Participation of the Hering-Breuer reflex in the control of breathing was to be indirectly investigated by analyzing the ratio of tidal volume ( $V_T$ ) to inspiratory time ( $t_I$ ).

**SUBJECTS AND METHODS:** The 9 active subjects who participated the study followed an incremental protocol on a cycle ergometer until peak criteria were reached. During exercise,  $V_T/t_I$  can be described in 2 phases, separated by activation of the Hering-Breuer reflex (inspiratory off-switch threshold). In phase I, ventilation increases because  $V_T$  increases, resulting in a slight decrease in  $t_I$ , whereas, in phase II, increased ventilation is due to both an increase in  $V_T$  and a decrease in  $t_I$ .

**RESULTS:** The mean (SD) inspiratory off-switch threshold was 84.6% (6.3%) when expressed relative to peak  $V_T$  (mean, 3065 [566.8] mL) and 48% (7.2%) relative to the forced vital capacity measured by resting spirometry. The inspiratory off-switch threshold correlated positively ( $r=0.93$ ) with the second ventilatory threshold, or respiratory compensation point.

**CONCLUSIONS:** The inspiratory off-switch threshold and  $V_T/t_I$  are directly related to one another. The inspiratory off-switch threshold was related to the second ventilatory threshold, suggesting that the Hering-Breuer reflex participates in control of the breathing pattern during exercise. Activation of the reflex could contribute by signaling the respiratory centers to change the breathing pattern.

**Key words:** Breathing pattern. Hering-Breuer reflex. Ventilatory threshold.

Respuesta de la relación volumen corriente-tiempo inspiratorio durante un esfuerzo incremental

**OBJETIVO:** La participación del reflejo de Hering-Breuer durante el ejercicio en seres humanos es objeto de discusión. El propósito del presente trabajo ha sido estudiar la respuesta del patrón respiratorio durante un esfuerzo incremental en cicloergómetro para comprobar, de forma indirecta, mediante el análisis de la relación volumen corriente-tiempo inspiratorio ( $V_T/t_I$ ), la participación del reflejo de Hering-Breuer en el control de la respiración.

**SUJETOS Y MÉTODOS:** Han participado en el estudio 9 sujetos activos que han llevado a cabo un protocolo incremental en cicloergómetro hasta alcanzar criterios máximos. Se ha comprobado que la relación  $V_T/t_I$  durante el ejercicio presenta 2 fases con un punto de ruptura, denominado punto de ruptura Hering-Breuer (PHB): fase I, donde el incremento de la ventilación se produce a expensas del aumento del  $V_I$  con ligero descenso del  $t_I$ , y fase II, durante la cual el incremento ventilatorio se produce tanto por el aumento del  $V_I$  como por el descenso del  $t_I$ .

**RESULTADOS:** En el estudio, el PHB se alcanzaba a un valor medio ( $\pm$  desviación estándar) del  $84,6 \pm 6,3\%$  respecto al máximo valor de  $V_T$  ( $3.065 \pm 566,8$  ml) y de un  $48 \pm 7,2\%$  respecto al valor de la capacidad vital forzada medida en la espirometría de reposo. El PHB se relacionó de forma positiva ( $r = 0,93$ ) con el umbral ventilatorio 2 o umbral de compensación respiratoria.

**CONCLUSIONES:** Existe relación directa entre el PHB y  $V_T/t_I$ . El PHB se relaciona con el umbral ventilatorio 2, de manera que intervendría en el control del patrón ventilatorio durante el ejercicio. La entrada en funcionamiento del reflejo podría contribuir informando a los centros respiratorios para llevar a cabo el cambio de patrón ventilatorio.

