Effects of exercise and CO_2 inhalation on intersubject variability in ventilatory and heart rate responses to progressive hypoxia

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Effects of exercise and CO_2 inhalation on intersubject variability in ventilatory and heart rate responses to progressive hypoxia. F. Sato, M. Nishimura, T. Igarashi, M. Yamamoto, K. Miyamoto, Y. Kawakami. ©ERS Journals Ltd 1996.
ABSTRACT: Although the ventilatory and heart rate responses to hypoxia are known to vary widely among subjects, it is not known how exercise or hypercapnia influence the intersubject variability of these responses. If the intersubject variability increases under such conditions, the inherent response of individuals will have more impact on ventilation and heart rate under a variety of hypoxic conditions during exercise or with hypercapnia than at rest or with normocapnia.

Seventeen healthy male volunteers underwent tests to measure ventilatory response to isocapnic progressive hypoxia three times respectively: at rest; during CO_2 inhalation (end-tidal carbon dioxide tension (PET,CO_2) raised by 5 torr from the baseline level); and during mild exercise with a cycle ergometer (12.5 W) in a supine position.

The mean (SEM) value of hypoxic ventilatory response (HVR) (Δ minute ventilation (V'E)/Δ arterial oxygen saturation (Sa,O_2)) was significantly increased both in the exercise and hypercapnic runs compared with that in the control run (0.45±0.12, 0.34±0.08, respectively, *vs* 0.12±0.02 L·min^{-1}/% fall), although the respiratory pattern was different under the two loaded conditions. The intersubject variation in HVR was also significantly increased during the two loaded conditions compared with the control, although a significant correlation remained between the control value and that obtained during either loaded condition (r=0.66 and r=0.60, respectively). The heart rate (HR) response evaluated by the slope factor (ΔHR/$\Delta$$S$a,$O_2$) was not significantly different either in the mean value or in the intersubject variability among the three experimental conditions.

In conclusion, exercise or CO_2 inhalation not only increase the slope value of HVR but also amplify the intersubject variability of the response. In contrast, the HR response to hypoxia evaluated as a slope factor does not change with exercise or CO_2 inhalation.
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It is known that the hypoxic ventilatory response (HVR) is enhanced by CO_2 inhalation [1] and during exercise [2, 3]. It is also known that hypoxic chemosensitivity evaluated by HVR has a wide interindividual variability [4, 5], and that the variability in hypoxic chemosensitivity is a factor accounting for intersubject variation in pathophysiological responses under a variety of hypoxic conditions. For instance, a lower HVR is shown to be associated with poorer performance at high altitude [6, 7], more severe nocturnal desaturation in sleep apnoea syndrome [8], hypercapnic respiratory failure in chronic obstructive pulmonary disease (COPD) [9–11], and even near-death cases of bronchial asthma [12]. It is, thus, clinically important to examine the interaction of HVR with exercise and/or hypercapnia. If the intersubject variability in HVR increases during exercise and hypercapnia, the inherent response of individuals will have far more impact on ventilation and heart rate whilst they are exercising or hypercapnic than whilst they are not. There have, however, been few studies that have specifically examined the effect of exercise and/or hypercapnia on the intersubject variability in HVR. In this study, we investigated whether the enhancement of HVR during exercise and/or CO_2 inhalation was the same in different subjects.

In addition, we also analysed the heart rate response to hypoxia under these conditions and attempted to gain insight into the interaction between ventilation and heart rate in hypoxia [13].

Materials and methods

Measurements

Seventeen healthy male volunteers, aged 21±2 (mean±SD) years, served as subjects and gave their informed consent. They were, however, not aware of the physiological purpose of the experiment. They had refrained from smoking and drinking beverages containing caffeine for at

least 5 h before the tests. All subjects had normal spirometric values. For all experiments, the subject was in a supine position and breathed spontaneously through a mouthpiece connected to a J-valve.

A dual-control system, developed in our laboratory [14], was used to regulate arterial oxygen tension (Pa,O_2) and arterial carbon dioxide tension (Pa,CO_2) simultaneously and independently. The system utilized end-tidal oxygen tension (PET,O_2) and end-tidal carbon dioxide tension (PET,CO_2) as guides to control arterial blood gases by computerized automatic changes in inspiratory gas composition. Minute ventilation (V'E) was measured every 15 s by electrical integration of the flow signals obtained from a hot-wire respiratory flowmeter (RF-H; Minato Medical Products). Respiratory gases were continuously monitored by a mass spectrometer (MGA-1100; Perkin-Elmer Medical Instruments). Tidal volume (VT), respiratory frequency (fR), inspiratory time (tI), inspiratory duty cycle (tI/total breath duration ($t$tot), where $t$tot is a reciprocal of fR), and mean inspiratory flow (VT/tI) were measured electronically from the respiratory airflow signal for analysis of the breathing pattern. VT was analysed by electronically integrating airflow, and tI was analysed by measuring time intervals between initial zero flow and subsequent zero flow. The arterial oxygen saturation (Sa,O_2) and heart rate (HR) were measured using a pulse oximeter applied to the finger. The signals of V'E, PET,O_2, PET,CO_2, and breathing pattern indices were continuously monitored and recorded on a multichannel recorder (type 8K-23-1-L; San-ei Sokki) and at the same time stored at 15 s intervals in an on-line signal processing computer (ATAC-450; Nihon-Kohden) for later analysis.

