Journal of Physiology (1989), **411**, *pp.* 27–43
With 7 text-figures
Printed in Great Britain

EFFECTS OF PERIPHERAL AND CENTRAL CHEMOREFLEX ACTIVATION ON THE ISOPNOEIC RATING OF BREATHING IN EXERCISING HUMANS

BY SUSAN A. WARD AND BRIAN J. WHIPP

From the Departments of Anesthesiology and Physiology, UCLA, Los Angeles, CA 90024, USA

(*Received 11 July 1988*)

SUMMARY

1. Respiratory sensation during exercise is generally considered to be related to respiratory mechanical factors which may be manifest as an abnormal relationship between the force applied to the lungs and chest wall and the resulting motion (if any); that is, a 'length–tension' inappropriateness (Campbell & Howell, 1963). This suggests that there should be a direct correlation between ventilation ($\dot{V}_E$) and the associated intensity of the perceived sensation, such that the sensation associated with a particular level of $\dot{V}_E$ should remain essentially constant regardless of the source of respiratory stimulation.

2. In order to establish whether certain respiratory stimuli might be 'dyspnoeagenic' (i.e. capable of evoking an intensity of respiratory sensation out of proportion to their influence on $\dot{V}_E$), we investigated the influence of both peripheral chemoreflex activation (induced by isocapnic hypoxia) and central chemoreflex activation (induced by hypercapnic hyperoxia) on the intensity of respiratory sensation in seven healthy adults during moderate cycle ergometer exercise (i.e. below the lactate threshold, θ_{lac}).

3. In each test, an 'isopnoea' was established for which a particular level of $\dot{V}_E$ was sustained over a prolonged period ($\sim$ 30 min) while the proportional contributions to the ventilatory drive from either exercise and the peripheral chemoreflex or from exercise and the central chemoreflex were slowly altered to new stable levels, without the subject's knowledge. $\dot{V}_E$, tidal volume, inspiratory and expiratory durations, mean inspiratory flow, and end-tidal P_{CO_2} and P_{O_2} (P_{ET,CO_2}, P_{ET,O_2}) were monitored breath-by-breath. The intensity of respiratory sensation was rated with a visual analogue scale.

4. Isopnoeic ratings of respiratory sensation were systematically greater for peripheral chemoreflex activation by isocapnic hypoxia during exercise at 50% θ_{lac} (for which the degree of peripheral chemoreflex activation, estimated by hyperoxic transition or 'Dejours' testing, averaged $\sim$ 23% of the total $\dot{V}_E$), compared to 90% θ_{lac} during isocapnic hyperoxia. Ratings during exercise at 50% θ_{lac} for central chemoreflex activation by hypercapnic hyperoxia were not systematically different from 90% θ_{lac} during isocapnic hyperoxia, however.

5. As $\dot{V}_E$ was stable throughout each isopnoea and the MVV (maximum voluntary

ventilation) was uninfluenced by the test condition, the dyspnoea index ($\dot{V}_E \times 100/$ MVV) was not affected. Breathing pattern was also unaffected.

6. We conclude that in normal subjects exercising moderately, activation of the peripheral chemoreceptors by isocapnic hypoxia evokes an intensity of respiratory sensation which is out of proportion to that evoked by an isopnoeic stimulation of the central chemoreceptors with hypercapnic hyperoxia at the same level of exercise. This supports the view that the carotid bodies appear to be dyspnoeagenic.

INTRODUCTION

Physiological factors which lead to a focusing of attention onto the need to increase pulmonary ventilation ($\dot{V}_E$) can be considered to be dyspnoeagenic, that is, inducing shortness of breath. Although in the last analysis, such sensations may not be corroborably transmitted (e.g. Quine, 1961), a reliable assessment of the apparent intensity can be made by using appropriately constructed rating scales (Aitken, 1962; Stark, Gambles & Lewis, 1981; Killian & Campbell, 1983; Adams, Chronos, Lane & Guz, 1985*a*). It has become apparent from studies of both normal subjects and patients with various pulmonary diseases that the rating of the dyspnoeic intensity increases in proportion to the fraction of the subject's maximum ventilatory performance capacity induced by the stimulus; typically, indices such as the maximum voluntary ventilation (MVV) or the maximum inspiratory pressure provide the frame of reference (Wright & Filley, 1951; Killian & Jones, 1984; Altose, 1985). In 1951, Wright & Filley defined the ratio ($\dot{V}_E \times 100$)/MVV as the dyspnoea index. The numerical value for this index, however, was independent of the stimuli which produced the increased $\dot{V}_E$ and, perhaps more importantly, was not dependent on how the subject actually perceived the level of ventilatory drive. More recently, Killian and Jones and their colleagues have demonstrated a good correlation between an individual's rating of dyspnoeic intensity and the pressure generated at the mouth expressed as a function of the maximum pressure capable of being generated by the inspiratory muscles (Killian & Jones, 1984; El-Manshawi, Killian, Summers & Jones, 1986).

However, recognizing that different respiratory stimuli are likely to evoke qualitative as well as quantitative differences in their perception, we considered whether the same level of induced ventilatory drive originating from different sources of ventilatory stimulation would be assigned the same dyspnoeic intensity. We therefore chose to study a particular level of $\dot{V}_E$ (i.e. an 'isopnoea') which was produced by the combination of moderate muscular exercise 'titrated' against either: (*a*) medullary (central) chemoreflex activation induced by hypercapnic hyperoxia, or (*b*) carotid (peripheral) chemoreflex activation induced by isocapnic hypoxia.

METHODS

Seven healthy subjects (six males, one female) gave their informed consent to participate in this investigation; their age, height and weight (mean $\pm$ S.D.) were $32{\cdot}3 \pm 9{\cdot}2$ years, $180{\cdot}6 \pm 13{\cdot}2$ cm and $74{\cdot}2 \pm 12{\cdot}2$ kg, respectively. Prior to the study, the subjects were familiarized with the laboratory and provided with a detailed description of the technique for scaling respiratory sensation. They

were told only that they would be exercising moderately throughout each test; that the O_2 and CO_2 levels in the inspirate might be altered at some point in the test; and that, at intervals, they would be asked to rate the perception of their breathing. Subjects initially underwent a ramp incremental exercise test on an electromagnetically braked, computer-controlled cycle ergometer (Collins, Pedalmate): work rate was increased by 15 W min^{-1} to the limit of tolerance; the pedalling rate was maintained between 60 and 70 min^{-1}. The lactate threshold θ_{lac} (i.e. the highest $\dot{V}_{O_2}$ that can be attained without sustained elevation of blood [lactate]) was estimated non-invasively as the $\dot{V}_{O_2}$ at which P_{ET,O_2} and $\dot{V}_E/\dot{V}_{O_2}$ started to rise systematically without a simultaneous decline in P_{ET,CO_2} (Whipp, Ward & Wasserman, 1986). The resting ventilatory responsiveness to inhaled CO_2 during hyperoxia ($\Delta\dot{V}_E/\Delta P_{ET,CO_2}$) and to isocapnic hypoxia (parameter A of the hyperbolic $\dot{V}_E$–P_{ET,O_2} relationship: Weil, Byrne-Quinne, Sodal, Friesen, Underhill, Filley & Grover, 1970) were established by conventional steady-state techniques.

