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Relationship between breathlessness and hypoxic and hypercap-

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Relationship between breathlessness and hypoxic and hypercapnic ventilatory response in patients with COPD. S. Kobayashi, M. Nishimura, M. Yamomoto, Y. Akiyama, K. Miyamoto, Y. Kawamaki. ©ERS Journals Ltd 1996.

ABSTRACT: The purpose of this study is to examine the relationship between breathlessness and the ventilatory response to hypercapnia or hypoxia in patients with chronic obstructive pulmonary disease (COPD).

Fifteen male patients (mean forced expiratory volume in one second (FEV_1): 1.13 L) underwent tests to determine hyperoxic hypercapnic ventilatory response (HCVR) and isocapnic hypoxic ventilatory response (HVR) with simultaneous quantification of breathlessness by modified Borg scale. The ventilatory output was evaluated by the ratio of minute ventilation (V'_E) divided by measured maximal voluntary ventilation (MVV). The magnitude of HCVR or HVR was assessed as the slope value of the V'_E/MVV-end-tidal carbon dioxide pressure (P_{ET,CO_2}) or arterial oxygen saturation (S_{a,O_2}) regression line, respectively. The breathlessness during the tests was evaluated not only linearly in relation to V'_E/MVV, but also at given levels of P_{ET,CO_2} or S_{a,O_2}.

The mean value of the breathlessness at two different levels of ventilation was greater during HVR than during HCVR, suggesting that hypoxia is dyspnogenic independently of ventilatory stimulation. The HCVR was inversely correlated with the breathlessness response to ventilation, while similar correlation was partly present for HVR. The HVR was positively correlated with the breathlessness at an S_{a,O_2} of 80%, whilst there was no such correlation between the HCVR and the breathlessness related to P_{ET,CO_2}. Therefore, patients with a higher breathlessness related to increased ventilation had a lower HCVR and HVR, whilst those with a higher breathlessness with desaturation, which might include a direct influence of hypoxia, had a higher HVR.

These findings suggest an interaction between ventilatory response and breathlessness during the test, which may partly include behavioural modulation of HCVR and HVR through the breathlessness in various ways, depending on the origin and nature of the sensation.

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It is generally thought that hypoxic (HVR) and hypercapnic (HCVR) ventilatory responses are primarily based on automatic chemoreflex mechanisms and purely reflect individual respiratory chemosensitivities. The responses are essentially endogenous in origin [1–3] and broadly distributed even among normal subjects. Although they are highly reproducible within subjects [4, 5], several lines of evidence suggest that a cortical process may influence the ventilatory responses when examined in a conscious state. These responses are known to depend on cortical activities [6–9], and vary with mental tasks [10] and behavioural patterns [1, 11, 12]. Therefore, the response may partly involve a behavioural component in addition to the automatic mechanism, although the relative contribution varies between subjects. This idea is supported by one study using a magnetic stimulation method, which has uniquely demonstrated cortical involvement in ventilation stimulated by reflex during CO_2 inhalation [13].

As the chemical drive increases during a ventilatory response test, the subject usually feels dyspnoeic or uncomfortable, although the sensation varies in its intensity and quality. Several investigators have speculated that breathing is consciously or subconsciously optimized to minimize the respiratory sensation [14–16]. If this notion applies to the ventilatory response test as well, the sensation felt during the test may become a behavioural source to optimize the respiratory output for relief. Such behavioural factors may influence the result of the test in various ways, depending on the origin and nature of the sensation.

If such behavioural mechanisms actually exist, there should be some correlation between the ventilatory response value and the breathlessness during the test. Previous studies have implied that the perception of inspiratory effort might modify the CO_2 responsiveness in normal subjects [17, 18]. However, this idea has not been examined in a group of patients with respiratory disease. The present study was designed to examine the relationship between the magnitude of HCVR or HVR and breathlessness during the tests, in patients with chronic obstructive pulmonary disease (COPD).