Experimental protocol

Each subject was examined for ventilatory responses to isocapnic progressive hypoxia, three times under different conditions (table 1). Firstly, the subject breathed room air through a mouthpiece connected to the above-described experimental set-up. After respiration had been stabilized for at least 5 min, the subject started to breathe the initial gas, which contained 22–23% O_2 balanced by N_2. The inspiratory oxygen concentration was first raised so that PET,O_2 exceeded 150 torr, and then progressively lowered over 6 min to a level where PET,O_2 was about 40 torr and Sa,O_2 was ≤80% as monitored by a pulse oximeter. Throughout the test, PET,CO_2 was maintained by the servo-control at the baseline value while the subject was breathing room air.

After an interval of 20 min for rest, the second test was performed in an identical way except for the PET,CO_2, which was regulated and maintained at a level 5 torr higher than the resting value throughout the test.

After another interval of 20 min for rest, the subject started a light level of exercise (12.5 W) by pedalling a cycle ergometer at a speed of 50 cycles·min^{-1} in a supine position. All subjects could maintain a constant pedalling frequency by maintaining rhythm with a metronome throughout the exercise. After 6 min of steady-state exercise, the third test was carried out as described above while the subject maintained constant exercise. PET,CO_2 was again kept constant at the baseline level while the subject was breathing room air during steady-state exercise.

Data analysis

The ventilatory response to isocapnic progressive hypoxia was evaluated by the slope of the Sa,O_2-V'E response line ($\Delta V'$E/ΔSa,O_2), which was calculated with the least-squares method. The heart rate response to isocapnic progressive hypoxia was evaluated in a similar way by the slope of the Sa,O_2-HR response line (ΔHR/ΔSa,O_2), assuming the relationship between Sa,O_2 and HR to be linear [15].

Table 1. – Individual data on ventilatory responses to progressive hypoxia

Subj. No.	Rest		Exercise		Hypercapnia	
	$\Delta V'$E/ΔSa,O_2 L·min^{-1}/% fall	PET,CO_2 torr	$\Delta V'$E/ΔSa,O_2 L·min^{-1}/% fall	PET,CO_2 torr	$\Delta V'$E/ΔSa,O_2 L·min^{-1}/% fall	PET,CO_2 torr
1	0.13	43.1±1.7	0.51	42.8±1.6	0.43	47.3±1.2
2	0.02	41.9±1.2	0.19	41.0±1.2	0.19	45.3±0.8
3	0.12	39.4±0.9	0.46	42.1±1.3	0.19	44.6±1.0
4	0.08	41.3±1.3	0.16	39.5±1.2	0.27	45.5±1.2
5	0.07	33.0±1.3	0.38	38.8±1.1	0.08	40.2±1.1
6	0.25	38.8±1.2	0.30	39.2±1.1	0.50	43.4±1.0
7	0.27	38.3±1.2	2.02	40.4±1.1	0.22	43.2±0.7
8	0.01	35.3±1.1	0.20	35.0±1.1	0.20	40.1±1.2
9	0.25	36.7±1.7	1.14	38.7±1.9	0.79	41.0±0.8
10	0.20	42.3±1.4	0.71	42.7±1.4	1.10	46.4±0.4
11	0.06	40.3±0.8	0.12	41.4±1.5	0.01	45.1±0.7
12	0.07	40.8±1.3	0.22	42.8±1.4	0.29	47.6±1.2
13	0.09	38.6±0.8	0.16	40.4±0.8	0.21	44.4±0.7
14	0.01	44.6±0.7	0.01	44.3±1.4	0.23	48.7±0.8
15	0.26	39.9±0.8	0.26	39.2±1.4	-	-
16	0.12	36.0±0.8	0.37	38.0±1.1	-	-
17	0.08	38.6±1.1	0.52	39.4±1.2	-	-

