# Individual differences in breathlessness during exercise, as related to ventilatory chemosensitivities in humans

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1. The present study attempted to test the hypothesis that breathlessness associated with exercise hyperpnoea is greater in subjects with greater activities of the central and peripheral chemoreceptors during exercise. The chemoreceptor activities were assessed by resting estimates of hypercapnic ventilatory response ($\Delta\dot{V}_E/\Delta P_{CO_2}$, HCVR) and hypoxic ventilatory response ($\Delta\dot{V}_E/-\Delta S_{O_2}$, HVR), respectively, where $\dot{V}_E$ is minute ventilation and $S_{O_2}$ is oxygen saturation.

2. Nine female and nine male subjects performed a 1 min incremental exercise test until exhaustion, during which breathlessness intensity (BS), assessed by a Borg category scale, and $\dot{V}_E$ were measured every minute. The maximum $O_2$ uptake ($\dot{V}_{O_2,max}$) was also determined.

3. Using a stepwise multiple linear regression analysis, the relative contributions of not only $\dot{V}_E$, HCVR and HVR, but also $\dot{V}_{O_2,max}$ and a predicted maximum voluntary ventilation ($MVV_p$) of the individuals to BS, were examined.

4. The analysis showed that $BS = 0{\cdot}1\dot{V}_E + 4{\cdot}9HVR - 0{\cdot}03MVV_p + 0{\cdot}55$ ($r^2 = 0{\cdot}71$), indicating that $\dot{V}_E$ accounted for 44% of the variance of BS, HVR for 12% and $MVV_p$ for 15%. No significant relation of HCVR and $\dot{V}_{O_2,max}$ to BS was found.

5. These results suggest a contribution of peripheral chemoreceptors to the generation of exertional breathlessness.

Although its precise mechanism is not fully clarified, the sensation of breathlessness has been considered to be produced primarily by a centrally generated respiratory motor command signal (Killian, Gandevia, Summers & Campbell, 1984; Adams, Lane, Shea, Cockcroft & Guz, 1985; Cherniack & Altose, 1987), with modulations by inhibitory afferent feedback from lung and chest wall mechanoreceptors (Chonan, Mulholland, Cherniack & Altose, 1987) and excitatory afferent feedback from central and peripheral chemoreceptors (Ward & Whipp, 1989; Chonan, Mulholland, Leitner, Altose & Cherniack, 1990). Concerning the modulation by the chemoreceptors, it has been demonstrated that increases in the chemoreceptor activities with hypercapnia (Stark, Gambles & Lewis, 1981; Chonan *et al.* 1990) or with hypoxia (Ward & Whipp, 1989) cause more intense breathlessness, while the ventilatory levels are kept the same as those before the changes in the blood-gas pressures.

The peripheral chemoreceptors appear to be activated during exercise, as shown by their involvement in the regulation of exercise hyperpnoea, such as $O_2$-labile ventilatory drive up to 20% of exercise hyperpnoea, acceleration of the ventilatory kinetics, respiratory compensation for lactic acidosis in heavy exercise (Whipp, 1994), and reaction to exercise-induced hyperkalaemia with a resultant increase in ventilation (Nye, 1994). The central chemoreceptors have been assumed to function during exercise, resulting in acid–base homeostasis through a fine tuning of the ventilatory response to increased $CO_2$ production (Ward, 1994).

Thus we hypothesized that the breathlessness associated with exercise hyperpnoea is greater in subjects with greater activities of the central and peripheral chemoreceptors during exercise. The present study was undertaken to test this hypothesis. Activities of the central and peripheral chemoreceptors during exercise were assessed by resting estimates of hypercapnic ventilatory responsiveness (HCVR) and hypoxic ventilatory responsiveness (HVR), respectively. It has been reported that HCVR (Poon & Greene, 1985) and HVR (Weil, Byrne-Quinn, Sodal, Kline, McCullough & Filley, 1972; Martin, Weil, Sparks, McCullough & Grover, 1978; Regensteiner, Pickett, McCullough, Weil & Moore, 1988) increase with increasing exercise intensity, and the exercise estimates of HVR depend on the resting estimates of HVR (Martin *et al.* 1978; Regensteiner *et al.* 1988; Igarashi, Nishimura, Akiyama, Yamamoto, Miyamoto & Kawakami, 1994). The relative contributions of these chemosensitivities to the determination of the breathlessness intensity during exercise were examined using a multiple regression analysis.