**Palabras clave:** Patrón respiratorio. Reflejo de Hering-Breuer. Umbral ventilatorio.

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## Introduction

The human breathing pattern has been studied at rest<sup>1</sup> and during both submaximal exercise<sup>2-4</sup> and maximal exercise.<sup>2,3,5</sup> All these studies report a response of the ratio of tidal volume ( $V_T$ ) to inspiratory time ( $t_I$ ) similar

to that described by Clark and von Euler<sup>6</sup> for animals breathing CO<sub>2</sub>-enriched air. These authors described  $V_T/t_I$  according to 2 phases. In phase 1, ventilation increases because  $V_T$  increases, whereas in phase 2, ventilation increases mainly because  $t_I$  decreases.

$V_T/t_I$  can provide an indirect indication of whether the Hering-Breuer reflex has been activated and shows 2 phases well defined by activation of pulmonary receptors, as described by Clark and von Euler.<sup>6,7</sup> The breathing pattern therefore indicates the transition from breathing in which ventilation increases largely because  $V_T$  increases to tachypneic breathing. Such a change in breathing pattern occurs during incremental exercise. In highly-trained cyclists, investigators concur that, above a given intensity,  $V_T$  reaches a stable value<sup>8-10</sup> or increases slightly.<sup>11</sup> The breathing rate also participates notably more in the increase in minute ventilation ( $V_E$ ) above a given intensity of exercise. The contribution of the Hering-Breuer reflex to the control of ventilation during exercise is subject to debate. The breathing pattern of doubly denervated (hilar and carotid-body) animals has been seen to differ to that of normal animals,<sup>12</sup> and recipients of a heart-lung transplant have achieved suitable ventilation during exercise through a large increase of  $V_T$  and a decrease in breathing rate,<sup>13</sup> suggesting that pulmonary receptors are activated during breathing control. These 2 observations, from both animals and humans, indicate that the increase in ventilation during exercise can be partly attributed to information from volume receptors or other types of receptor which communicate with the breathing control centers via the vagal nerve.<sup>7</sup>

The second ventilatory threshold (VT<sub>2</sub>) is one of the most widely used variables for spirometric assessment during ergometry. It is defined as the load at which the oxygen uptake is no longer proportional to CO<sub>2</sub> production.<sup>14-16</sup> Given that this variable is sensitive to training,<sup>11</sup> we think it should be measured in studies of chronic obstructive pulmonary disease (COPD).

The objective of this study was to analyze the response of breathing pattern and so indirectly determine whether the Hering-Breuer reflex participates in the regulation of breathing and whether activation of this reflex is related to VT<sub>2</sub>. According to our initial hypothesis, the change in  $V_T/t_I$  during incremental exercise is similar or identical to that described for the first time by Clark and von Euler<sup>6</sup> during inhalation of CO<sub>2</sub>—an experiment that showed vagal activation by means of volume receptors. A relationship between the 2 variables that characterize the breathing pattern could have important applications in COPD.

## Subjects and Methods

### Subjects

Descriptive statistics of the population are presented in Table 1. Nine amateur male cyclists, triathletes, and physical education students who were regular cyclists were recruited. All gave written informed consent to participate in the study.

The study was conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki for investigation with human subjects.<sup>17</sup>

### Measurement of Gas Exchange

The composition and volume of expired air were measured with a Jaeger Oxycon Pro<sup>®</sup> gas analyzer (Erich Jaeger, Würzburg, Germany). The 2-way digital turbine sensor (Triple V<sup>®</sup>, Jaeger) had low dead space and resistance and complied with the guidelines of the American Thoracic Society and the European Community for Steel and Coal.<sup>18</sup> Gas exchange data were collected breath by breath and averaged over 15 seconds. Heart rate was measured with a Hellige Cardiotest EK 53 3-lead electrocardiograph (Hellige, Freiburg, Germany).