Methods

Subjects

Fifteen male patients with COPD (all pulmonary emphysema) participated in this study. The diagnosis was made on the basis of a combination of clinical history, present illness, physical examination, chest radiograph and pulmonary function data. All of the subjects gave informed consent, although they were not informed of the physiological purpose of the study. Their age distribution and physical characteristics are summarized in table 1. Ages ranged from 45–71 yrs (65±11 yrs, mean± SD). None of the subjects had any other chronic disorders at the time of the study. They usually took some regular medications, such as aminophylline and bronchodilators, but did not take any within 24 h before the study.

The subjects underwent pulmonary function tests within 1 week before the measurement of the ventilatory response and while in a clinically stable condition. The tests included a spirogram (forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), peak expiratory flow rate (PEFR)), lung volumes measured by a helium dilution method (total lung capacity (TLC), functional residual capacity (FRC) and residual volume (RV)), a body plethysmograph (airway resistance (R_{aw})) and a single-breath measurement of transfer factor for carbon monoxide ($T_{L,CO}$). The results are summarized in table 1. For the lung volumes and $T_{L,CO}$ the measured values were expressed as a percentage of the predicted value.

Measurements of ventilatory response

The subjects refrained from smoking and drinking caffeine-containing beverages for at least 4 h before the study. Before the ventilatory response test, maximal voluntary ventilation (MVV) was measured over 15 s and converted to a 1 min value by calculation. Since reliable measurement of MVV was vital for the study, it was measured three times with sufficient rest intervals and the mean of the larger two values was used for analysis. The subjects then rested for 15 min. Throughout the following study, they were in a supine position and breathed spontaneously through a mouthpiece. Ventilation was analysed breath-by-breath using a hot-wire flowmeter (RF-H; Minato Medical Science Co.) placed in an expiratory line. Minute ventilation (V'_E) was calculated every 15 s by integrating the airflow. Expiratory gas was continuously monitored by a mass spectrometer (Medical Gas Analyzer MGA-1100; Perkin-Elmer, Pomona, CA, USA) and partial pressures of CO_2 and O_2 in end-tidal samples (P_{ET,CO_2} and P_{ET,O_2}, respectively) were used to represent the levels of chemical drives. Arterial oxygen saturation (S_{a,O_2}) was monitored by a finger-tip pulse oximeter (Biox 3740; Ohmeda, Liberty Cornercity, NJ, USA). The inspiratory gas mixture was automatically controlled by equipment developed in our laboratory, which can control P_{ET,O_2} and P_{ET,CO_2} simultaneously and independently in a predetermined manner [19].

Table 1. – Anthropometric and pulmonary function data (n=15)

Age yrs	65±11
Height cm	162±4
Weight kg	51±9
FVC % pred	78±20
FEV_1 L	1.13±0.55
FEV_1/FVC %	48±11
TLC % pred	110±16
FRC % pred	139±16
RV % pred	163±35
RV/TLC %	53±10
MVV % pred	44±26
$T_{L,CO}$/VA % pred	46±18
R_{aw} $cmH_2O \cdot L^{-1} \cdot s^{-1}$	1.94±0.92
PEFR $L \cdot s^{-1}$	3.71±1.95

Values are presented as mean±SD. FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; MVV: maximal voluntary ventilation; $T_{L,CO}$/VA: transfer factor of the lungs for carbon monoxide corrected by alveolar volume; R_{aw}: airway resistance; PEFR: peak expiratory flow rate.

HCVR and HVR were measured with simultaneous assessment of the ongoing breathlessness according to the Borg scale every 30 s. The following three tests were conducted for each subject with an interval of at least 20 min between the tests. The first run was HCVR and ensured that the subject became accustomed to the experimental procedure. The data from this training run were discarded from the analysis, since several subjects admitted that they had failed to adequately quantify the sensation. After this, the HCVR and HVR tests were conducted in random order.