# METHODS

## Subjects

Nine female subjects (aged 22 ± 5 years (mean ± S.D.); weight, 49 ± 5 kg; height, 158 ± 5 cm) and nine male subjects (aged 24 ± 4 years; weight, 65 ± 6 kg; height, 172 ± 4 cm) volunteered for this study, after giving written, informed consent. They were all healthy non-smokers, and had taken part in recreational sports. All subjects were unaware of the purpose of this study, but knew that it involved the measurement of breathlessness during exercise. The experiment was carried out at least 3 h after the subject's last meal.

## Measurements

The subjects breathed through a respiratory mask (dead space, 200 ml) to which a hot-wire flowmeter was fixed in order to measure respiratory flow. Respiratory gas was continuously sampled (200 ml $min^{-1}$) from a nostril and introduced into a $CO_2$–$O_2$ gas analyser (MG-360, Minato Medical Co., Japan), with which the $CO_2$ and $O_2$ concentrations were analysed through an infrared absorption and zirconium oxide reaction, respectively. Signals from the flowmeter and gas analyser were fed into a computer (RM-200, Respiromonitor, Minato Medical Co.) and processed breath by breath to obtain pulmonary ventilation ($\dot{V}_E$), $O_2$ uptake ($\dot{V}_{O_2}$), $CO_2$ elimination ($\dot{V}_{CO_2}$) and end-tidal $P_{O_2}$ and $P_{CO_2}$. Heart rate (HR) was monitored through an electrocardiogram. Arterial oxygen saturation ($S_{O_2}$) was measured using a finger oximeter (Oximet, Minoruta Camera Co., Osaka, Japan).

The intensity of breathlessness during exercise (BS) was assessed with the use of a modified Borg category scale (Borg, 1982). The subjects were asked 'How severe is your discomfort when breathing?' ('Ikigurushisa ha donokurai ka?' in Japanese), and in response were required to point to a score on a scale that had eleven values ranging from 0 (not at all breathless) to 10 (maximally breathless), accompanied by adjectival descriptions, as shown in Fig. 1. The subjects were required to avoid rating the magnitude of breath and non-respiratory sensations such as headache or leg fatigue.

## Tests

Three tests were given to the subjects in the following order.

**Transient hypoxic test for HVR assessment.** This was based on the method of Shaw, Schonfeld & Whitcomb (1982). A reservoir bag containing pure $N_2$ was connected to an inspiratory port of a J-valve, which was fixed to a hot-wire flowmeter. After $\dot{V}_E$ and HR reached steady state during air breathing, the inspired gas was switched to $N_2$ and three to eight breaths of $N_2$ were imposed on the subjects, followed by air breathing. Subsequent hypoxic transients with a different number of $N_2$ breaths were resumed after end-tidal $P_{O_2}$, $S_{O_2}$ and HR returned to the air-breathing levels. Peak $\dot{V}_E$ (actually calculated as the mean value of the two highest consecutive $\dot{V}_E$) and the lowest $S_{O_2}$ that occurred within 10–20 s following the last breath of $N_2$ were obtained in each hypoxic transient, and then using the data from all the six hypoxic transients a linear regression of peak $\dot{V}_E$ against the lowest $S_{O_2}$ was analysed for each subject by a least-squares method. The slope of the regression line, $\Delta\dot{V}_E/-\Delta S_{O_2}$, was designated as HVR.