### Study Protocol

On arrival at the laboratory, each subject underwent a medical examination, which consisted of a medical and sporting history, basal electrocardiogram, and spirometry testing. The tests were done on a Jaeger ER800<sup>®</sup> variable resistance cycle ergometer with electromagnetic braking. Loads covered by the ergometer ranged from 25 W to 1000 W with minimum increments of 1 W/s. The exercise protocol consisted of 1 minute at full rest, 3 minutes warm-up at 50 W, and progressive testing with increments of 5 W every 12 seconds. At the end of the exercise program, the subjects had 2 minutes of active recovery at 50 W (70 rpm), and 3 minutes of complete rest on the bicycle. The pedal rate was set at between 70 rpm and 90 rpm. All tests were done under similar atmospheric conditions (temperature range, 21°C to 24°C; relative humidity, 45% to 55%; and atmospheric pressure, 700 mm Hg to 715 mm Hg). Values were expressed in standard temperature and pressure dry conditions.

### Analysis of Anaerobic Threshold

Data on gas exchange were analyzed by visual inspection as proposed by Wassermann et al<sup>19</sup> in 1973. In accordance with this method,  $V_E/\text{CO}_2$  production,  $V_E/\text{oxygen}$  uptake, partial pressure of CO<sub>2</sub>, and partial pressure of oxygen were measured at different loads to determine the anaerobic threshold using standard criteria. A combination of different methods has been shown to be the most reliable to determine ventilatory thresholds.<sup>15</sup>

For each subject, the values of  $V_T$  from the exercise test were plotted against  $t_I$  in order to visualize the 2 phases of the breathing pattern equivalent to those reported by Clark and von Euler during inhalation of CO<sub>2</sub>.<sup>6</sup> In phase 1, increases in ventilation are due to increases in  $V_T$  with a slight decrease in  $t_I$ . In phase 2, the ventilatory increase occurs because of both increases in  $V_T$  and decreases in  $t_I$ , with an inverse relationship. This variation in ventilatory response is reached when  $V_T$  is about 2 times the resting value.

In the Clark and von Euler breathing pattern, the phase transition occurs suddenly and is known as the inspiratory off-switch threshold. Visual examination reveals the point at which  $V_T/t_I$  shifts to the left on the plot, that is, the point where  $t_I$  decreases significantly with a small increase in  $V_T$ . Two independent observers, blinded to the identity of the subject, determined VT<sub>2</sub> and the inspiratory off-switch threshold at different times.