The HCVR was measured while S_{a,O_2} was maintained at over 98%. After achieving an initial steady state whilst inhaling 3% CO_2, the CO_2 content in the inspiratory gas was gradually raised over 6 min, until P_{ET,CO_2} finally reached 8 kPa (60 Torr), or the subject could not endure anymore. The HVR was examined while monitored P_{ET,CO_2} was kept constant at the subject's resting value of P_{ET,CO_2} by controlling the inspiratory CO_2 content. After inhalation of a hyperoxic gas, S_{a,O_2} was progressively lowered over 6 min by changing the inspiratory O_2 content until S_{a,O_2} was less than 80%. In three subjects, the HCVR test was discontinued at P_{ET,CO_2} of 7.33–8.0 kPa (55–60 Torr) when they reached their limit of endurance of symptoms, whilst all the subjects completed the HVR test with S_{a,O_2} reduced to 80%.

In this study, the ventilatory output was evaluated from the ratio of V'_E to measured MVV (as a percentage) instead of V'_E itself. This was necessary to standardize the interindividual variability in body size and extent of airway obstruction between subjects, since they were COPD patients with variable airway limitation. The HCVR was evaluated by the slope value of the V'_E/MVV-P_{ET,CO_2} regression line (as $\%\cdot kPa^{-1}$) using the least-squares method. The analysis was made in the P_{ET,CO_2} range from the value whilst inhaling 3% CO_2 to the end of the test. The HVR was similarly assessed by the slope value of the V'_E/MVV-S_{a,O_2} regression line (dimensionless) in the S_{a,O_2} range from 98–80%.

Assessment of breathlessness

The subjects were requested to quantify the intensity of breathlessness every 30 s by relating to their common experience of the sensation. They were asked to carefully avoid indicating merely their fatigue or the extent

to which their breathing had increased. The scale was a continuous vertical linear display 100 mm in length, associated with 10 verbal descriptors of the extent of the symptom, which corresponded to those of the 10 point Borg category scale [20]. The verbal descriptors in the original Borg scale were carefully translated into Japanese. The subjects were instructed to indicate with a hand-controlled potentiometer how dyspnoeic they felt, with reference to the category descriptors. Therefore, the scoring system used should be described as a Borg scale without numbers. After each run, the subjects commented on the adequacy of the rating procedure during the test.

The breathlessness was evaluated against the ventilatory output. Linear regression analysis was used to evaluate the individual sensation, since the relationship of the breathlessness/ventilation could be regarded as linear in every subject. The correlation coefficients for the breathlessness/ventilation ranged 0.95–0.99 during HCVR (the number of sampling points varied from 5 to 8 between subjects), and from 0.94–0.99 during HVR (the number of sampling points varied from 7 to 10 between subjects). The analysis was made in the same range of P_{ET,CO_2} or S_{a,O_2} as the evaluation of the ventilatory responses. The relationship of breathlessness to ventilation was compared using both the slope value of the breathlessness-V'_E/MVV regression line and the breathlessness at the V'_E/MVV of 60%.

The breathlessness in each subject was also evaluated in relation to the chemical drives. For the HCVR, the score was assessed at the P_{ET,CO_2} while inhaling 3% CO_2 and at 7.33 kPa (55 Torr). On the other hand, the score was assessed at the S_{a,O_2} of 95% (under sufficient oxygenation) and 80% (during moderate desaturation) for the HVR.

Statistics

The analysis of variance (ANOVA) followed by Student's paired t-test, and Spearman's rank correlation (correlation coefficient (r_s)) were used for evaluating the significance of the data obtained. Statistical significance was accepted at the conventional p-value less than 0.05 level by two-tailed evaluation.