**$CO_2$ rebreathing test for HCVR assessment.** This was based on the method of Read (1967). After $\dot{V}_E$ and HR reached steady state during air breathing, the subjects rebreathed a 7% $CO_2$–93% $O_2$ gas contained in a reservoir bag for 4 min, during which end-tidal $P_{CO_2}$ and $\dot{V}_E$ were measured. A regression line of the end-tidal $P_{CO_2}$–$\dot{V}_E$ relationship was calculated and the slope ($\Delta\dot{V}_E/\Delta P_{CO_2}$) was defined as HCVR.

**Incremental exercise test.** After 2 min unloaded cycling on a bicycle ergometer, the subjects exercised at a 1 min incremental work load until exhaustion. The rate of increment of the load was 25 W $min^{-1}$ at the pedalling rate of 70 r.p.m. for the male subjects and 15 W $min^{-1}$ at 50 r.p.m. for the female subjects. The subjects adjusted the pedalling rates by watching a speedometer. At each incremental work load, BS was measured at 45 s of the 1 min period and $\dot{V}_E$ was assessed by averaging the breath-by-breath data during the last half-minute of the 1 min period. Maximum $O_2$ uptake ($\dot{V}_{O_2,max}$) was determined as the average value of breath-by-breath data of $\dot{V}_{O_2}$ during the last 1 min of the exercise test and was normalized for body weight.

Before the tests, the subjects underwent a training session in order to familiarize them with the use of the modified Borg category scale for breathlessness scoring, while wearing the respiratory mask and exercising.

## Multiple linear regression analysis

We hypothesized that BS is related linearly and additively to $\dot{V}_E$ during exercise and to HVR, HCVR and other variables, if present, of the individual subjects, giving an equation such as $y = a_1x_1 + a_2x_2 + \ldots + a_nx_n + \text{constant}$, where $y$ is a dependent variable (i.e. BS), $x_1$ to $x_n$ independent variables, and $a_1$ to $a_n$, respectively, regression coefficients. A stepwise multiple linear regression analysis was applied to test the hypothesis. All the independent variables were introduced first for the analysis, and then more suitable variables were chosen so that the $F$ value of a final multiple regression model, and partial $F$ values of the independent variables chosen became maximum and significant at $\alpha < 0.05$ for the $F$ distribution. Standardized regression coefficients of the independent variables, which were defined as regression coefficients standardized for the units of the variables and calculated as $a_n \text{S.D.}_{x_n}/\text{S.D.}_y$ (where S.D. is standard deviation), were considered to indicate the relative contribution of the independent variables to BS.

# RESULTS

Figure 1 shows $\dot{V}_E$–BS relationships during incremental exercise in all subjects, indicating progressive increases in BS with increasing $\dot{V}_E$. BS at given levels of $\dot{V}_E$ varied greatly among the subjects, partly due to individual differences in the exercise ventilatory response. Therefore, BS was plotted against $\dot{V}_E/MVV_p$ (%), as shown in Fig. 2, where $MVV_p$ was a predicted maximum voluntary ventilation and was calculated using Nishida's formula (Nishida *et al.* 1986). The individual variations in $\dot{V}_E$–BS and $\dot{V}_E/MVV_p$–BS relationships were assessed in terms of the coefficient of variance (c.v., mean/S.D., as a percentage) of $\dot{V}_E$ levels, at which BS was 5. The c.v. was 44% in the $\dot{V}_E$–BS relationship and 27% in the $\dot{V}_E/MVV_p$–BS relationship, indicating a 39% reduction of the individual variation of BS with normalization of $\dot{V}_E$ for $MVV_p$ and hence a dependency of BS on $MVV_p$. Thus $MVV_p$ was adopted as an independent variable in the multiple regression analysis. In addition, $\dot{V}_{O_2,max}$ was taken into consideration as another independent variable, since Adams, Chronos, Lane & Guz (1986) have reported a significant correlation between physical fitness of subjects and the breathlessness intensity during exercise. Consequently, five independent variables that were assumed