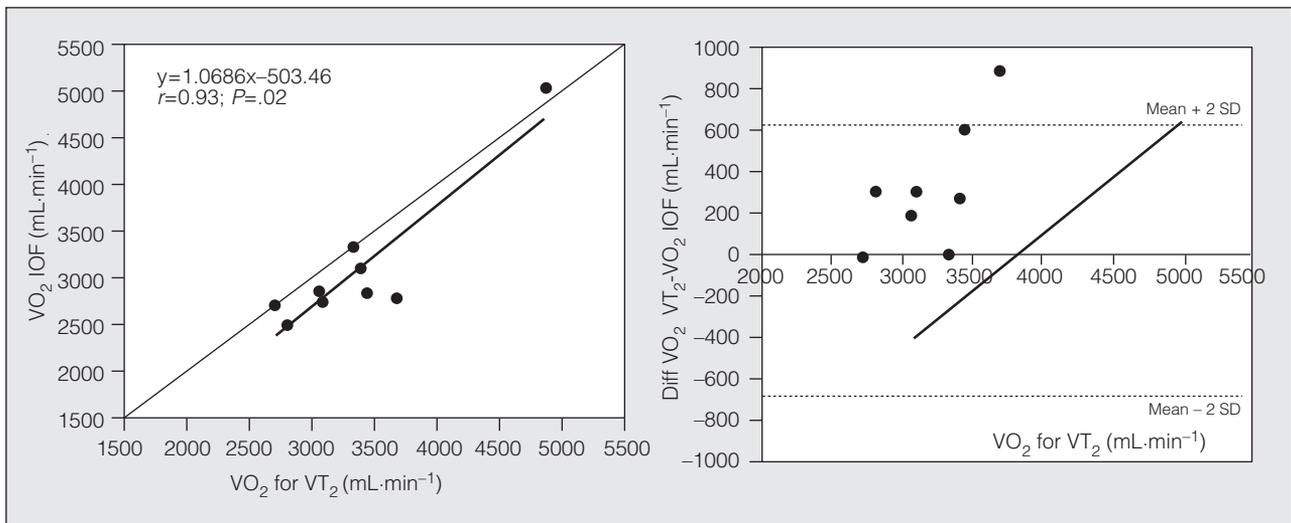


Figure 1. Left panel: ratio of oxygen uptake (VO<sub>2</sub>) on reaching the inspiratory off-switch threshold (IOF) to VO<sub>2</sub> on reaching the second ventilatory threshold (VT<sub>2</sub>). Right panel: Bland and Altman procedure<sup>20</sup> (1986) for analysis of the reliability of the procedure for identification of VT<sub>2</sub>. Diff indicates difference.

Statistical Analysis

Mean (SD) values were calculated for all variables. After testing for a normal distribution, the Student *t* test was applied for paired variables. A Pearson correlation study was used to test whether there was a positive relationship between the anaerobic threshold and the inspiratory off-switch threshold. The Bland and Altman procedure<sup>20</sup> was used to investigate the

TABLE 1  
Characteristics of the Subjects Included in the Study\*

	Mean (SD)
Age, years	24.1 (3)
Weight, kg	70.5 (6.5)
Height, cm	176 (6.6)
FVC, L	5.4 (0.9)
FEV <sub>1</sub> , L	4.6 (0.6)
VO <sub>2</sub> , mL×kg×min <sup>-1</sup>	57.1 (12.1)
Maximum load, W	336 (8)

\*FVC indicates forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 second; VO<sub>2</sub>, peak oxygen uptake adjusted to body weight. Maximum load is defined as the mean peak load reached during the tests.

TABLE 2  
Results of the Analysis of the Ratio of Tidal Volume (V<sub>T</sub>) to Inspiratory Time (t<sub>I</sub>) at Peak Exercise and Analysis of Comparison of Means\*

	VO <sub>2</sub> IOF, mL×min <sup>-1</sup>	VO <sub>2</sub> VT <sub>2</sub> , mL×min <sup>-1</sup>	V <sub>T</sub> IOF, mL	Peak V <sub>T</sub> , mL
Mean	3103	3375†	2576	3065
SD	751	637	441	566
	V <sub>T</sub> OIF/ Peak V <sub>T</sub>	V <sub>T</sub> OIF/ FVC	Peak V <sub>T</sub> / FVC	Peak V <sub>T</sub> / FEV <sub>1</sub>
Mean	84.6%	48.0%	56.8%	66.1%
SD	6.3%	7.2%	7.6%	8.1%

\*VO<sub>2</sub> IOF indicates oxygen uptake on reaching the inspiratory off-switch threshold; VO<sub>2</sub> VT<sub>2</sub>, oxygen uptake on reaching the second ventilatory threshold; V<sub>T</sub> IOF, tidal volume on reaching the inspiratory off-switch threshold; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 second. †Significant differences VO<sub>2</sub> IOF versus VO<sub>2</sub> VT<sub>2</sub>; *t* (8)=2.559; *P*=.034.

reliability of the V<sub>T</sub>/t<sub>I</sub> plots for determining VT<sub>2</sub>. The results of statistical tests were significant when *P* was less than .05. For statistical analysis, the SPSS program, version 11.5 (SPSS Worldwide Headquarters, Chicago, Illinois, USA) was used.

Results

Table 1 shows the anthropometric data, resting spirometric variables, and peak oxygen uptake in the study population. The values of peak oxygen uptake (mean 57.1 [12.4] mL×kg×min<sup>-1</sup>) were greater than those reported for the sedentary population. A maximum load of 336 W was reached. Table 2 shows the corresponding values at the moment when the breathing pattern changed phase. The 2 phases described in the previous section could be discerned in the exercise tests of all volunteers.