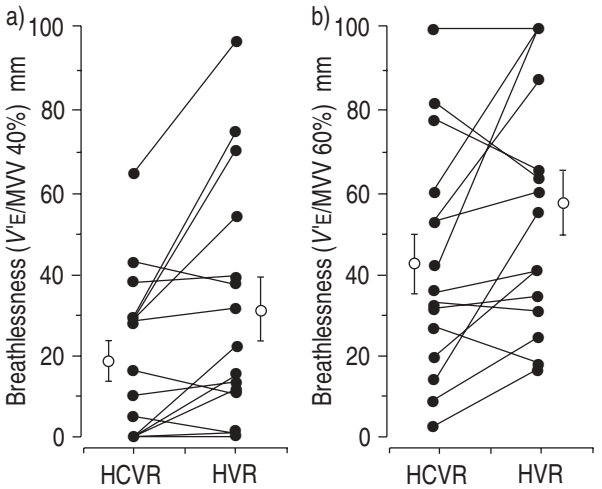

Fig. 1. – Comparison of breathlessness between HCVR and HVR, assessed using a 100 mm modified Borg scale. The mean value (±SEM) of breathlessness (○) at two given levels of ventilation was significantly greater during HVR than during HCVR, both when it was compared at: a) the V'_E/MVV of 40% and; b) at the V'_E/MVV of 60%. It suggests dyspnogenic effect of hypoxia, independent of ventilatory stimulation. HVR: hypoxic ventilatory response; HCVR: hypercapnic ventilatory response; V'_E/MVV: minute ventilation/maximal voluntary ventilation.

Results

The mean value of HCVR ($\Delta V'_E/MVV/\Delta P_{ET,CO_2}$) was 19.0±4.8%·kPa^{-1} (mean±SD) (range 11.2–27.7), while that of HVR ($\Delta V'_E/MVV/\Delta S_{a,O_2}$) was 1.40±0.90 (0.34–2.94). There was no correlation between the magnitude of HCVR or HVR and the extent of airway obstruction (FEV1, FEV1/FVC and R_{aw}).

Figure 1 shows the comparison of individual breathlessness between HVR and HCVR at two different levels of ventilation. The mean value of the sensation was significantly greater during HVR than during HCVR, both when it was compared at the V'_E/MVV of 40% (HCVR 19.1±5.1 (mean±SEM); HVR 31.7±7.8) and at that of 60% (HCVR 42.3±7.3; HVR 55.5±7.7) by using analysis of variance followed by a paired t-test (both $p<0.05$). Therefore, hypoxia itself might have a dyspnogenic effect, which could not be attributed to increased ventilation alone. The slope value of the breathlessness-V'_E/MVV regression line was not significantly different between hypercapnia and hypoxia (HCVR 1.44±0.14; HVR 1.59±0.20; $p<0.10$).

Figure 2 shows the relationship between the ventilatory response and the breathlessness related to ventilation