PET,CO_2 values are presented as mean±SD. The data of three subjects, whose PET,CO_2 in the hypercapnic run was poorly controlled and whose averaged PET,CO_2 was raised by less than 3 torr from the resting value, were discarded from later analysis. V'E: minute ventilation; Sa,O_2: arterial oxygen saturation; PET,CO_2: end-tidal carbon dioxide tension; Subj: subject.
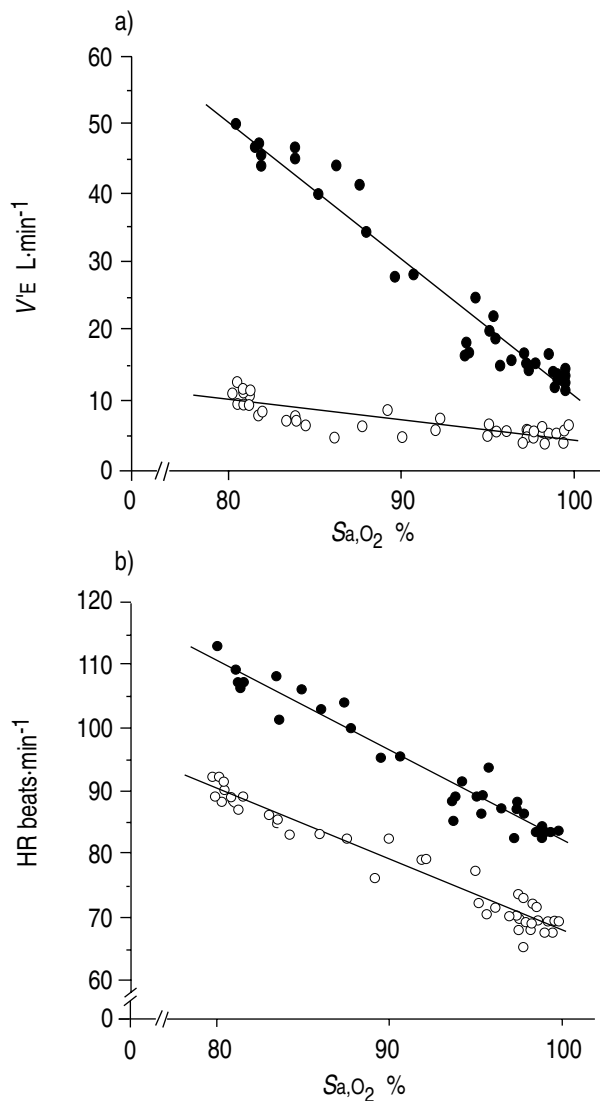
Fig. 1. – Representative data from one subject. a) The relationship between Sa,O_2 and $V'E$. b) The relationship between Sa,O_2 and HR. ○: at rest; ●: during exercise. Both $V'E$ and HR had significant correlations with Sa,O_2. $V'E$ during exercise was higher than $V'E$ at rest at the beginning of the hypoxic ventilatory response test, and the slope value of the linear regression line ($\Delta V'E/\Delta Sa,O_2$) during exercise was also greater than that at rest. HR during exercise was also higher than HR at rest at the beginning of the test; however, the slope value of the linear regression line ($\Delta HR/\Delta Sa,O_2$) was similar under the two conditions. Sa,O_2: arterial oxygen saturation; $V'E$: minute ventilation; HR: heart rate.

Series of data under the three different conditions were analysed by single-factorial analysis of variance. Comparison of the data between two different conditions was made by Student's paired t-test and the Wilcoxon test where appropriate. Relations of the two values between the two different experimental conditions were examined by the linear correlation coefficient (r) and Spearman's rank correlation coefficient (r_s). The intersubject variance of HVR during CO_2 inhalation or during exercise was compared with that measured with normocapnia at rest by a two-tailed F test. Values are expressed as mean± SE unless otherwise specified. Statistical significance was accepted at a p-value of less than 0.05 for all statistics.

Results

Representative data from one subject are shown in figure 1. $V'E$ during exercise was higher than at rest at the beginning of the hypoxic ventilatory response test, and the slope value of the linear regression line ($\Delta V'E/ \Delta Sa,O_2$) during exercise was also greater than that at rest (fig. 1a). HR during exercise was also higher than at rest at the beginning of the test; however, the slope value of the linear regression line ($\Delta HR/\Delta Sa,O_2$) was similar under the two conditions (fig. 1b).

The data of three subjects, whose PET,CO_2 in the hypercapnic run was poorly controlled and whose averaged PET,CO_2 was raised by less than 3 torr from the resting value, were discarded from later analysis. PET,CO_2 was well controlled throughout the experiment in the remaining subjects, so that change in PET,CO_2 in each experimental run was within 2 torr and the averaged PET,CO_2 in the hypercapnic run was raised sufficiently, as expected. The mean±SEM values of averaged PET,CO_2 in HVR for all the subjects were 39.4±0.7 torr in the control run, 40.4±0.5 torr in the exercise run, and 44.5±0.7 torr in the hypercapnic run. The PET,CO_2 in the hypercapnic run was significantly higher than that of the others by about 5 torr (table 1).