The inspiratory off-switch threshold occurred when t<sub>I</sub> was 0.96 (0.11) seconds and V<sub>T</sub> was 2576 (441) mL, equivalent to 84.6% (6.3%) of peak V<sub>T</sub> (3065 [566] mL) at maximum exercise intensity, and 48% (7.2%) of peak forced vital capacity measured at rest by spirometry (5416 [823] mL). Peak V<sub>T</sub> during the test was 56.8% (7.6%) of the forced vital capacity.

The inspiratory off-switch threshold correlated positively (*r*=0.93; *P*=.02) with VT<sub>2</sub> (Figure 1). According to the Bland and Altman test, only 1 subject had a discrepancy between the 2 measurements. Table 2 shows mean oxygen uptake when the inspiratory off-switch threshold was reached. The threshold occurred at a mean oxygen uptake approximately 300 mL less than that when VT<sub>2</sub> occurred.

Discussion

According to the results of this study, the pattern of V<sub>T</sub>/t<sub>I</sub> during incremental exercise is similar to that observed by Clark and von Euler in animals forced to

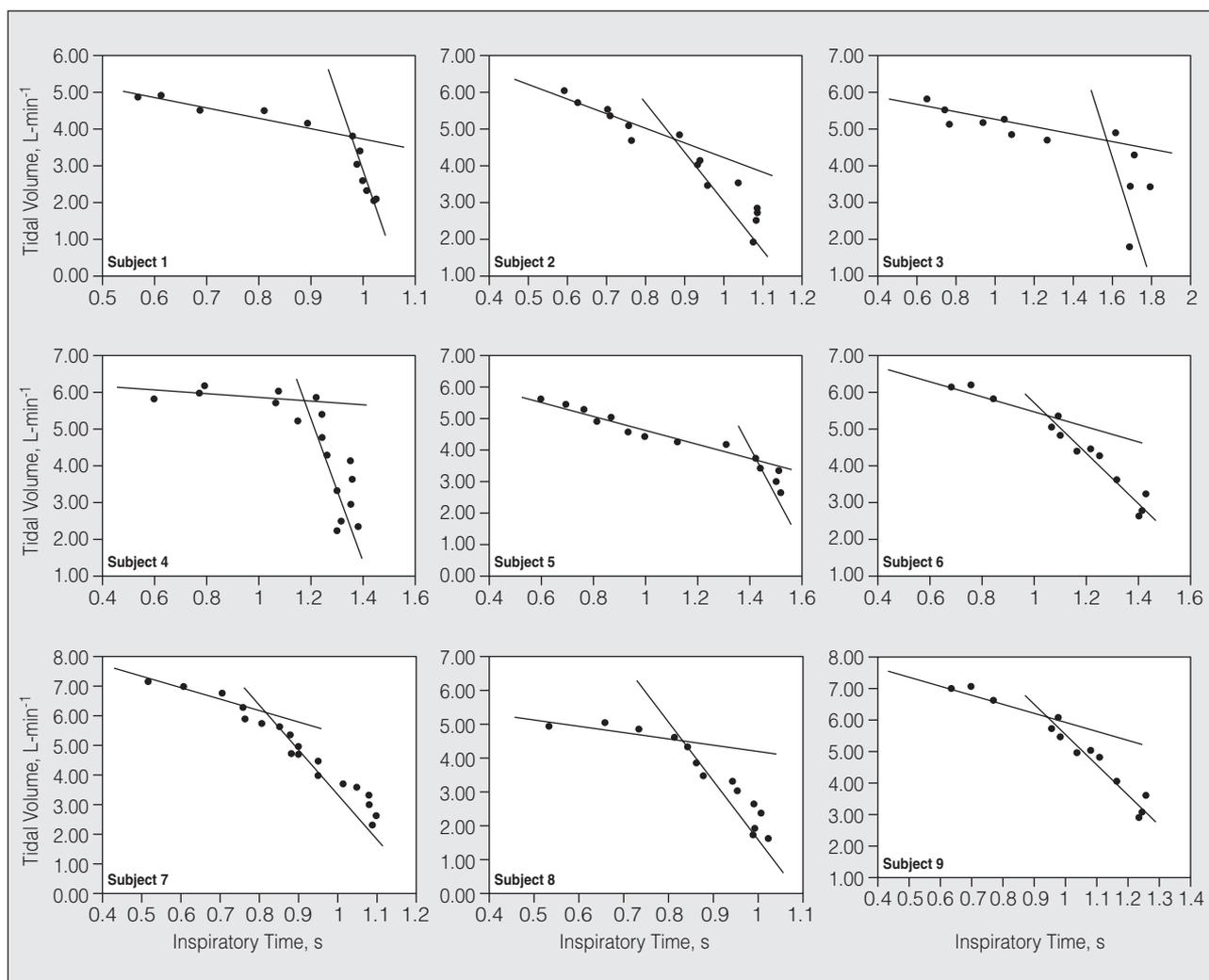


Figure 2. Plots of the ratio between tidal volume and inspiratory time for the subjects who participated in the study. The lines correspond to regression fits to determine the inspiratory off-switch threshold. Individual scales are adjusted to illustrate the threshold more clearly.

breathe  $\text{CO}_2$ .<sup>6</sup> The response of the ratio shows 2 well differentiated phases (Figure 2). In phase 1,  $V_E$  increases mainly because  $V_T$  increases and  $t_I$  decreases. In contrast, in phase 2, hyperventilation occurs as a result of a greater reduction in  $t_I$  with a slight increase in  $V_T$ . The moment when the phase change occurs is known as the inspiratory off-switch threshold, which, in this study, is related to  $\text{VT}_2$ . There is consensus that, above a certain point,  $V_T$  reaches a stable value<sup>9,10,21</sup> or increases slightly,<sup>11</sup> according to the subject's level of fitness. Some authors have shown that high intensity strength training can increase  $V_T$  in patients with COPD.<sup>22</sup> No change in the breathing pattern at rest was observed by Kay et al,<sup>23</sup> however; nor has change been seen under anesthetic,<sup>10</sup> although changes have been reported in recipients of a heart-lung transplant.<sup>13,24</sup> The findings of Kay et al<sup>23</sup> may differ from ours because the subjects in their study followed an exercise protocol with a limited load of 50 W to 200 W, whereas we used a incremental protocol that reached the maximum load.