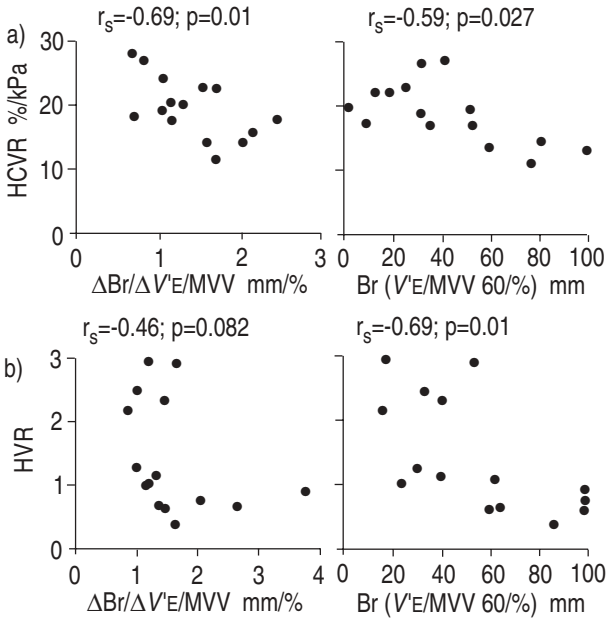

Fig. 2. – Relationship between ventilatory response and breathlessness (Br) related to ventilation. a) The HCVR, evaluated as $\Delta V'_E/MVV/\Delta P_{ET,CO_2}$ was inversely correlated with the breathlessness related to ventilation, using either the slope value of the breathlessness-V'_E/MVV line (left panel; $p<0.05$) or the breathlessness at the V'_E/MVV of 60% (right panel; $p<0.05$). Therefore, patients with a higher hypercapnic response had less breathlessness related to ventilation. b) The HVR, evaluated as $\Delta V'_E/MVV/\Delta S_{a,O_2}$, was inversely correlated with the breathlessness at the V'_E/MVV of 60% (right panel; $p<0.01$). Therefore those with a higher hypoxic response had less breathlessness for a given level of ventilation. Such a relationship was weak when evaluated using the slope of the breathlessness-V'_E/MVV line (left panel; p=0.082). r_s: Spearman's rank correlation coefficient; S_{a,O_2}: arterial oxygen saturation. For further definitions see legend to figure 1.

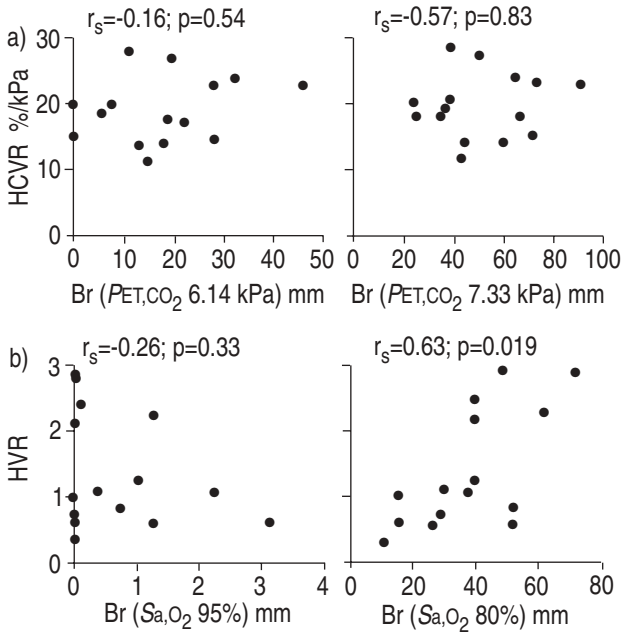

Fig. 3. – Relationship between ventilatory response and breathlessness (Br) related to chemical drive. a) HCVR. There was no correlation between the HCVR and the breathlessness related to P_{ET,CO_2} (left panel: at the P_{ET,CO_2} while inhaling 3% CO_2; right panel: at the P_{ET,CO_2} of 7.33 kPa (55 Torr)). The mean values (±SD) of the breathlessness were 17.6±12.7 mm during 3% CO_2 inhalation and 51.7±19.7 mm at the P_{ET,CO_2} of 7.33 kPa, respectively. b) HVR. The HVR was positively correlated with the breathlessness during moderate desaturation at the S_{a,O_2} of 80% (right panel; p<0.05), while such a correlation was negative under sufficient oxygenation at the S_{a,O_2} of 95% (left panel; p=0.33). Therefore, patients with a high hypoxic response had a high level of breathlessness for a given level of moderate desaturation. The mean values of the breathlessness were 5.0±7.2 mm at an S_{a,O_2} of 95% and 51.7±19.7 mm at an S_{a,O_2} of 80%. P_{ET,CO_2}: end-tidal carbon dioxide tension. For further definitions see legends to figures 1 and 2.

during the test. The HCVR was inversely correlated with the breathlessness response to ventilation when it was evaluated as either the slope of the breathlessness-V'_E/MVV line (r_s=-0.69; p<0.05) or the breathlessness at the V'_E/MVV of 60% (r_s=-0.59; p<0.05). Therefore, patients with a higher HCVR had less breathlessness related to ventilation. On the other hand, the HVR had an inverse correlation with breathlessness at the V'_E/MVV of 60% (r_s=-0.69; p<0.01). Thus, patients with a higher HVR had less breathlessness for a given level of ventilation. This relationship was weak when evaluated using the slope of the breathlessness-V'_E/MVV line (p=0.082).