The slope value of the HVR ($\Delta V'E/\Delta Sa,O_2$) was significantly higher both in the exercise run and in the hypercapnic run than in the control run (0.45±0.12, 0.34±0.08 vs 0.12±0.02 L·min^{-1}/% fall, respectively, (p<0.01 for both, by Student's paired t-test and the Wilcoxon test) (table 2). The intersubject variation in HVR was also significantly increased, both during exercise and during CO_2 inhalation, compared with the control (F=6.1 and F=5.0, respectively; p<0.01 for both) (figs. 2 and 3).

Table 2. – Ventilatory and heart rate responses to progressive hypoxia

		Rest (normocapnia) (n=17)	Exercise (n=17)	Hypercapnia (n=14)
$\Delta V'E/\Delta Sa,O_2$	L·min^{-1}/% fall	0.12±0.02	0.45±0.12*	0.34±0.08*
$V'E(Sa,O_2=100\%)$	L·min^{-1}/% fall	4.31±0.33	11.71±0.71*	8.76±0.74*
$\Delta HR/\Delta Sa,O_2$	beats·min^{-1}/% fall	0.80±0.10	0.95±0.07	0.95±0.11
$HR(Sa,O_2=100\%)$	beats·min^{-1}	59.4±1.2	79.5±1.6*	60.3±1.1
PET,CO_2	torr	39.4±0.7	40.4±0.5	44.5±0.7*

Values are presented as mean±SEM. $V'E(Sa,O_2=100\%)$: values calculated from the Sa,O_2-$V'E$ response line at $Sa,O_2=100\%$; $HR(Sa,O_2=100\%)$: values calculated from the Sa,O_2-HR response line at $Sa,O_2=100\%$; PET,CO_2: mean values of averaged PET,CO_2 in HVR for all the subjects; HR: heart rate; HVR: hypoxic ventilatory response. *: p<0.01 compared with value at rest. For further abbreviations see legend to table 1.
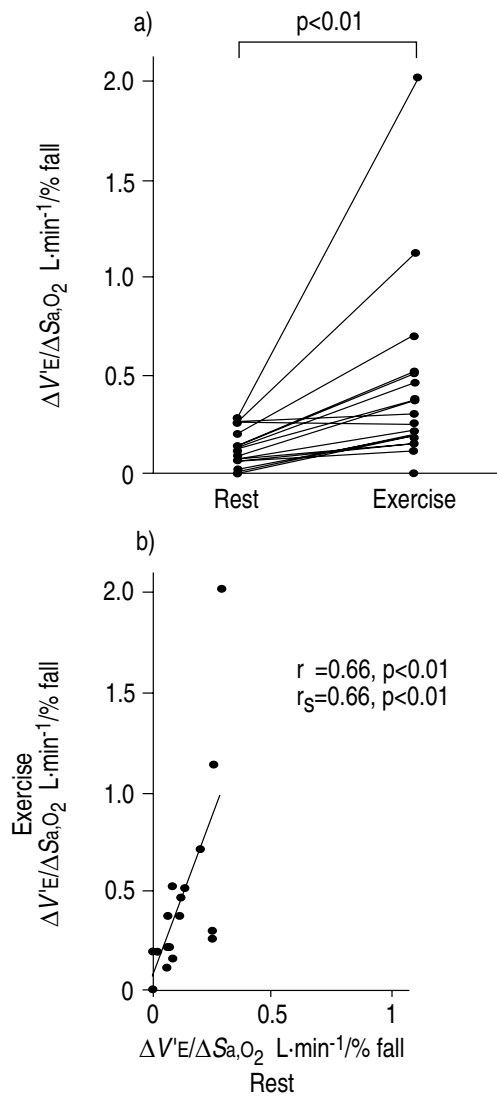
Fig. 2. – Hypoxic ventilatory responses (HVR) measured at rest and during exercise in 17 subjects. a) Exercise significantly enhanced the slope value ($\Delta V'\text{E}/\Delta S\text{a,O}_2$) of hypoxic ventilatory response ($p<0.01$ both by Student's t-test and by the Wilcoxon test). The intersubject variability in HVR also increased during exercise by two-tailed F test ($F=6.1$, $p<0.01$). b) There was a significant positive correlation between the slope values at rest and during exercise both by linear correlation coefficient (r) and by Spearman's rank correlation coefficient (r_s) ($r=0.66$, $p<0.01$; $r_s=0.66$, $p<0.01$). For abbreviations see legend to figure 1.
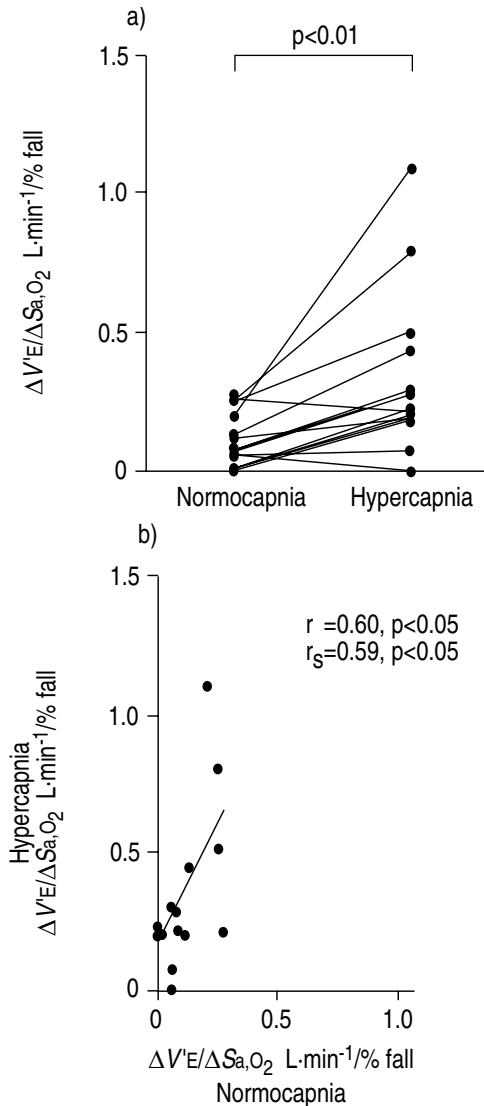
Fig. 3. – Hypoxic ventilatory responses (HVR) measured under normocapnia and hypercapnia in 14 subjects. a) Hypercapnic stimuli caused a significant increase in HVR ($p<0.01$). The intersubject variability in HVR in the presence of CO_2 was also found to increase by a two-tailed F test ($F=5.0$, $p<0.01$). b) There was a significant positive correlation between the HVR measured under normocapnia and hypercapnia both by linear correlation coefficient (r) and by Spearman's rank correlation coefficient (r_s) ($r=0.60$, $p<0.05$; $r_s=0.59$, $p<0.05$). For abbreviations see legend to figure 1.