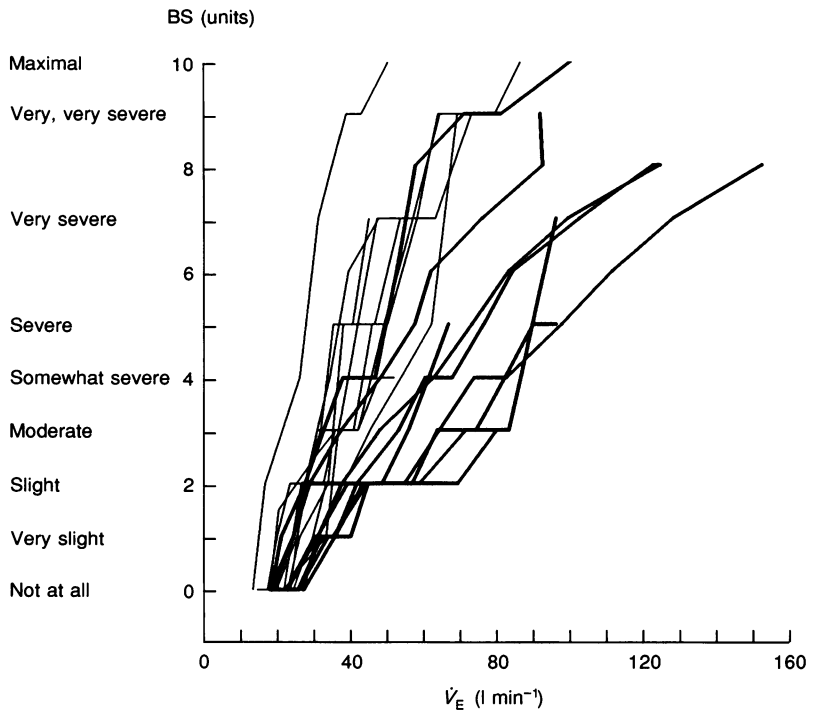


**Figure 1. $\dot{V}_E$–BS relationship during incremental exercise in individual subjects**
The thin lines represent females, and thick lines represent males.

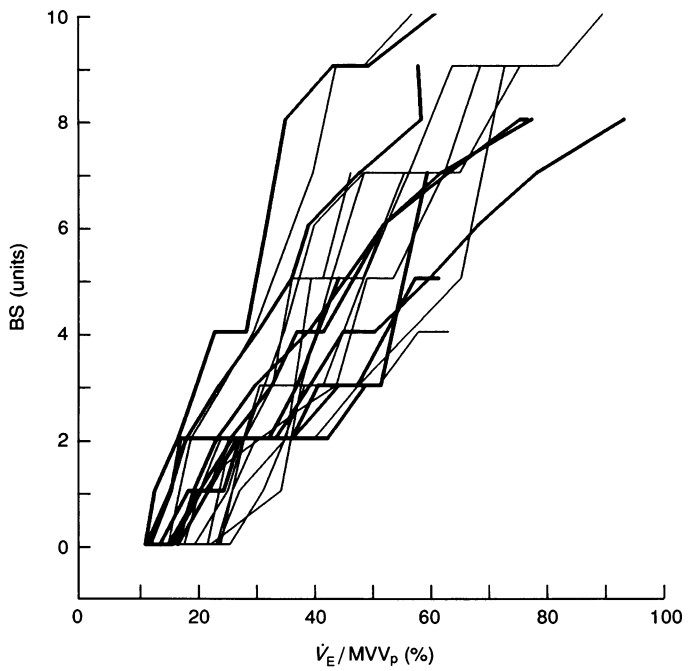


**Figure 2. $\dot{V}_E$/MVV$_p$–BS relationship during incremental exercise in individual subjects**
For explanation, see Fig. 1.