Each subject then completed a series of 'isopnoeic' exercise tests, all of which were conducted $< \theta_{lac}$. The purpose of this procedure was to attain a level of $\dot{V}_E$ which would remain essentially constant over a prolonged period ($\sim$ 30 min) while the proportional contributions from the three sources of ventilatory drive under investigation (exercise, medullary chemoreflex, carotid chemoreflex) were altered surreptitiously. Inspiratory gas mixtures, humidified and warmed to 37 °C, were delivered to the subject by a simple demand system from O_2, CO_2 and N_2 cylinders connected to a series of rotameters. This arrangement allowed inspired $[O_2]$ and $[CO_2]$ ($[O_2]_I$, $[CO_2]_I$) to be adjusted rapidly as needed to maintain $\dot{V}_E$ at the required level. A typical test format is shown in Fig. 1: unloaded pedalling ('0' W) for $\sim$ 6 min followed by $\sim$ 8 min of exercise at 90% θ_{lac}, breathing room air throughout; a further $\sim$ 4 min at 90% θ_{lac} while breathing 100% O_2 (isocapnic hyperoxia); a transitional phase in which the work rate was slowly and progressively reduced (by $\sim$ 5 W each 30 s) to 50% θ_{lac}, while any tendency for $\dot{V}_E$ to fall was simultaneously counteracted by either an appropriately progressive increase in $[CO_2]_I$ (hypercapnic hyperoxia) or decrease in $[O_2]_I$ throughout which P_{ET,CO_2} was maintained constant by appropriately increasing $[CO_2]_I$ (isocapnic hypoxia); and $\sim$ 8 min at 50% θ_{lac} breathing the final composition of either the hypercapnic hyperoxic inspirate or the isocapnic hypoxic inspirate. The reverse sequence was also used: unloaded pedalling breathing room air; exercise at 50% θ_{lac} breathing either hypercapnic hyperoxia or isocapnic hypoxia; a transitional period in which work rate was increased slowly to 90% θ_{lac} while the humoral stimulation was progressively withdrawn; and exercise at 90% θ_{lac} breathing 100% O_2. This design permitted the isopnoeic comparison of three different test conditions: isocapnic hyperoxia at 90% θ_{lac}, hypercapnic hyperoxia at 50% θ_{lac} and isocapnic hypoxia at 50% θ_{lac}. Subjects typically completed two to three repetitions of each protocol. Control tests for each of the isopnoeic test conditions were also undertaken in which the isopnoeic level of $\dot{V}_E$ was maintained for 30 min with each of three stimulus combinations.

A 40 cm horizontal visual analogue scale (Aitken, 1962), situated a few feet in front of the cycle, was used for rating respiratory sensation; the extremes of the scale were '0' and '100', defined respectively as 'not at all difficult' and 'extremely difficult'. A pointer could be positioned along the scale by means of a manually controlled linear potentiometer attached to the handlebars. Prior to each experiment, both the rating cue ('Would you please rate the difficulty of your breathing') and the sensation intensities associated with the '0' and '100' points were described for the subject. Subjects were asked to make ratings on request; this occurred typically 2–3 times during the final 3 min of each steady-state phase of the isopnoeic portion of the test (Fig. 1); after each rating, the pointer was returned to '0'. The ventilatory responses prior to each rating were taken as the average of the preceding four to five breaths. At the end of each test, subjects were asked to comment on the experiment.

Conditions between experiments were standardized as far as possible: subjects were studied when at least 12 h post-absorptive, having been requested to refrain from taking alcohol, caffeine, drugs or medications; tests on a given subject were conducted at the same time of day, in a randomized sequence; laboratory conditions were maintained as uniform as possible, with sources of extraneous noise being kept to a minimum; the same experimenter conducted all tests. Only those tests in which a reasonably stable $\dot{V}_E$ could be maintained over the ispnoeic portion were analysed.

During each test, inspiratory and expiratory flows were measured continuously with a pneumotachograph manometer system (Collins; linear up to 600 l min^{-1}) calibrated with known volumes of room air and also with gas mixtures similar to those used in each steady state (100% O_2;

95% O_2–5% CO_2; 14% O_2–3% CO_2) at several mean flows with various flow profiles. The pneumotachograph was attached to the mouthpiece by a short rigid connector (dead space: < 100 ml) and was maintained at 37 °C by a thermal feed-back device. Rapidly responding analysers continuously monitored P_{CO_2} (Collins; infra-red) and P_{O_2} (Collins; zirconium dioxide fuel cell) in respired gas sampled from the mouthpiece; precision-analysed gas mixtures were used for

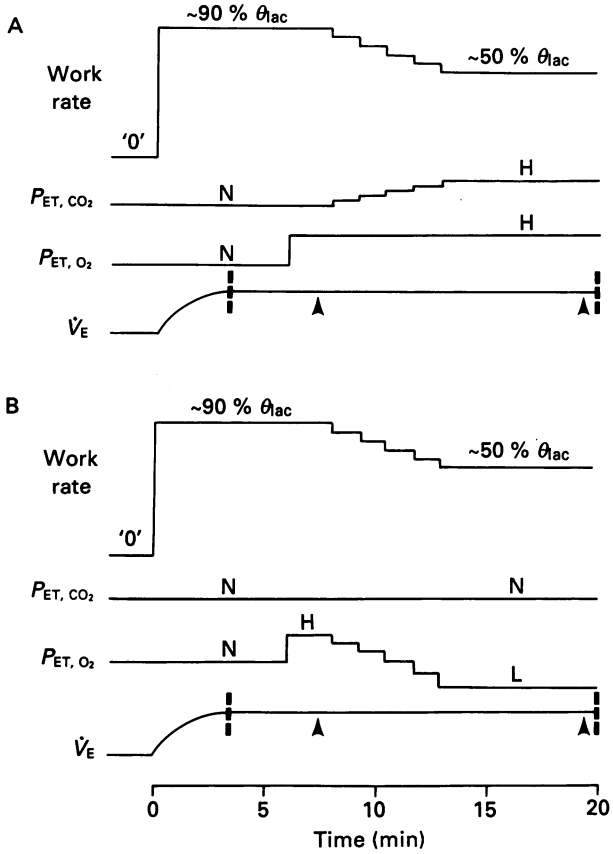

Fig. 1. Schematized time course for isopnoeic exercise tests. Panel *A*: transition from exercise at 90% θ_{lac} during isocapnic hyperoxia to 50% θ_{lac} during hypercapnic hyperoxia (central chemoreflex activation); panel *B*: transition from exercise at 90% θ_{lac} during isocapnic hyperoxia to 50% θ_{lac} during isocapnic hypoxia (peripheral chemoreflex activation). Vertical dashed lines denote isopnoeic portion of test; arrows indicate points at which ratings of respiratory sensation were made. θ_{lac}: lactate threshold; '0': '0' W; N, H, L: normal, high and low, respectively; P_{ET,CO_2}, P_{ET,O_2}, $\dot{V}_E$: end-tidal P_{CO_2} and P_{O_2} and ventilation, respectively. See text for further details.

calibration. The electrical signals from these devices underwent analog-to-digital conversion and computer analysis (Collins; MC/PLUS system) for on-line, breath-to-breath determination of: $\dot{V}_E$, BTPS (body temperature and pressure, saturated); tidal volume (V_T, BTPS); inspiratory and expiratory durations (T_I, T_E); mean inspiratory flow (V_T/T_I, BTPS); CO_2 output ($\dot{V}_{CO_2}$, STPD (standard temperature and pressure, dry)); O_2 uptake ($\dot{V}_{O_2}$, STPD); ventilatory equivalents for CO_2 and O_2 ($\dot{V}_E/\dot{V}_{CO_2}$, $\dot{V}_E/\dot{V}_{O_2}$); respiratory exchange ratio (R); and end-tidal P_{CO_2} and P_{O_2} (P_{ET,CO_2}, P_{ET,O_2}) (Beaver, Wasserman & Whipp, 1973).

In a series of separate tests, for each of the three isopnoeic conditions, the inspirate was abruptly

and surreptitiously switched to 100% O_2 (warmed and humidified) for three to four breaths; all switches were made during expiration. The difference between the prior steady-state $\dot{V}_E$ and the nadir of any ensuing decrement of $\dot{V}_E$ was taken as an index of the degree of pre-existing carotid chemoreflex drive (Dejours, 1963; Whipp & Wasserman, 1980). In addition, the MVV was measured for each of the three conditions, and the dyspnoea index $((\dot{V}_E \times 100)/\text{MVV}$; Wright & Filley, 1951) calculated.