Table 3. – Comparisons of breathing pattern variables at $S\text{a,O}_2=95$, 90 and 80% between rest and exercise conditions (n=17)

	$S\text{a,O}_2$ 95%		$S\text{a,O}_2$ 90%		$S\text{a,O}_2$ 80%	
	Rest	Exercise	Rest	Exercise	Rest	Exercise
$V\text{T}$ L	0.47±0.05	0.82±0.09*	0.49±0.07	0.91±0.08†*	0.59±0.06	1.15±0.10†*
$f\text{R}$ breaths·min⁻¹	12.5±1.4	20.9±2.7*	13.0±1.5	20.9±2.5*	13.3±1.7	22.1±3.1*
$t\text{I}$ s	3.42±0.42	1.75±0.30	3.09±0.35	1.88±0.41	3.34±0.44	1.71±0.31
$t\text{I}/t\text{tot}$	0.60±0.05	0.46±0.04	0.60±0.03	0.47±0.03	0.61±0.04	0.44±0.22
$V\text{T}/t\text{I}$ L·s⁻¹	0.15±0.02	0.61±0.11*	0.22±0.04	0.76±0.17*	0.22±0.03	1.10±0.24†*

Values are presented as mean±SEM. $V\text{T}$: tidal volume; $f\text{R}$ breathing frequency; $t\text{I}$: inspiratory time; $t\text{I}/t\text{tot}$: duty cycle; $V\text{T}/t\text{I}$: mean inspiratory flow. †: $p<0.05$ compared with data at $S\text{a,O}_2$ 95% in each trial; *: $p<0.05$ compared with data at rest. Both tidal volume ($V\text{T}$) and respiratory frequency ($f\text{R}$) were greater during exercise at all levels of $S\text{a,O}_2$ compared to those at rest.

Table 4. – Comparisons of breathing pattern variables at Sa,O$_2$=95, 90 and 80% between normocapnic and hypercapnic conditions (n=14)

	Sa,O$_2$ 95%		Sa,O$_2$ 90%		Sa,O$_2$ 80%	
	Normocapnia	Hypercapnia	Normocapnia	Hypercapnia	Normocapnia	Hypercapnia
VT L	0.47±0.05	0.78±0.08*	0.49±0.07	0.93±0.11[†]*	0.59±0.06	1.19±0.15[†]*
fR breaths·min^{-1}	12.5±1.4	13.7±1.6	13.0±1.5	13.2±1.8	13.3±1.7	14.5±2.0
tI s	3.42±0.42	2.92±0.33	3.09±0.35	3.33±0.48	3.34±0.44	3.16±0.52
tI/$t$tot	0.60±0.05	0.54±0.01	0.60±0.03	0.53±0.03	0.61±0.04	0.56±0.04
VT/tI L·s^{-1}	0.15±0.02	0.51±0.20	0.22±0.04	0.66±0.29	0.22±0.03	0.70±0.16