Figure 3 demonstrates the relationship between ventilatory response and breathlessness related to P_{ET,CO_2} or S_{a,O_2}. There was no correlation between the HCVR and the breathlessness response related to P_{ET,CO_2}. In contrast, the HVR was positively correlated with the breathlessness during moderate desaturation at the S_{a,O_2} of 80% (r_s=0.63; p<0.05). Therefore, those with a higher HVR had a higher breathlessness for a given level of desaturation. However, such a relationship was negative under sufficient oxygenation at the S_{a,O_2} of 95%.

Discussion

In summary, breathlessness at a given level of ventilation was significantly greater during HVR than HCVR. The HCVR was inversely correlated with the breathlessness response to ventilation, while similar correlation was partly present for the HVR. On the other hand, the HVR was positively correlated with the breathlessness during moderate desaturation, while there was no such correlation between the HCVR and the breathlessness related to P_{ET,CO_2}.

In the present study, breathlessness in each subject was evaluated against ventilation. Although breathlessness is a very complex sensation which involves the activation of various sensory systems, including both chemical and mechanical events in response to respiratory stimuli, the sensation is thought to be largely based on a sense of effort reflecting centrally generated motor commands [21, 22]. Since the subjects had a variable extent of airway obstruction due to COPD, V'_E was corrected by measured MVV to normalize the interindividual variability in the body size and the extent of airway limitation. The HCVR curve of patients with COPD is known to correspond with that of normal subjects if ventilation is corrected by MVV [23, 24]. The V'_E/MVV ratio is also known as the "dyspnoeic index", which provides a good reflection of a subject's shortness of breath both in normal subjects and patients [25]. We assume that the breathlessness evaluated in relation to ventilation reflects the respiratory sensation associated with increasing motor commands.

The results of the present study suggest that there may be some interaction between the ventilatory response to hypercapnia or hypoxia and the ongoing respiratory sensation during the tests. The inverse correlation between the breathlessness response and the ventilatory response can be interpreted in two ways regarding the cause-effect relationship between them. In the first place, the ventilatory responses to hypercapnia and hypoxia may simply shape the respiratory sensation responses. Before the study, it was anticipated that subjects with the largest ventilatory response to hypercapnia or hypoxia would show the greatest increase in the breathlessness, but this was not true. It is possible that patients with smaller HCVR and HVR values may feel more dyspnoeic against increasing ventilation because of their impaired ventilatory capacities due to airway limitation. However, this possibility seems minor, since V'_E was standardized with measured MVV and, thus, there was no correlation between the ventilatory response value and the airway limitation. By using the corrected V'_E, it was intended to quantify how much effort the subject made to maintain needed ventilation compared to the limit of the ventilatory capacity.

Another tentative interpretation is that the respiratory sensation to changes in respiratory motor output shapes the ventilatory responses. It has been generally believed that the HCVR or HVR is determined through a purely automatic process, and eventually has effects on the genesis of the breathlessness during tests. However, if the subject feels dyspnoeic through the perception of motor commands due to increasing ventilation, the sensation may in turn restrict the respiratory centre output to ameliorate unpleasant feelings, such as the effort sensation. In this case, the sensation related to increasing motor commands may have a negative feedback effect on the ventilatory output and, thus, a negative modulatory influence on the slope of HCVR. If such behavioural

mechanisms actually exist, the breathlessness at least partly influences the results of the ventilatory response test, either consciously or unconsciously.

Although the slope values of HVR and HCVR are thought to reflect the intrinsic respiratory chemosensitivities, considerable evidence suggests that the responses are behaviourally modulated through a cortical process in the awake state [1, 6–12]. Cortical involvement was demonstrated with a magnetic stimulation method not only during volitional inspiration but also during the ventilatory response stimulated by reflex with CO_2 inhalation [13]. In healthy subjects, the increasing sense of thoracic distortion associated with breathing, by allowing them to prejudge the lung volume, results in a reduction of the subsequently measured CO_2 responsiveness [26]. In normal subjects, the magnitude of HCVR was inv-ersely correlated with the slope of the effort sensation P_{ET,CO_2} regression line, which suggests that the perception of inspiratory efforts may modify the CO_2 responsiveness [17, 18]. Therefore, it is reasonable to assume also in patients with COPD that similar behavioural mechanisms may modulate the ventilatory response values through the breathlessness. The present findings support such a hypothesis, although this study alone could not finally conclude the cause-effect relationship between the ventilatory response and the respiratory sensation.