Mean values are presented ± 1 standard error of the mean, unless otherwise stated. The influence of test condition was established by a standard two-way analysis of variance that included a paired-comparisons analysis for selected pairs of conditions ($P < 0.05$).

RESULTS

At the end of each test and without any specific prompting, subjects were routinely asked to comment on the test. Tests were well tolerated, and in no case did a subject complain of fatigue or discomfort. Subjects were aware that they were breathing more than at rest, but again in no case was this perceived as being particularly uncomfortable. The alterations in work rate imposed in the isopnoeic phase of the test were not perceived. But in those few instances where comments were forthcoming, the inhalation of the hypoxic inspirate (which, as described below, was typically associated with an increased rating of respiratory sensation) was perceived to be an increase in work rate.

Subjects evidenced normal values for the ventilatory responsiveness to inhaled CO_2 during hyperoxia at rest, averaging 2.96 ± 0.53 l min^{-1} Torr^{-1} (Rebuck & Slutsky, 1981); and to isocapnic hypoxia at rest, averaging 130.2 ± 25.2 l min^{-1} Torr^{-1} (Weil *et al.* 1970).

We found that our subjects generally rated their respiratory sensation in a consistent fashion. That is, from day to day (and in some cases over periods of several weeks), the magnitude of the rating for a given condition was reasonably stable and the rating profile across the different conditions was preserved (Fig. 2). Representative examples of the steady-state ventilatory and gas exchange responses are shown in Fig. 3, together with the corresponding ratings of respiratory sensation; these responses were obtained during a single experimental session. The required isopnoea was established quite closely, with $\dot{V}_E$ remaining at ~ 30 l min^{-1} throughout. In panel *C*, although the work rate (50% θ_{lac}) was almost half that of the previous phase of the test (panel *A*) during which 100% O_2 was breathed at 90% θ_{lac} (i.e. 56 W *vs.* 100 W), $\dot{V}_E$ was prevented from falling by increasing P_{ET,CO_2} by ~ 4.5 Torr. Similarly, isocapnic hypoxia (P_{ET,O_2} being reduced to 67 Torr) provided the means of sustaining $\dot{V}_E$ in panel B. The rating associated with hypercapnic hyperoxic exercise (i.e. 21) was not greatly different from that associated with the higher work rate during isocapnic hyperoxia (i.e. 29). In contrast, however, a substantial increase in the rating was observed during isocapnic hypoxia (i.e. 55).

The isopnoeic comparisons are illustrated in Fig. 4; typically, $\dot{V}_E$ in a test pair differed by less than 3 l min^{-1}. There was no systematic effect of test condition on the MVV; this averaged 183.1 ± 17.1 l min^{-1} for the isocapnic hyperoxic test at 90% θ_{lac}, 181.7 ± 15.5 l min^{-1} for the hypercapnic hyperoxia test at 50% θ_{lac}, and 179.7 ± 14.9 l min^{-1} for the isocapnic hypoxic test at 50% θ_{lac}. As a result, the dyspnoea index was also not systematically affected by the test condition (Fig. 4).

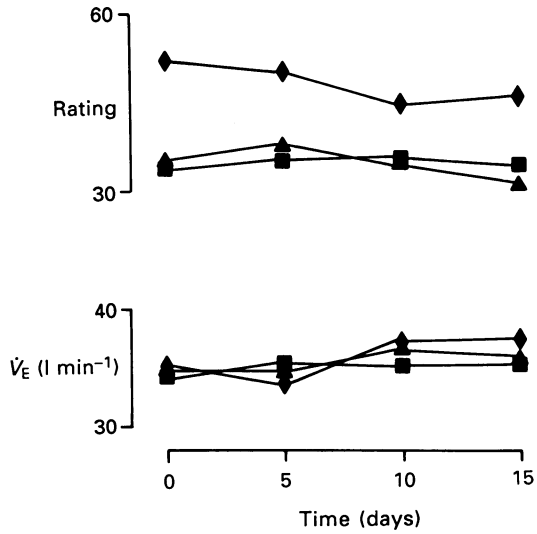

Fig. 2. Rating and ventilatory ($\dot{V}_E$) responses for a single subject to exercise at 90% θ_{lac} during isocapnic hyperoxia (■), 50% θ_{lac} during hypercapnic hyperoxia (central chemoreflex activation) (▲) and 50% θ_{lac} during isocapnic hypoxia (peripheral chemoreflex activation) (◆) for a series of isopnoeic tests conducted over a 15 day period.

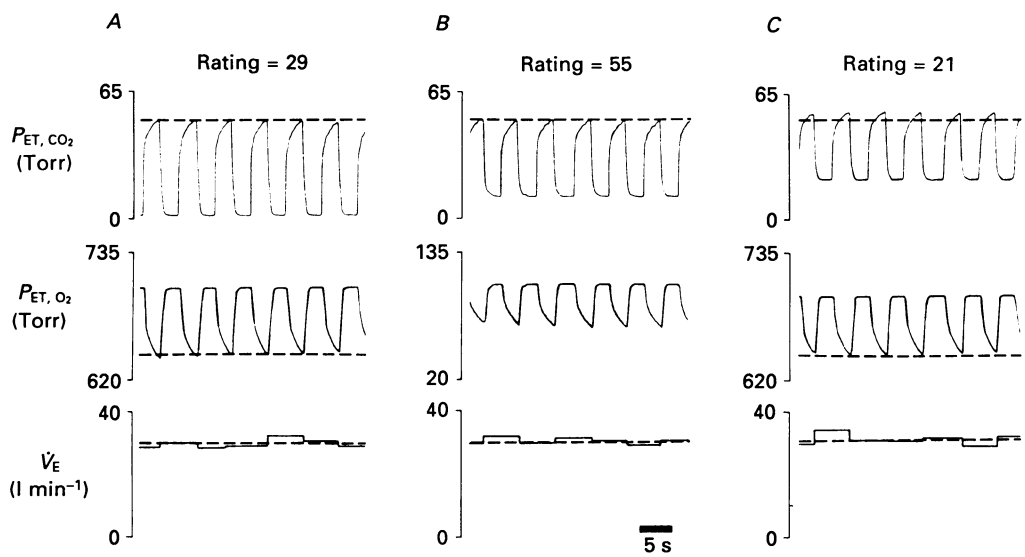

Fig. 3. Representative examples of breath-by-breath responses of end-tidal P_{CO_2} (P_{ET,CO_2}), end-tidal P_{O_2} (P_{ET,O_2}) and ventilation ($\dot{V}_E$) for a single subject to exercise at 90% θ_{lac} during isocapnic hyperoxia (panel *A*), 50% θ_{lac} during isocapnic hypoxia (peripheral chemoreflex activation; panel *B*) and 50% θ_{lac} during hypercapnic hyperoxia (central chemoreflex activation; panel *C*). Dashed horizontal lines indicate isocapnic value on P_{ET,CO_2} record, hyperoxic value on P_{ET,O_2} record, and isopnoeic value on $\dot{V}_E$ record.