**Table 1. Variabilities of four independent variables in eighteen subjects**

| Independent variable | Mean ± S.D. | Range |
|---|---|---|
| HVR (l min$^{-1}$ (−%)$^{-1}$) | 0·37 ± 0·15 | 0·16–0·64 |
| HCVR (l min$^{-1}$ mmHg$^{-1}$) | 2·71 ± 1·74 | 0·93–7·27 |
| $MVV_p$ (l min$^{-1}$) | 127 ± 35 | 82–165 |
| $\dot{V}_{O_2,max}$ (ml min$^{-1}$ kg$^{-1}$) | 42·5 ± 6·0 | 32·8–57·3 |

to affect BS, i.e. $\dot{V}_E$ during exercise and HVR, HCVR, $MVV_p$ and $\dot{V}_{O_2,max}$ of the subjects, were included in a multiple linear regression analysis, by which the interaction of these variables to determination of BS was analysed. Variabilities between the subjects of the latter four independent variables are shown in Table 1.

As shown in Table 2, the multiple regression analysis gave the result that BS during exercise was related positively to $\dot{V}_E$ and HVR, but inversely to $MVV_p$. Neither HCVR nor $\dot{V}_{O_2,max}$ was related to BS.

Consequently, the multiple linear regression equation was: $BS = 0{\cdot}1\dot{V}_E + 4{\cdot}9HVR - 0{\cdot}03MVV_p + 0{\cdot}55$, which explained 71% of the variance. The equation indicates that BS increased linearly with increasing $\dot{V}_E$ during exercise, and that this regression line on a $\dot{V}_E$–BS graph was located more to the left (upward) in the subjects with higher HVR and more to the right in those with higher $MVV_p$. Based on the results of $r^2$ and standardized regression coefficients, it was estimated that on average, $\dot{V}_E$ accounted for 44% of BS ($0{\cdot}71 \times 0{\cdot}91 \times 100/(0{\cdot}91 + 0{\cdot}24 + 0{\cdot}32)$), HVR for 12% and $MVV_p$ for 15%. Needless to say, as $\dot{V}_E$ increased, the contribution of $\dot{V}_E$ increased, while that of the other two variables decreased.

## DISCUSSION

The working hypothesis of this study was that subjects with higher HVR and/or HCVR perceive more intense breathlessness associated with exercise hyperpnoea, probably due to greater activities of the chemoreceptors during exercise. To test the hypothesis, a multiple linear regression analysis with five independent variables of not only HVR and HCVR but also $MVV_p$ and $\dot{V}_{O_2,max}$ of the subjects and $\dot{V}_E$ during exercise was used. The values of HVR and HCVR in our subjects (Table 1) were within the ranges of the previously reported values for HVR (Edelman, Epstein, Lahiri & Cherniack, 1973; Shaw *et al.* 1982) and HCVR (Irsigler, 1976), measured using virtually identical tests as in this study.

The analysis demonstrated that the intensity of breathlessness during exercise could be explained by a multiple regression model with three independent variables of $\dot{V}_E$ during exercise, HVR and $MVV_p$ of the subjects. The model explained 71% of the variance, and indicated that the breathlessness intensity increases linearly with increasing $\dot{V}_E$, and the $\dot{V}_E$-associated breathlessness is augmented by HVR and reduced by $MVV_p$ of the subjects. In other words, subjects with higher levels of HVR perceive greater intensities of breathlessness at given levels of $\dot{V}_E$ and those with higher levels of $MVV_p$ perceive lower intensities of breathlessness.

### Breathlessness during exercise and $\dot{V}_E$

Proportional increases in exertional breathlessness to $\dot{V}_E$ have been observed by various investigators (e.g. Adams *et al.* 1986; Leblanc, Bowie, Summers, Jones & Killian, 1986; Chonan *et al.* 1990; Lane, Adams & Guz, 1990). The multiple regression model revealed that compared with HVR and $MVV_p$, $\dot{V}_E$ was a more predominant determinant