Given that our study was with human subjects, it was not possible to conclusively demonstrate that vagal reflexes were participating in ventilatory control during exercise because we could not control for many of the variables that might influence the behavior of  $V_T/t_I$ . The physiological mechanisms that may regulate breathing during exercise can be classed as feedforward, feedback, and short-term potentiation,<sup>25</sup> although such mechanisms would not completely explain the response of  $V_E$ . Feedback could arise from structures in the central nervous system structures (central feedback) or receptors located in the respiratory tract (parenchyma and thorax), in the locomotor muscles, or in the cardiovascular system (peripheral chemoreceptors), that is, peripheral feedback. Therefore, we could not control information from the implicated group III muscle nerve endings, peripheral chemoreceptors, or receptors sensitive to certain molecules and ions (potassium, protons).

Despite these limitations, the results of the study show that  $V_T/t_I$  followed a biphasic pattern during

incremental exercise, the inspiratory off-switch threshold being reached when  $V_T$  was 84.6% (6.3%) of the peak value. Such a pattern could be explained by activation of the Hering-Breuer reflex. This reflex mechanism has been shown to participate in control of breathing in animal models.<sup>26</sup> Activation of the Hering-Breuer reflex is suggested by the fact that the inverse relationship between  $V_T$  and  $t_I$  is affected in a variety of experimental conditions (vagotomy, hilar denervation, hypercapnia,  $\beta$ -receptor blockade, and mouth pressure) both in animals and human beings.

Vagotomy causes an increase in  $V_E$  because  $V_T$  increases with a minimum decrease in  $t_I$ , such that  $V_T/t_I$  would be in phase 1.<sup>13,27</sup> In an interesting study that aimed to demonstrate the effects of double denervation (hilar denervation and carotid chemoreceptor denervation), lung afferents via the hilar nerves influenced the breathing pattern of ponies at rest and during exercise.<sup>12</sup> The effect was also associated with attenuation of lung volume feedback.