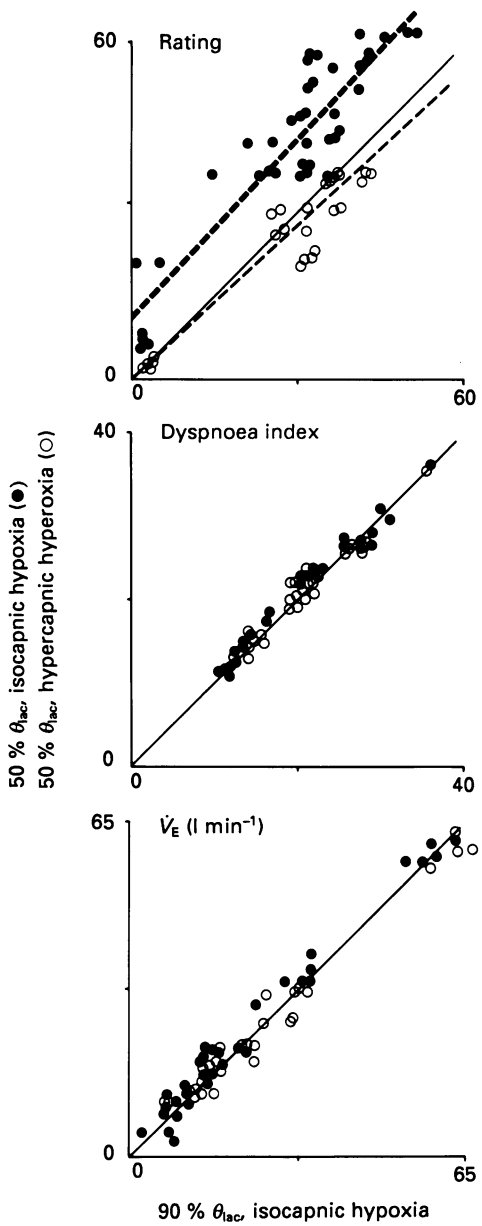

Fig. 4. Collected responses of rating (top panel), dyspnoea index (centre panel) and ventilation ($\dot{V}_E$) (bottom panel) for: (i) exercise at 90% θ_{lac} during isocapnic hyperoxia *vs.* 50% θ_{lac} during isocapnic hypoxia (peripheral chemoreflex activation; ●) and (ii) exercise at 90% θ_{lac} during isocapnic hyperoxia *vs.* 50% θ_{lac} during hypercapnic hyperoxia (central chemoreflex activation; ○) with linear regressions superimposed (thick and thin dashed lines, respectively).

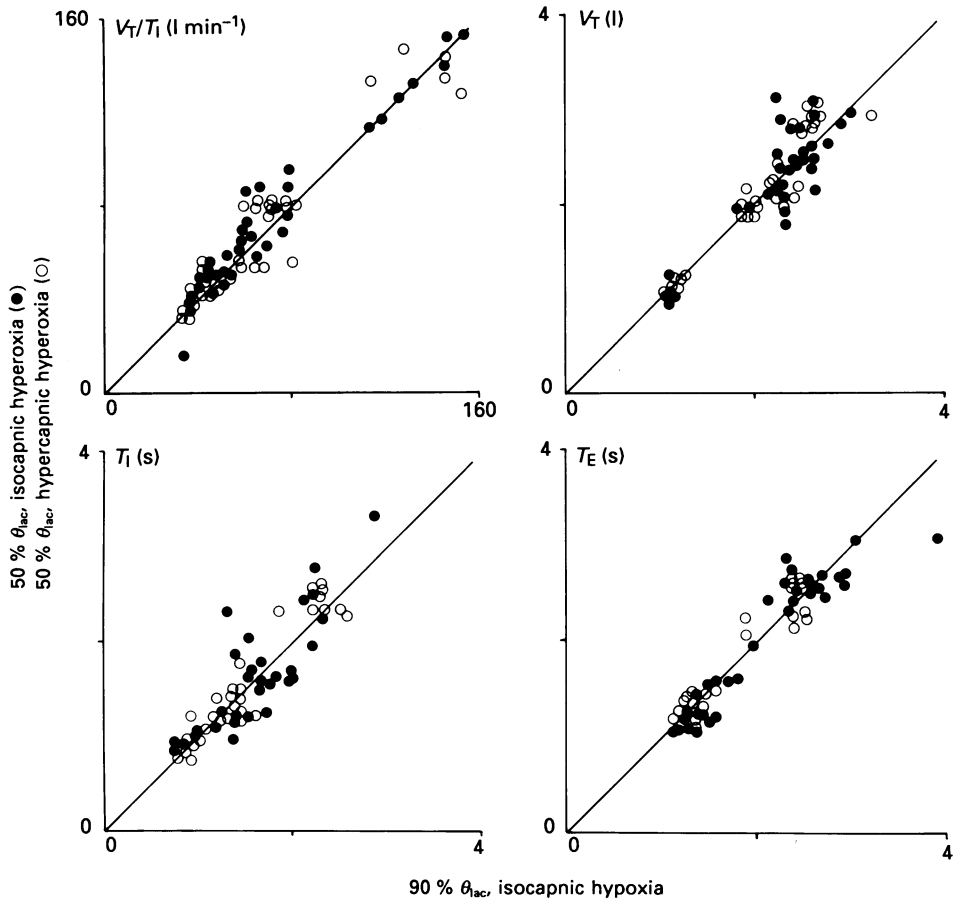

Fig. 5. Collected responses of mean inspiratory flow (V_T/T_I) (top left panel), tidal volume (V_T) (top right panel), inspiratory duration (T_I) (bottom left panel) and expiratory duration (T_E) (bottom right panel) for: (i) exercise at 90% θ_{lac} during isocapnic hyperoxia *vs.* 50% θ_{lac} during isocapnic hypoxia (peripheral chemoreflex activation; ●) and (ii) exercise at 90% θ_{lac} during isocapnic hyperoxia *vs.* 50% θ_{lac} during hypercapnic hyperoxia (central chemoreflex activation; ○).

While the magnitude of ratings associated with a particular condition showed some variability between subjects, there was a systematically greater rating for exercise at 50% θ_{lac} during isocapnic hypoxia than at 90% θ_{lac} during isocapnic hyperoxia. In all comparisons except one (i.e. 39 out of 40), the rating for isocapnic hypoxic exercise was greater than that for isocapnic hyperoxic exercise. In the one remaining case, the ratings were identical (Fig. 4). This resulted in a significant positive y-intercept of 10·21 in the linear regression analysis of these data; the slope of 1·08, however, did not differ significantly from unity (Fig. 4). In contrast, the ratings for exercise at 50% θ_{lac} during hypercapnic hyperoxia and at 90% θ_{lac} during isocapnic hyperoxia were not systematically different; i.e. the regression slope (0·89) did not differ significantly from unity, and the y-intercept (0·24) was not different from zero (Fig. 4). Breathing pattern was not affected in any systematic fashion by test condition (Fig. 5).

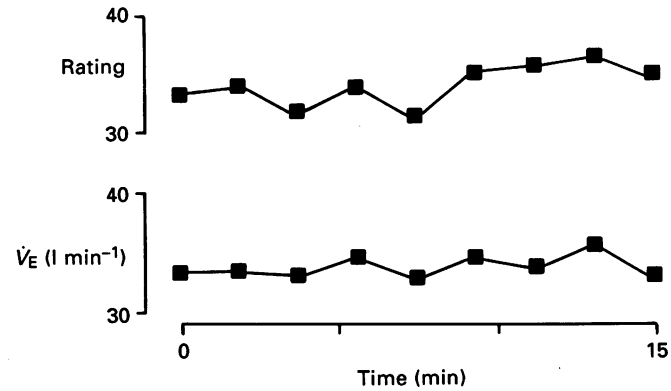

Fig. 6. Rating and ventilatory ($\dot{V}_E$) responses for a single subject to exercise at 50% θ_{lac} during isocapnic hypoxia (peripheral chemoreflex activation).

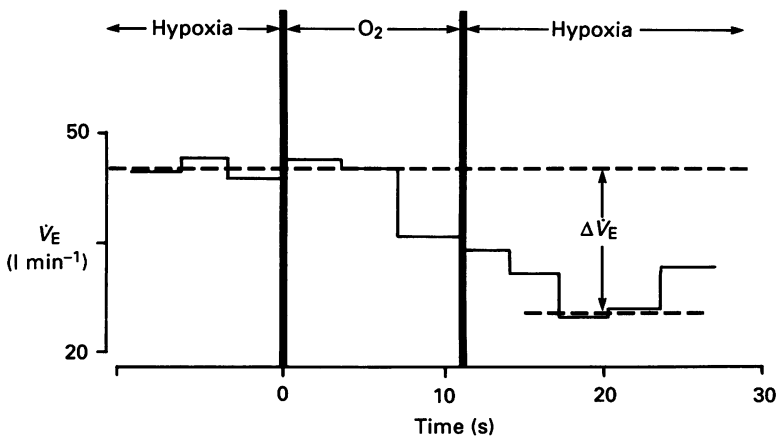

Fig. 7. Representative example of breath-by-breath response of ventilation ($\dot{V}_E$) to abrupt, transient O_2 inhalation from a prior background of hypoxia during exercise at 50% θ_{lac}. Upper dashed line indicates mean level of $\dot{V}_E$ prior to O_2 inhalation; lower dashed line indicates nadir of subsequent transient decline in $\dot{V}_E$; $\Delta\dot{V}_E$ represents magnitude of $\dot{V}_E$ decline to nadir.