**Table 2. Multiple linear regression equation for determining the breathlessness intensity during exercise**

| Independent variable | Regression coefficient | Standard regression coefficient | Partial $F$ value | $\alpha$ |
|---|---|---|---|---|
| $\dot{V}_E$ | 0·098 | 0·912 | 413·6 | < 0·01 |
| HVR | 4·884 | 0·244 | 32·3 | < 0·01 |
| HCVR | n.s. | n.s. | n.s. | n.s. |
| $MVV_p$ | −0·027 | −0·316 | 47·4 | < 0·01 |
| $\dot{V}_{O_2,max}$ | n.s. | n.s. | n.s. | n.s. |
| Constant | 0·554 | — | 0·7 | n.s. |

Multiple regression model $r^2 = 0{\cdot}710$ ($F = 142{\cdot}5$, $\alpha < 0{\cdot}01$). The equation is given as $BS = a\dot{V}_E + b$HVR + $c$HCVR + $d MVV_p + e\dot{V}_{O_2,max}$ + constant, in which $a$ to $e$ are regression coefficients. $r^2$ is the coefficient of determination of the model. n.s., not significant.

of the breathlessness intensity during exercise. Although the model did not clarify sensory mechanisms mediating the $\dot{V}_E$-associated breathlessness, the perception of respiratory muscle effort mediated by the motor command signals appears to be involved (Killian *et al.* 1984; Leblanc *et al.* 1986).

### Breathlessness during exercise and $MVV_p$

A dyspnoea index defined as $\dot{V}_E/MVV_p$ (Wright & Filley, 1951) has been available to patients for assessing the attainability of dyspnoea to an intolerable level during exercise, implying that attainability is dependent on maximum breathing capacities of the patients. Dependency of the breathlessness intensity on $MVV_p$ was also observed in our healthy subjects, such as those with lower $MVV_p$ perceiving greater intensities of exertional breathlessness. Adams *et al.* (1986) have attributed 50% of the individual difference in exertional discomfort at a $\dot{V}_E$ of 50 l min$^{-1}$ to $MVV_p$ of individuals. In the present study, the multiple regression model indicated that at a given level of $\dot{V}_E$, $MVV_p$ explained, on average, 41% ($0{\cdot}71 \times 0{\cdot}32 \times 100/(0{\cdot}32 + 0{\cdot}24)$) of the individual difference of the breathlessness intensity, this result being compatible with that of Adams *et al.* (1986).

### Breathlessness during exercise and HVR

The multiple regression model indicated that HVR of the subjects acted to increase the sensation of breathlessness during exercise, and at a given level of $\dot{V}_E$ it accounted for 31% ($0{\cdot}71 \times 0{\cdot}24 \times 100/(0{\cdot}32 + 0{\cdot}24)$) of the breathlessness intensity. HVR was assessed under resting conditions, on the assumption that it is indicative of not only HVR during exercise but also the magnitude of the peripheral chemoreceptor activity during exercise. Martin *et al.* (1978) have demonstrated that in light exercise the $O_2$ drive estimated by the Dejours' $O_2$ test varied from 5 to 45% of total $\dot{V}_E$ among subjects and was correlated with the resting estimate of HVR. However, the entire magnitude of the peripheral chemoreceptor activity might not be assessable by HVR and $O_2$ drive, even if they were measured during exercise, since during exercise the chemoreceptors are likely to be activated by not only hypoxic but also non-hypoxic stimuli, such as increased arterial $[K^+]$ and $[H^+]$ (Nye, 1994; Whipp, 1994), under which abolition of carotid body activity by hyperoxia appears to be incomplete (Rausch, Whipp, Wasserman & Huszczuk, 1991). With these reservations and based on the study of Ward & Whipp (1989), it is suggested that the peripheral chemoreceptor activities during exercise increased more markedly in those with higher HVR, resulting in more intense breathlessness.

Ward & Whipp (1989) observed that during moderate exercise with hypoxia, subjects perceived more intense breathlessness than during exercise with hyperoxia; in both exercise conditions $\dot{V}_E$ was kept isopnoeic and the sensation of breathlessness was qualified as the difficulty in breathing. It was suggested that an increased activity of the carotid bodies is likely to augment the sensation of breathlessness. Such an augmented breathlessness was not confirmed in the study of Lane *et al.* (1990), in which increases in the breathlessness intensity during incremental exercise were found to be similar in normoxic and hypoxic conditions. In their study the breathlessness sensation was defined as 'an uncomfortable need to breathe'. Inconsistent results between the two studies may be due to the adoption of different experimental protocols and definitions of breathlessness.