Several lines of evidence suggest that awake humans optimize respiratory activity in order to minimize the perception of the respiratory muscle force necessary for maintaining required ventilation or to minimize uncomfortable feelings associated with breathing [14–16]. At fixed levels of P_{ET,CO_2}, the breathlessness grows when ventilation is voluntarily raised or lowered from spontaneous levels, supporting the notion that ventilation is regulated to minimize the sensation of respiratory effort and discomfort [15]. There is an optimization theory that ventilation is determined to minimize the total cost due to chemical stimuli and the resultant work of the respiratory muscles [16]. These findings suggest that there may be interactions between metabolic demands on the respiratory apparatus and voluntary respiratory control. The subjects may choose to compromise between the chemical drive to increase the ventilation to maintain eupnoea and the behavioural need to reduce awareness of the respiratory effort.

The relationship between breathlessness and ventilatory response was remarkably different between hypercapnia and hypoxia. The slope value of HVR was positively correlated with the sensation related to S_{a,O_2}, while no such relationship was detected for HCVR. The correlation was positive under enhanced chemical drives during moderate desaturation (S_{a,O_2} 80%), while it was negative during sufficient oxygenation (S_{a,O_2} 95%). It is known that the change in respiratory sensation produced by increasing P_{a,CO_2} is primarily a consequence of increasing respiratory efferent activity, and, thus, an increasing sense of effort reflecting the motor commands [21, 22] rather than a direct effect of CO_2 [27]. On the other hand, some investigators propose a direct dyspnogenic effect of hypoxia itself, which is independent of its ventilatory stimulation [28, 29].

In the present study, the intensity of the breathlessness related to ventilation was greater during HVR than during HCVR, when the sensation was compared at the isopnoeic level. If the sensation is produced primarily as a consequence of increasing respiratory efferent activity, the breathlessness should be the same between hypoxia and hypercapnia. Therefore, these data support the dyspnogenic effect of hypoxia. Although the slope value of the breathlessness/ventilation line was larger in HVR, the difference was not significant. It may suggest that the difference in the two stimuli lies particularly in the threshold point at which breathlessness was firstly perceived by the subjects. The threshold was not established in this study, since most subjects admitted that it was actually difficult to detect the point during "progressive" ventilatory stimulation. If the subject feels dyspnoeic directly as a result of enhanced chemical drive as S_{a,O_2} decreases, the ventilatory response may be promoted through the perception. Therefore, the correlation between the breathlessness during desaturation and the HVR may suggest the positive modulatory effect of the breathlessness associated with desaturation on the slope of HVR. Hypoxic stimuli may influence the respiratory output not only through purely automatic reflex mechanisms but also, at least partly, through behavioural modulation at the higher brain centre.

In conclusion, we examined the relationship between breathlessness and the ventilatory response to hypoxia or hypercapnia in patients with chronic obstructive pulmonary disease. The breathlessness at a given level of ventilation was significantly greater during hypoxic ventiatory response than during hypercapnic ventilatory response, suggesting the dyspnogenic influence of hypoxia. The patients with a higher level of breathlessness to increased ventilation had a lower hypercapnic and hypoxic ventilatory response, while those with a higher level of breathlessness against desaturation, which might include a direct effect of hypoxia, had a higher hypoxic ventilatory response. These findings suggest an interaction between ventilatory response and breathlessness during the test in patients with chronic obstructive pulmonary disease. It may, in part, include behavioural mechanisms, which modulate the ventilatory response through the breathlessness in various ways depending on the origin and nature of the sensation.

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