During the control tests, in which work rate, $[CO_2]_I$ and $[O_2]_I$ were maintained constant throughout (e.g. Fig. 6), there was no systematic variation in the rating of respiratory sensation for a 15 min period of sustained isocapnic hypoxia at 50% θ_{lac}.

The $\dot{V}_E$ responses to the abrupt substitution of 100% O_2 varied with the inspirate. During the isocapnic hypoxic tests conducted at 50% θ_{lac} (e.g. Fig. 7), $\dot{V}_E$ typically started to fall some two to four breaths after the onset of O_2 breathing and reached a nadir ~ 10–15 s later which, in this example, was 11·4 l min^{-1} or 27·8% of the prior control value; the average for all subjects was 9·8 ± 1·0 l min^{-1} or 22·8 ± 1·4%. In contrast, $\dot{V}_E$ was unaffected by the O_2 substitution in either of the hyperoxic tests (i.e. for isocapnic hyperoxia at 90% θ_{lac} or hypercapnic hyperoxia at 50% θ_{lac}).

DISCUSSION

We have demonstrated in this investigation that the perception of a particular level of ventilation can vary depending on the source of the ventilatory drive, in normal subjects. That is, the perception of the level of $\dot{V}_E$ associated with the combination of a low work rate ($\sim 50\% \theta_{lac}$) and isocapnic hypoxia was found to be substantially greater in all our subjects than when the same level of $\dot{V}_E$ was achieved at a somewhat higher work rate in the absence of any hypoxic drive ($\sim 90\% \theta_{lac}$) (Figs 3 and 4). In contrast, there were no systematic differences in the intensity of their respiratory perception between hypercapnic hyperoxia at the lower work rate ($\sim 50\% \theta_{lac}$) and the isocapnic hyperoxia at the higher work rate ($\sim 90\% \theta_{lac}$).

The most likely explanation for these findings is that activation of the carotid bodies during exercise appears to evoke a greater intensity of respiratory sensation than that evoked by an isopnoeic stimulation of the medullary chemoreceptors at the same level of exercise. Such an explanation presupposes that not only are the carotid bodies the primary site of hypoxic ventilatory responsiveness in humans, but also that they are reversibly 'silenced' by O_2 inhalation. Evidence from various sources provides good support for these proposals. The typical hyperventilatory response to experimentally induced hypoxaemia is either absent or present only weakly when the carotid chemoreflex is inactivated by anaesthetic blockade of the IXth cranial nerve (Guz, Noble, Widdicombe, Trenchard & Mushin, 1966) or by carotid body denervation (Holton & Wood, 1965; Wade, Larson, Hickey, Ehrenfeld & Severinghaus, 1970; Lugliani, Whipp, Seard & Wasserman, 1971; Swanson, Whipp, Kaufman, Aqleh, Winter & Bellville, 1978; Honda, Watanabe, Hashizume, Satomura, Hata, Sakakibara & Severinghaus, 1979; Whipp & Wasserman, 1980). In addition, certain features of the dynamic $\dot{V}_E$ response to step-forcing of P_{ET,CO_2} are consistent with O_2 inactivating the carotid bodies: (i) the response latency during hyperoxia is prolonged significantly compared to that observed during either normoxia (Ward & Bellville, 1983) or hypoxia (Miller, Cunningham, Lloyd & Young, 1974); and (ii) the response is normally well fitted by a two-compartment model of carotid and medullary chemoreflex CO_2 responsiveness (incorporating gains, delays and time constants) during normoxia, but the carotid component cannot be resolved either during hyperoxia (Bellville, Wiberg, Ward, Aqleh & Kaufman, 1978) or in subjects having previously undergone bilateral carotid body resection (BCBR; Bellville, Whipp, Kaufman, Swanson, Aqleh & Wiberg, 1979).

Studies on breath-holding provide one source of evidence that the carotid bodies may be involved in the genesis of respiratory sensations. While it is widely recognized that the duration of breath-holding is dictated by a complex interaction of factors which include lung volume and humoral influences (Mithoefer, 1965), the importance of arterial oxygenation has been well illustrated by the characteristic shortening of breath-hold duration in association with reductions in $[O_2]_I$ prior to the breath-hold (Mithoefer, 1965; Davidson, Whipp, Wasserman, Koyal & Lugliani, 1974; Honda *et al.* 1979); a response which, in BCBR subjects, has been reported to be either absent (Davidson *et al.* 1974) or of only marginal significance (Honda *et al.* 1979). Davidson *et al.* (1974) have also speculated that the prolongation of breath-holding following bilateral anaesthetic blockade of the IXth and Xth cranial nerves, which Guz *et al.*

(1966) documented in a group of normal subjects, and ascribed to blockade of pulmonary mechanoreceptor traffic in the vagus nerves, might also result in part from interference with transmission of carotid body afferent discharge through the glossopharyngeal nerves.

On this basis of these considerations, Whipp, Ward & Wasserman (1983) tentatively suggested that the carotid bodies may also contribute to the dyspnoeic sensation associated with conditions in which respiratory drive is increased by spontaneous hypoxaemia. However, such a view should be tempered with the recognition that the sensations which accompany a breath-hold are not necessarily synonymous with those related to more typical respiratory motor acts. It is therefore notable that several investigators have reported changes in the intensity with which breathing is perceived in response to alterations of $[O_2]_I$. For example, Bannister & Cunningham (1954) made brief mention of there being a marked reduction in respiratory sensation in four normal subjects exercising at high work rates when breathing hyperoxic gas mixtures, relative to air-breathing. However, as $\dot{V}_E$ was lower during the hyperoxia, it is unclear whether the perceptual changes merely reflected the changes in $\dot{V}_E$ rather than an effect specific to the carotid bodies. (Interestingly, the reduction in breathlessness was reported to be more striking when the $[O_2]_I$ was raised to 66% than to 100%; this might simply reflect the higher level of V_E that was evident in several instances when $[O_2]_I$ was 100%.) Essentially similar observations have been reported more recently by Chronos, Adams & Guz (1988). In addition, many patients with chronic obstructive pulmonary disease (COPD) report a reduction in breathlessness when pure O_2 is breathed during exercise, and this is frequently associated with an improved exercise tolerance (Cotes & Gilson, 1956; Whipp *et al.* 1986; Hodgkin, 1987; Lane, Cockcroft, Adams & Guz, 1987*a*).

While more recent investigations have come to recognize the need to distinguish between the perception of a given degree of respiratory mechanical response and the perception of its means of induction, there is no clear consensus as to whether the carotid bodies do exert a specific and potent dyspnoeagenic influence. For example, using techniques of threshold discrimination, West, Ellis & Campbell (1975) were unable to demonstrate any systematic difference in the level of tidal volume at which a group of normal subjects became aware of an increase in their ventilation, regardless of whether air-breathing exercise or isocapnic hypoxia was the means of stimulation. In contrast, Adams *et al.* (1985*a*, 1986) observed that the level of $\dot{V}_E$ at which subjects first perceived breathlessness was lower for progressive isocapnic hypoxia than for incremental air-breathing exercise. Rather than advocating a specific dyspnoeagenic role for hypoxia, these authors suggested that during exercise subjects may be less 'concerned' about or more 'distracted' from the sensation of breathlessness.