Values are presented as mean±SEM. For abbreviations see legend to figure 3. [†]: p<0.05 compared with data at Sa,O$_2$ 95% in each trial; *: p<0.05 compared with data with normocapnia. Tidal volume, but not respiratory frequency, was greater in the hypercapnic trial at all levels of Sa,O$_2$ compared to that in the normocapnic trial.
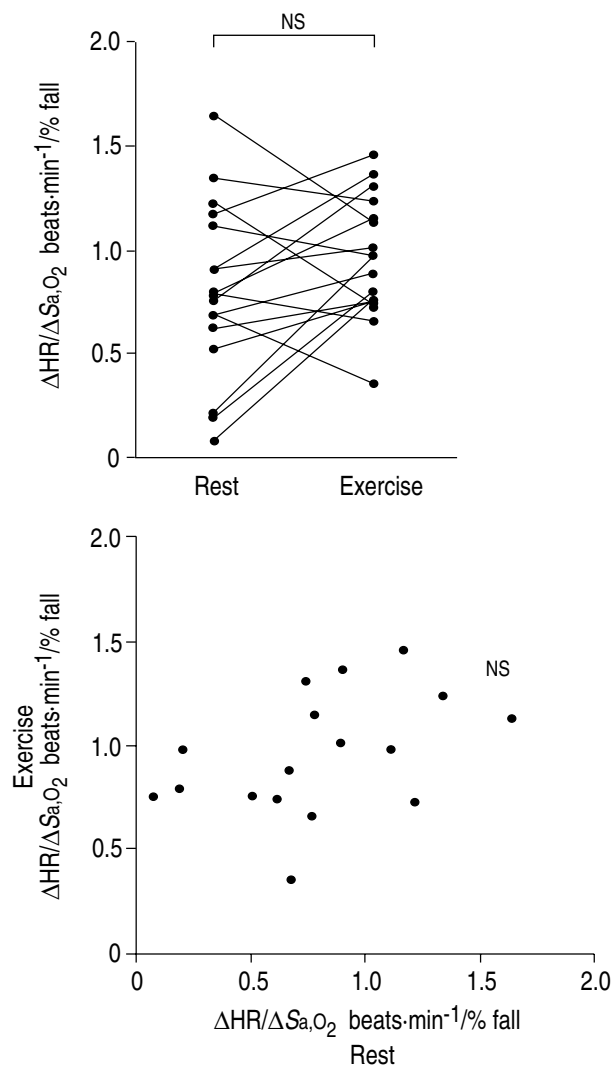

Fig. 4. – Heart rate (HR) responses to hypoxia at rest and during exercise in 17 subjects. No correlation was found between both variables. Sa,O$_2$: arterial oxygen saturation; NS: nonsignificant.
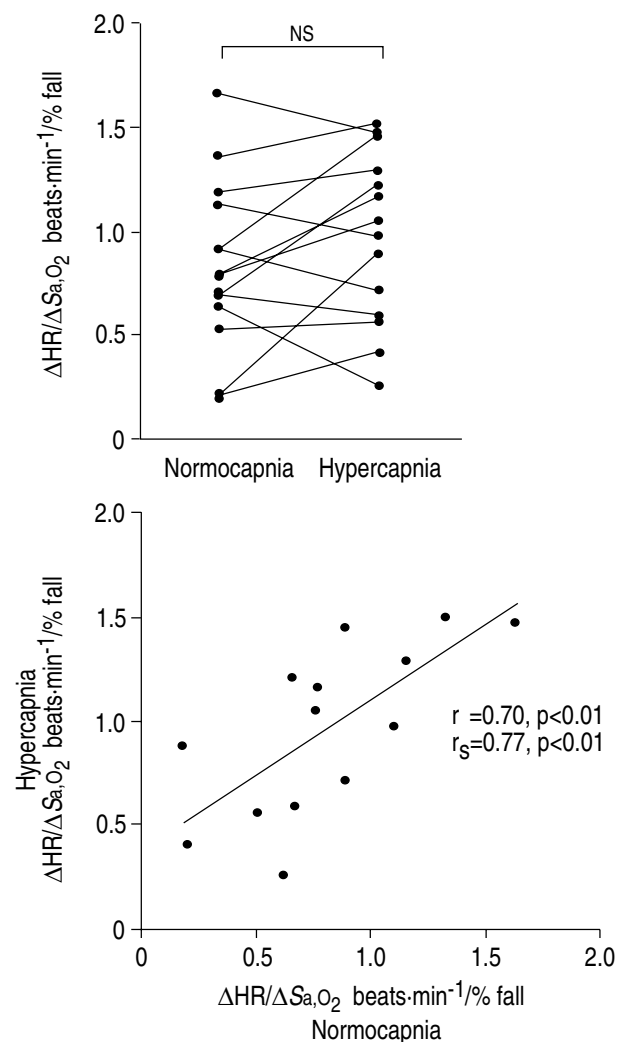

Fig. 5. – Heart rate (HR) responses to hypoxia under normocapnic and hypercapnic conditions in 14 subjects. There was a significant positive correlation between heart rate responses to hypoxia measured under normocapnia and those under hypercapnia both by the linear correlation coefficient (r) and by Spearman's rank correlation coefficient (r$_s$) (r=0.70, p<0.01; r$_s$=0.77, p<0.01).