There is vagal participation in control of breathing when hypercapnia occurs during exercise in both animals<sup>28</sup> and humans.<sup>9</sup> Joyner et al<sup>29</sup> showed that blockade of  $\beta_1$ - and  $\beta_2$ -receptors led to larger decreases in  $V_T$  than blockade of  $\beta_1$ -receptors only.

Studies done using the simplest technique, that is, mouth pressure at 0.1 seconds after onset of inspiration<sup>5,30,31</sup> to determine  $V_T/t_I$ , showed that increases in ventilation during easy exercise occurred due to increases in  $V_T$ .

In view of the findings of these studies, our results point to the importance of information from airway receptors and receptors in the lung parenchyma. The change in breathing pattern after passing the inspiratory off-switch threshold could be due to feedback from volume receptors or another type of receptor. Such receptors would be partly responsible for the decrease in  $t_I$  when  $V_T$  increases. The role of the Hering-Breuer reflex in regulation of breathing at rest has been extensively debated,<sup>26</sup> as the receptors not only detect changes in volume, but also variations in the concentrations of certain molecules. Other physiological mechanisms, such as variations in  $CO_2$  concentration and increase in the values of certain other variables may therefore explain the results obtained for the inspiratory off-switch threshold.

Slight changes in partial pressure of  $CO_2$  are understood to affect the stimulation of receptors implicated in the Hering-Breuer reflex.<sup>32</sup> Stimulated receptors could trigger a strong activation of the bulbar centers by way of vagal inputs during breathing. In our study, given that the inspiratory off-switch threshold is related to  $VT_2$ , above which the partial pressure of exhaled  $CO_2$  increases, variations in partial pressure of  $CO_2$  could have occurred which would explain stimulation of pulmonary receptors sensitive to this gas.

At high intensities, the concentration of plasma protons increases (metabolic acidosis) and potassium concentration varies, sometimes reaching values as high

as 7 mEq/L. This would partly explain hyperventilation during exercise, whether by stimulation of peripheral or central chemoreceptors.<sup>33,34</sup> We did not measure variables to determine the acid-base status, and so there is no way of knowing whether the concentration of potassium and protons in blood could have led to the change in breathing pattern. Nevertheless, the partial pressure of  $CO_2$  changes after exceeding the inspiratory off-switch threshold, such that slight variations in this variable could explain stimulation of volume receptors or other types of  $CO_2$  receptors.<sup>35</sup>

Analysis of  $VT_2$  can also be used to determine  $V_T/t_I$ , although caution should be exercised, as the inspiratory off-switch threshold is exceeded at a value of approximately 300 mL lower. The inspiratory off-switch threshold very likely forms part of the process of anticipation of increased ventilation. Our measurements of the ratio of  $V_T$  to forced vital capacity agree with those of other authors who have measured this variable and who also found statistically significant differences between those with and without COPD.<sup>36</sup> This variable has also proved to be a good indicator of the improvement in ventilation with training.<sup>22</sup> Therefore, the measurement of the inspiratory off-switch threshold could be a useful method for following the progress of patients with COPD.

In conclusion, the behavior of  $V_T/t_I$  during incremental exercise can be divided into 2 phases. The first of these phases shows an increase in ventilation because  $V_T$  increases and, to a lesser extent, breathing rate increases (that is,  $t_I$  decreases). The second phase shows increased breathing rate, so limiting further increases in  $V_T$ . The phase transition occurs at the inspiratory off-switch threshold, which is related to  $VT_2$ . While aware of the limitations of the study, we suggest that the inspiratory off-switch threshold may arise because of stimulation of volume receptors, such that information is sent to the regulatory centers to increase ventilation at a given extent of pulmonary distension. Measurement of the threshold could be useful in patients with COPD.

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