Further dissent is evident from a series of investigations which exploited the carotid chemoreflex dynamics as a means of temporally dissociating a hypoxic stimulus from its ensuing ventilatory response: it is widely acknowledged that the change of $\dot{V}_E$ which results from an abrupt change in $[O_2]_I$ is not instantaneous, but rather requires a few minutes to develop fully (Swanson *et al.* 1978). For example, in resting subjects Adams *et al.* (1985*a*, *b*) imposed constant-amplitude hypoxic oscillations of arterial O_2 saturation (S_{a,O_2}) with periods of 2 min and 30 s, observing

predictably that the magnitude of the resulting oscillation in $\dot{V}_E$ was smaller at the higher stimulation frequency. Interestingly, breathlessness throughout this procedure was found to bear a close temporal relationship to the $\dot{V}_E$ fluctuation, in that not only did it oscillate but also with a smaller amplitude at the higher frequency. These authors therefore concluded that the breathlessness was not the result of carotid chemoreceptor activation *per se*, but more likely arose from perception of the associated $\dot{V}_E$ response. More recent experiments from the same laboratory appear to contradict this view, however. In subjects undergoing constant-load exercise, Chronos *et al.* (1988) observed that, for a step change in $[O_2]_I$, the magnitude of breathlessness changed in closer association with the relatively rapid change of S_{a,O_2} than with the more slowly developing $\dot{V}_E$ response and concluded that hypoxia, in fact, could contribute to the genesis of breathlessness. It is unclear how these two sets of observations can be reconciled, although there are several aspects of the study by Chronos *et al.* (1988) which are deserving of comment. Recognizing that the subjects were exercising at work rates which were likely to evoke a lactic acidosis, insufficient time had been allowed for a ventilatory steady state to be attained ($\dot{V}_E$ at a given $[O_2]_I$ continued to rise throughout the work). Furthermore, the magnitude of the compensatory hyperventilation (as judged by the magnitude of the decline in the estimated arterial P_{CO_2}) was non-existent during O_2 inhalation, slight during normoxia, and more marked during hypoxia ($[O_2]_I = 15\%$). This, coupled with the possibility that the magnitude of the metabolic acidosis itself is likely to be exacerbated by the hypoxaemia, argues for a complex and variable temporal spectrum of humoral drives at each $[O_2]_I$.

A further source of debate surrounds the effects of increased $[O_2]_I$ on breathlessness during exercise in patients with COPD. Swinburne, Wakefield & Jones (1984) could demonstrate no systematic alteration in the magnitude of breathlessness at a particular $\dot{V}_E$ during incremental exercise, whether the patients inhaled air or 60% O_2; unfortunately, however, hypoxic ventilatory responsiveness was not assessed in this study. Lane *et al.* (1987*a*), on the other hand, described a modest reduction of $\dot{V}_E$ in patients undergoing a self-paced walk when they breathed supplemental O_2 (sufficient to prevent S_{a,O_2} from falling below normal) rather than room air, which was accompanied by a substantial reduction in breathlessness. These authors concluded that, as the decrease in breathlessness was far greater than could be explained by the fall of $\dot{V}_E$, hypoxia *per se* may influence respiratory perception.

A criticism which can be levelled at many of these investigations is fundamental, and concerns the conditions under which the perceptual ratings were made. In many instances, little attention appears to have been accorded to the possibility that subjects may perceive a particular modality of ventilatory stimulation quite differently if the stimulus and/or the ensuing $\dot{V}_E$ response is not stable but instead changes in some fashion at the time of the rating; this is clearly the case in the investigations of West *et al.* (1975), Adams *et al.* (1985*a*, *b*, 1986), Chronos *et al.* (1988) and Swinburne *et al.* (1984). We contend, therefore, that the design of these investigations cannot allow an unequivocal resolution of whether the carotid bodies are indeed dyspnoeagenic.

The design of our investigation was formulated expressly to avoid complexities of this nature. Not only was sufficient time allowed for new ventilatory steady states to

be reached prior to any assessment of respiratory sensation, but in each test the combination and magnitude of the three ventilatory drives was manipulated to maintain a stable level of $\dot{V}_E$ throughout (Fig. 3). We elected to quantify the perceptual responses by means of a visual analogue scale (Aitken, 1962; Stark *et al.* 1981; Adams *et al.* 1985*a*); that is, while the extremes of the scale are fixed ('0' and '100', which correspond to 'not at all difficult' and 'extremely difficult', respectively), the intervening portion of the scale – unlike that of Borg – remains undefined. In agreement with other investigators, we found the reproducibility of respiratory sensation ratings over periods as long as several weeks to be good (Fig. 2), and the range of variability between our subjects to be typical (Stark *et al.* 1981; Adams *et al.* 1985*a*, *b*, 1986).

Traditional hypotheses regarding the genesis of respiratory sensation, while acknowledging that the spectrum of influences evoking sensations of breathlessness may be complex and diverse, are unified by the proposal that the mechanical behaviour of the lungs and chest wall are of fundamental and often over-riding importance. This is exemplified by the pioneering work of Campbell and his colleagues (Campbell & Howell, 1963) which led to the concept that the sensation of breathlessness is the consequence of an abnormal relationship between the force applied to the lungs and chest wall and the motion (if any) which results from it; that is, a 'length–tension' inappropriateness. The formulation of specific indices – such as the dyspnoea index (Wright & Filley, 1951), the ratio of inspiratory muscle pressure to the maximum inspiratory muscle pressure, P_{mus}/P_{max} (Killian & Jones, 1984), and a multivariate expression incorporating inspiratory muscle pressure, inspiratory flow, breathing frequency and the inspiratory duty cycle (T_I/T_T; El-Manshawi *et al.* 1986) – has provided a useful means of quantifying the relationship between stimulus and sensation for a variety of altered respiratory mechanical conditions (Wright & Filley, 1951; Killian & Jones, 1984; Altose, 1985; El-Manshawi *et al.* 1986). It should be pointed out, however, that when ventilation changed volitionally, the breathlessness associated with a particular $\dot{V}_E$ has been found to be minimal compared with those conditions in which $\dot{V}_E$ is increased by hypercapnia, hypoxia or exercise (Adams *et al.* 1985*b*; Lane, Cockroft & Guz, 1987*b*). Hence, these investigators concluded that the intensity of breathlessness is not simply determined by the level of ventilation, but depends also on whether ventilation is driven reflexly or not.

The null hypothesis of our investigation therefore predicts that the sensation associated with a particular level of ventilation would remain essentially constant regardless of the source of respiratory stimulation. This evidently was not the case in our investigation. Rather, our observations provide support for the notion put forward by Chronos *et al.* (1988) that hypoxia *per se* is dyspnoeagenic. The mechanisms by which hypoxia exerts its effect on respiratory sensation therefore warrant consideration; of these, that of carotid body origin appears deserving of most attention.

The carotid chemoreflex was clearly active during the hypoxic phase of our experiments. This is indicated by the characteristic transient undershoot of $\dot{V}_E$ in response to the Dejours O_2 test (Fig. 7). This $\dot{V}_E$ profile is widely acknowledged to reflect an O_2-induced silencing of the carotid bodies, as its latency bears a close relationship to the estimated circulation delay between the lungs and the carotid

bodies (Dejours, 1963; Jain, Subramanian, Julka & Guz, 1972) and also because of its dependence on the integrity of the carotid bodies (Whipp & Wasserman, 1980). On average, therefore, we have assumed that the carotid bodies were responsible for $\sim 23\%$ of the $\dot{V}_E$ response during the isocapnic hypoxic exercise; i.e. the magnitude of the fall in $\dot{V}_E$ to its nadir in response to the abrupt increase in $[O_2]_I$ (Dejours, 1963; Whipp & Wasserman, 1980).

The view that the carotid bodies can be potent generators of respiratory sensation is supported by clinical investigations on the carotid body agonist, almitrine bismesylate. This agent has been reported to cause an acute increase in breathlessness in patients with COPD which occurs at a time when arterial oxygenation is frequently improved (owing to more homogeneous ventilation-to-perfusion relationships) and when $\dot{V}_E$ may be increased at most by only 1–2 l min^{-1} (reviewed by Tweney, 1987).