There was a significant correlation between the value of the hypoxic ventilatory response at rest and that obtained during exercise or during CO_2 inhalation (r=0.66, p<0.01, r$_s$=0.66, p<0.01; and r=0.60, p<0.05, r$_s$=0.59, p<0.05, respectively) (figs. 2 and 3).

Breathing pattern analysis revealed different effects of CO_2 inhalation and exercise on the changes in fR and VT. During hypercapnic stimuli, VT was larger than that of the control run at all levels of Sa,O$_2$, whilst no change was observed in Rf. On the other hand, both VT and fR were significantly larger during exercise than in the control run. In progressive hypoxia, an increase in V'E was caused by an increase in VT in every experimental protocol (tables 3 and 4).

The HR responses to hypoxia evaluated as $\Delta HR/\Delta S$a,O_2 were 0.80 ± 0.10 beats·min^{-1}/% fall in the control run, 0.95 ± 0.07 beats·min^{-1}/% fall in the exercise run, and 0.95 ± 0.11 beats·min^{-1}/% fall in the hypercapnic run, between which no significant difference was observed. Although there was a significant correlation between $\Delta HR/\Delta S$a,O_2 in the control run and that in the hypercapnic run ($r=0.70$, $p<0.01$; $r_s=0.77$, $p<0.01$), no significant relationship was found between the values in the control and exercise runs (figs. 4 and 5).

Discussion

In the present study, we demonstrated that exercise and CO_2 inhalation not only increase the slope of HVR but also amplify the intersubject variability of HVR. Since each individual's slope of HVR measured during exercise or CO_2 inhalation was well-correlated with that measured at rest, when PET,CO_2 was maintained at baseline level, it could be reasonably assumed that the individual characteristics of hypoxic chemosensitivity were maintained under a variety of conditions. In other words, those who were high responders to hypoxia in ventilation at rest showed even higher responses during exercise or in the presence of hypercapnia compared to low responders. In contrast to the ventilatory response, the slope values of the HR response to hypoxia did not significantly change even during exercise or CO_2 inhalation. Of particular note was the HR response to hypoxia under hypercapnic conditions, which was very similar to that of normocapnic conditions, despite variable augmentation of HVR with hypercapnia. These results indicate that the HR increase in response to hypoxia was not significantly modulated by increased ventilation caused either by exercise or CO_2 inhalation.

It is well-known that the hypoxic sensitivity in the carotid body is influenced by the level of Pa,CO_2 and seems to be enhanced during exercise, at least in humans, although the latter finding is based largely on circumstantial evidence and the mechanisms proposed, so far, have all been speculative [2]. To our knowledge, there have been no studies focusing specifically on the intersubject variability in terms of the interaction of HVR with exercise and CO_2 inhalation. HVR is known to span a wide range in healthy subjects [4, 5], as well as in patients with cardiopulmonary disease. This intersubject variability is explained, at least in part, by genetic factors [16–18] and remains unchanged for many years in healthy subjects [19]. Low HVR values have been shown to be associated with poor exercise capacity at high altitude [6, 7], severe nocturnal desaturation in sleep apnoea syndrome [8], hypercapnic respiratory failure in COPD [9–11], and possibly even fatal asthma attacks [12]. Since these conditions are all associated with exercise or hypercapnia, the strong influence on the pathophysiology of hypoxic chemosensitivity may be a consequence of enhancement of hypoxic chemosensitivity itself and also amplification of intersubject variability under such conditions. Indeed, this study clearly demonstrated that even mild exercise or mild hypercapnic stress significantly enhanced not only the magnitude of HVR as a whole, but also the intersubject variability in HVR. These findings may also explain intersubject differences in exertional dyspnoea and/or exercise tolerance

in patients with COPD. The nocturnal hypoxaemia associated with variable levels of elevation in Pa,CO_2 seen in such patients may also be influenced by the individual hypoxic chemosensitivity.