### Breathlessness during exercise and HCVR

The present finding of a lack of significant correlation between BS and HCVR suggests less involvement of the central chemoreceptors in determination of the breathlessness intensity during exercise. This seems to be in line with the studies of Ward & Whipp (1989) and Lane *et al.* (1990), which demonstrated that stimulation of the central chemoreceptors by $CO_2$ inhalation during exercise exerted no influence on the breathlessness intensity, while $\dot{V}_E$ was isopnoeic compared with normocapnic exercise.

### Breathlessness during exercise and physical fitness

Adams *et al.* (1986) have reported an inverse correlation between the breathlessness intensity at a $\dot{V}_E$ of 50 l min$^{-1}$ during exercise and physical fitness of the individuals, which was evaluated by the heart rate response during exercise. If a correlation analysis with a single independent variable of $\dot{V}_{O_2,max}$ is applied to the present results, a similar result to that of Adams *et al.* (1986) is obtained, such as an inverse correlation between BS at a $\dot{V}_E$ of 50 l min$^{-1}$ and $\dot{V}_{O_2,max}$ in the individuals ($r = -0{\cdot}77$, $n = 18$, $P < 0{\cdot}01$). That is the case in BS at $\dot{V}_E$ of 30, 40 and 60 l min$^{-1}$ ($r = -0{\cdot}61$ to $-0{\cdot}73$, $P < 0{\cdot}05$). The multiple regression analysis, in which the interaction of the five independent variables ($\dot{V}_E$, HVR, HCVR, $MVV_p$ and $\dot{V}_{O_2,max}$) to BS was analysed, however, showed no significant contribution of $\dot{V}_{O_2,max}$ to BS determination (Table 2). In our subject group ($n = 18$), a significant correlation between $\dot{V}_{O_2,max}$ was seen in HCVR ($r = 0{\cdot}50$), HVR ($r = -0{\cdot}58$), and $MVV_p$ ($r = 0{\cdot}60$). The inverse correlation between $\dot{V}_{O_2,max}$ and HVR leads us to speculate that an effect of $\dot{V}_{O_2,max}$ giving rise to a lower intensity of breathlessness during exercise might be exerted secondary to a reduction of HVR. Regarding a reduction of HVR with increasing physical fitness, some investigators have argued for this (Byrne-Quinn, Weil, Sodal, Filley & Grover, 1971; Scoggin, Doekel, Kryger, Zwillich & Weil, 1978) but others have argued against it (Godfrey, Edwards, Copland & Gross, 1971; Martin *et al.* 1978; Mahler, Moritz & Loke, 1982). A longitudinal study with long-term exercise training may elucidate the interrelation between changes in exertional breathlessness, physical fitness and the peripheral chemosensitivity.

In conclusion, it was examined how the peripheral and central chemosensitivities (HVR and HCVR, respectively) of the subjects were involved in determination of the BS associated with $\dot{V}_E$ during exercise. The interrelations of not only $\dot{V}_E$, HVR and HCVR, but also $MVV_p$ and $\dot{V}_{O_2,max}$ to BS were tested using a multiple linear regression analysis. It

showed that $BS = 0{\cdot}1\dot{V}_E + 4{\cdot}9HVR - 0{\cdot}03MVV_p + 0{\cdot}55$ ($r^2 = 0{\cdot}71$), indicating that $\dot{V}_E$ accounted for 44% of the variance of BS, HVR for 12% and $MVV_p$ for 15%. No significant relation of HCVR and $\dot{V}_{O_2,max}$ to BS was found.

These results suggest an involvement of peripheral chemoreceptors, but less involvement of central chemoreceptors in the generation of exertional breathlessness.


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