In our study, medullary chemoreflex activation during exercise was found to be no more potent a generator of respiratory sensation than exercise alone (Figs 3 and 4); it was, however, appreciably less effective than carotid chemoreflex activation during exercise. It should be pointed out that our results do not cohere with those of Stark *et al.* (1981) who found subjects to be more breathless during hyperoxic CO_2 rebreathing at rest than during progressive treadmill walking, for the same level of $\dot{V}_E$. However, these differences might simply reflect: (i) the rather substantial increases in $[CO_2]_I$ typically encountered in rebreathing procedures, which increases the likelihood of the added CO_2 being tasted; (ii) the CO_2 and exercise drives were both imposed in a progressively increasing fashion which, as discussed earlier, may affect the perceptual process; and (iii) importantly, because the time constant of the $\dot{V}_E$ response to hypercapnic hyperoxia is a minute or so (Bellville *et al.* 1979), the central CO_2-H^+ stimulus will be relatively high at a given level of $\dot{V}_E$ during the non-steady-state conditions of the rebreathing. In our experiments, the increase in $[CO_2]_I$ was modest (e.g. Fig. 3) and thus it is unlikely to have been detected; and, indeed, none of our subjects made any comment to that effect. Therefore, within the conservative limits of hypercapnic stimulation that we used here, there is no indication of a systematically greater level of respiratory perception associated with the hypercapnic hyperoxic exercise at 50% θ_{lac} than with the hyperoxic exercise at 90% θ_{lac}. Whether some systematic difference may emerge with more marked degrees of hypercapnic stimulation cannot be ruled out, however.

This raises the issue of identifying a 'point of departure' in the carotid and medullary chemoreflex pathways which could lead to such strikingly different perceptual responses at the same level of $\dot{V}_E$. One possibility is that however respiratory sensations are generated within the cortex, the influence of carotid chemoreceptor activation is somehow more potent consequent to differences in central neural circuitry. Afferent fibres from the carotid bodies in the cat have been demonstrated to project to respiratory neurones in the nucleus tractus solitarius (Davies & Edwards, 1975), a region thought to represent the initial brain stem site for integration of respiratory afferent information. There is less certainty about projections from the central chemoreceptors, owing to the problems associated with identifying these sensors unequivocally (Loeschcke, 1982). However, the demonstration of long-latency evoked potentials within the nucleus tractus solitarius

following electrical stimulation of the caudal region of the ventral medullary complex is suggestive of a functional connection, although one that is probably not monosynaptic (Loeschcke, 1982). One tantalizing possibility is that carotid chemoreceptor traffic appears to project to regions of the cerebral cortex which are associated with conscious perception (Hugelin, Bonvallet & Dell, 1959). Whether the same holds for the medullary chemoreceptors is unknown at present.

An alternative explanation is that carotid and medullary chemoreceptor activation influence respiratory motor structures differently, such that for the same level of $\dot{V}_E$, the requirements for pressure and/or flow generation are not identical. According to respiratory mechanical hypotheses of perception, this would affect the magnitude of the respiratory perception associated with a given level of $\dot{V}_E$. This might occur, for example, if the pattern of breathing adopted to maintain $\dot{V}_E$ in each condition was different (Killian & Jones, 1984; El-Manshawi *et al.* 1986): were there to be less time available for inspiration (i.e. a shorter T_I), then higher instantaneous pressures and flows would be required. However, we could discern no systematic differences in breathing pattern between the three conditions investigated (Fig. 5). A second consideration is that airway smooth muscle tone might have been affected differently, such that a greater driving pressure would be required during isocapnic hypoxia than during hypercapnic hyperoxia. In dogs, the carotid bodies have been shown to evoke a vagally mediated reflex bronchoconstriction in response to a decrease in arterial P_{O_2} (Nadel & Widdicombe, 1962). The significance of this mechanism in healthy humans is less clear; isocapnic hypoxia, however, has been reported to have no effect on airways resistance (Saunders, Betts, Pengelly & Rebuck, 1977). The evidence from focal cooling of the intermediate area of the ventral medullary complex in the cat suggests that medullary chemosensory structures may modulate parasympathetic drive to the airways (Deal, Haxhiu, Norcia, van Lunteren & Cherniack, 1987). Although we did not measure airways resistance in our experiments, our demonstration that the MVV was similar for the isocapnic hypoxic exercise and the hypercapnic hyperoxic exercise does seem to suggest that, were airway tone to have been affected in some fashion, the significance of such effects must have been minor at most.

Extreme hypoxia has been reported to evoke a metabolic acidosis in the brain through stimulation of anaerobic glycolysis (Siesjo, Johannsson, Norberg & Salford, 1975). Any consequent fall of cerebral pH could serve as an additional drive to $\dot{V}_E$ and the generation of a greater degree of breathlessness, by way of the medullary chemoreceptors. However, the modest degree of hypoxia which we utilized in the present experiments did not approach the low levels of P_{a,O_2} at which this effect is evident.

REFERENCES

ADAMS, L., CHRONOS, N., LANE, R. & GUZ, A. (1985*a*). The measurement of breathlessness induced in normal subjects: validity of two scaling techniques. *Clinical Science* **69**, 7–16.

ADAMS, L., CHRONOS, N., LANE, R. & GUZ, A. (1986). The measurement of breathlessness induced in normal subjects: individual differences. *Clinical Science* **70**, 131–140.

ADAMS, L., LANE, R., SHEA, S. A. & GUZ, A. (1985*b*). Breathlessness during different forms of ventilatory stimulation: a study in normal subjects and respiratory patients. *Clinical Science* **69**, 663–672.

AITKEN, R. C. B. (1962). Measurements of feelings using visual analogue scales. *Proceedings of the Royal Society of Medicine* **62**, 989–993.

ALTOSE, M. D. (1985). Assessment and management of breathlessness. *Chest* **88**, suppl., 77–83S.

BANNISTER, R. G. & CUNNINGHAM, D. J. C. (1954). The effects on the respiration and performance during exercise of adding oxygen to the inspired air. *Journal of Physiology* **125**, 119–137.

BEAVER, W. L., WASSERMAN, K. & WHIPP, B. J. (1973). On-line computer analysis and breath-by-breath graphical display of exercise function tests. *Journal of Applied Physiology* **34**, 128–132.

BELLVILLE, J. W., WHIPP, B. J., KAUFMAN, R. D., SWANSON, G. D., AQLEH, K. A. & WIBERG, D. M. (1979). Central and peripheral chemoreflex loop gain in normal and carotid body-resected subjects. *Journal of Applied Physiology* **46**, 843–853.

BELLVILLE, J. W., WIBERG, D. M., WARD, S. A., AQLEH, K. & KAUFMAN, R. D. (1978). Relationship of central peripheral chemoreceptor gain to oxygen tension in man. In *Modelling of a Biological Control System – The Regulation of Breathing*, ed. CARSON, E. R., CUNNINGHAM, D. J. C., HERCZYNSKI, R., MURRAY-SMITH, D. J. & PETERSEN, E. S., p. 189. Oxford.

CAMPBELL, E. J. M. & HOWELL, J. B. L. (1963). The sensation of breathlessness. *British Medical Bulletin* **19**, 36–40.

CHRONOS, N., ADAMS, L. & GUZ, A. (1988). Effect of hyperoxia and hypoxia on exercise-induced breathlessness in normal subjects. *Clinical Science* **74**, 531–537.

COTES, J. E. & GILSON, J. C. (1965). Effect of oxygen on exercise ability in chronic respiratory insufficiency. Use of portable apparatus. *Lancet* i, 872–876.

DAVIDSON, J. T., WHIPP, B. J., WASSERMAN, K., KOYAL, S. N. & LUGLIANI, R. (1974). Role of the carotid bodies in the sensation of breathlessness during breath-holding. *New England Journal of Medicine* **290**, 819–822.