It is beyond the scope of this study to discuss the mechanisms underlying the enhancement of HVR during exercise or CO_2 inhalation. It should, however, be remembered that there have been numerous historical debates concerning HVR during exercise. Possible factors involved in the enhancement of HVR during exercise include effects of changes in body temperature [20], sympathetic nerve stimulation [21], humoral adrenergic mechanisms [22, 23], increased metabolic rate *per se* [24], and the augmentation of carbon dioxide flow to the lung [25]. In addition, oscillatory behaviour in Pa,CO_2 may contribute to an increase in the carotid body activity [26]. Recent studies indicate that an increase in plasma potassium concentration [K$^+$] during exercise may exert a greater effect on carotid chemoreceptor activity and, thus, ventilation than at rest, particularly in hypoxia [27–29]. Other possible endogenous potentiators of chemosensitivity include circulating adenosine, which may be released together with potassium from exercising muscles [30, 31]. Whatever mechanism is involved, it does not fully explain why the intersubject variability in HVR is increased during exercise. The specific activity in the carotid body during hypoxia is so variable among subjects [32] that any endogenous potentiator for the activity may amplify the intersubject variability in a nonspecific fashion. We have recently shown, in a twin study, that the genetic control for hypercapnic ventilatory response is apparent when the test is conducted in hypoxia but is not so in hyperoxia [33]. This may be another example of the hypoxia-hypercapnia interaction amplifying the intersubject variability in respiratory chemosensitivity and, thus, making genetic factors more detectable.

Breathing pattern analysis revealed different effects of exercise and CO_2 inhalation on respiratory frequency. In the case of HVR with exercise, both tidal volume and respiratory frequency were greater during exercise than at rest at all levels of Sa,O_2. On the other hand, only tidal volume response was enhanced in the case of HVR with CO_2 breathing. Although the underlying mechanisms for this discrepancy are unknown, a possible explanation for the higher fR during exercise is the entrainment of fR to the locomotive rhythm whilst cycling the ergometer [34, 35]. The change in fR during progressive hypoxia was not significant either in the case of exercise or CO_2 inhalation.

In contrast with the ventilatory response, the HR response to hypoxia evaluated as a slope factor did not increase either in average value or in interindividual variability. This may not be surprising considering the complexity of HR regulation in hypoxia, particularly during exercise. This is supported by the fact that there was no correlation of the HR responses to hypoxia at rest and during exercise. In general, sino-atrial (S-A) node activity is continuously modulated by several reflex mechanisms originating from various peripheral receptors [13], although there may be a direct effect of hypoxia on sinus slowing as a result of an impairment of oxygen supply to the S-A node [36]. Indirect effects of hypoxia on S-A node function are mediated through the interaction of several opposing influences. The bradycardia

resulting from carotid body chemoreceptor stimulation is opposed by cardioaccelerator reflexes from lung inflation receptors stimulated as a result of hyperventilation and from hypoxia of the central nervous system [37]. The increase in arterial blood pressure resulting from hypoxia may also stimulate the baroreflexes, thereby contributing to cardiac slowing [38]. In addition, there is accumulating evidence that the aortic chemoreceptors, in contrast to the carotid body, may cause tachycardia rather than bradycardia [39]. As a result, hypoxia leads to an increase in HR that is linearly related to $Sa_{,O_2}$ [15].

Considering the reflexes mentioned above, if cardio-acceleration mediated through pulmonary stretch receptors dominates, then the HR response to progressive hypoxia should follow the ventilatory response to hypoxia. However, this was not the case either during exercise or CO_2 inhalation. Despite marked increases both in the mean value and the intersubject variability of HVR under both conditions, the HR response to hypoxia did not significantly change. In particular, the HR response to hypoxia was similar in the conditions with and without hypercapnia. These results indicated that hypoxia-hypercapnia interaction was much less apparent in HR regulation than in the ventilatory response, and that the pulmonary vagal reflex through pulmonary stretch receptors did not play a major role in HR regulation during hypoxia.

Finally, mention should be made of a weakness of the present study. Unfortunately, we did not randomize the order of the experimental protocols, partly because we focused on the intersubject variability of HVR in this study and, thus, wanted to avoid differences in the protocol among subjects. This could explain some variation of the findings. We do not believe, however, that the order effect alone can explain the major conclusions of this study, since no studies have ever shown that the order effect is more apparent in subjects with a higher HVR. Another weak point of this study may be that we made only a single measurement for each response under different conditions. However, since the intrasubject coefficient of variation for HVR in our laboratory is about 20% [19], the much larger increase in the mean value of HVR during exercise or with hypercapnia appears real.

In conclusion, we demonstrated that exercise and CO_2 inhalation not only increase the slopes of hypoxic ventilatory response but also amplify the intersubject variability of the response. In contrast to the ventilatory response, the heart rate response to hypoxia evaluated as a slope factor does not change with exercise or CO_2 inhalation. Individual characteristics in inherent hypoxic ventilatory chemosensitivity may be far more important as a determinant of clinical manifestations during exercise or in some clinical settings associated with hypercapnia than at rest under normocapnic conditions.

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