DAVIES, R. O. & EDWARDS, M. W. (1975). Medullary relay neurons in the carotid body chemoreceptor pathway of cats. *Respiration Physiology* **24**, 69–79.

DEAL JR, E. C., HAXIHU, M. A., NORCIA, M. P., VAN LUNTEREN, E. & CHERNIACK, N. S. (1987). Cooling the intermediate area of the ventral medullary surface affects tracheal responses to hypoxia. *Respiration Physiology* **69**, 335–345.

DEJOURS, P. (1963). Control of respiration by arterial chemoreceptors. *Annals of the New York Academy of Sciences* **109**, 682–695.

EL-MANSHAWI, A., KILLIAN, K. J., SUMMERS, E. & JONES, N. L. (1986). Breathlessness during exercise with and without resistive loading. *Journal of Applied Physiology* **61**, 896–905.

GUZ, A., NOBLE, M. I. M., WIDDICOMBE, J. G., TRENCHARD, D. & MUSHIN, W. W. (1966). Peripheral chemoreceptor block in man. *Respiration Physiology* **1**, 38–40.

HODGKIN, J. E. (1987). Exercise testing and training. In *Chronic Pulmonary Disease*, ed. HODGKIN, J. E. & PETTY, T. L., pp. 120–164. Philadelphia: Saunders.

HOLTON, P. & WOOD, J. B. (1965). The effects of bilateral removal of the carotid bodies and denervation of the carotid sinuses in two human subjects. *Journal of Physiology* **181**, 365–378.

HONDA, Y., WATANABE, S., HASHIZUME, I., SATOMURA, Y., HATA, N., SAKAKIBARA, Y. & SEVERINGHAUS, J. W. (1979). Hypoxic chemosensitivity in asthmatic patients two decades after carotid body resection. *Journal of Applied Physiology* **46**, 632–638.

HUGELIN, BONVALLET, M. & DELL, P. (1959). Activation réticulaire et corticale d'origine chémoréceptive au cours de l'hypoxie. *Electroencephalography and Clinical Neurophysiology* **2**, 325–340.

JAIN, S. K., SUBRAMANIAN, S., JULKA, D. B. & GUZ, A. (1972). Search for evidence of lung chemoreflexes in man: study of respiratory and circulatory effects of phenyldiguanide and lobeline. *Clinical Science* **42**, 163–177.

KILLIAN, K. J. & CAMPBELL, E. J. M. (1983). Dyspnea and exercise. *Annual Review of Physiology* **5**, 465–479.

KILLIAN, K. J. & JONES, N. L. (1984). The use of exercise testing and other methods in the investigation of dyspnea. *Clinics in Chest Medicine* **5**, 99–108.

LANE, R., COCKCROFT, A., ADAMS, L. & GUZ, A. (1987*a*). Arterial oxygen saturation and breathlessness in patients with chronic obstructive airways disease. *Clinical Science* **72**, 693–698.

LANE, R., COCKCROFT, A. & GUZ, A. (1987*b*). Voluntary isocapnic hyperventilation and breathlessness during exercise in normal subjects. *Clinical Science* **73**, 519–523.

LOESCHCKE, H. H. (1982). Central chemosensitivity and the reaction theory. *Journal of Physiology* **332**, 1–24.

LUGLIANI, R., WHIPP, B. J., SEARD, C. & WASSERMAN, K. (1971). Effect of bilateral carotid body resection on ventilatory control at rest and during exercise in man. *New England Journal of Medicine* **285**, 1105–1111.

MILLER, J. D., CUNNINGHAM, D. J. C., LLOYD, B. B. & YOUNG, J. M. (1974). The transient respiratory effects in man of sudden changes in alveolar CO_2 in hypoxia and in high oxygen. *Respiration Physiology* **20**, 17–31.

MITHOEFER, J. C. (1965). Breath holding. In *Handbook of Physiology*, section 3, *Respiration*, vol. 2, ed. FENN, W. O. & RAHN, H., pp. 1011–1025. Washington, DC: American Physiological Society.

NADEL, J. A. & WIDDICOMBE, J. G. (1962). Effect of changes in blood gas tensions and carotid sinus pressure on tracheal volume and total lung resistance to air flow. *Journal of Physiology* **163**, 13–33.

QUINE, W. V. O. (1961). *From a Logical Point of View*. Cambridge, MA: Harvard University Press.

REBUCK, A. S. & SLUTSKY, A. S. (1981). Measurement of ventilatory responses to hypercapnia and hypoxia. In *Regulation of Breathing*, part II, ed. HORNBEIN, T. F., pp. 745–771. New York: Dekker.

SAUNDERS, N. A., BETTS, M. F., PENGELLY, L. D. & REBUCK, A. S. (1977). Changes in lung mechanics induced by acute isocapnic hypoxia. *Journal of Applied Physiology* **42**, 413–419.

SIESJO, B. K., JOHANNSSON, H., NORBERG, K. & SALFORD, L. (1975). Brain function, metabolism and blood flow in moderate and severe arterial hypoxia. In *Brain Work*, ed. INGVAR, D. H. & LASSEN, N. A., pp. 101–109. Copenhagen: Munksgaard.

STARK, R. D., GAMBLES, S. A. & LEWIS, J. A. (1981). Methods to assess breathlessness in healthy subjects: a critical evaluation and application to analyse the acute effects of diazepam and promethazine on breathlessness induced by exercise or by exposure to raised levels of carbon dioxide. *Clinical Science* **61**, 429–439.

SWANSON, G. D., WHIPP, B. J., KAUFMAN, R. D., AQLEH, K. A., WINTER, B. & BELLVILLE, J. W. (1978). Effect of hypercapnia on hypoxic ventilatory drive in normal and carotid body-resected man. *Journal of Applied Physiology* **45**, 971–977.

SWINBURN, C. R., WAKEFIELD, J. M. & JONES, P. W. (1984). Relationship between ventilation and breathlessness during exercise in chronic obstructive airways disease is not altered by prevention of hypoxaemia. *Clinical Science* **67**, 515–519.

TWENEY, J. (1987). Almitrine bismesylate: current status. *Bulletin Européen Physiologie Pathologie Respiratoire* **23**, 153–165s.

WADE, J. G., LARSON JR, C. P., HICKEY, R. F., EHRENFELD, W. K. & SEVERINGHAUS, J. W. (1970). Effect of carotid endarterectomy on carotid chemoreceptor and baroreceptor function in man. *New England Journal of Medicine* **282**, 823–829.

WARD, S. A. & BELLVILLE, J. W. (1983). Peripheral chemoreflex suppression by hyperoxia during moderate exercise in man. In *Modelling and Control of Breathing*, ed. WHIPP, B. J. & WIBERG, D. M., pp. 54–61. New York: Elsevier.

WEIL, J. V., BYRNE-QUINNE, E., SODAL, I. E., FRIESEN, W. O., UNDERHILL, B., FILLEY, G. F. & GROVER, R. F. (1970). Hypoxic ventilatory drive in normal man. *Journal of Clinical Investigation* **49**, 1061–1072.

WEST, D. W. M., ELLIS, G. & CAMPBELL, E. J. M. (1975). Ability of man to detect increases in his breathing. *Journal of Applied Physiology* **39**, 372–376.

WHIPP, B. J., WARD, S. A. & WASSERMAN, K. (1983). Reflex control of ventilation by peripheral arterial chemoreceptors in man. In *Physiology of the Peripheral Arterial Chemoreceptors*, ed. ACKER, H. & O'REGAN, R. G., pp. 299–323. Amsterdam: Elsevier.

WHIPP, B. J., WARD, S. A. & WASSERMAN, K. (1986). Respiratory markers of the anaerobic threshold. *Advances in Cardiology* **35**, 47–64.

WHIPP, B. J. & WASSERMAN, K. (1980). Carotid bodies and ventilatory control dynamics in man. *Federation Proceedings* **39**, 2668–2673.

WRIGHT, G. W. & FILLEY, G. F. (1951). Pulmonary fibrosis and respiratory function. *American Journal of Medicine* **10**, 642–661.