# Effect of hypercapnia on hypoxic ventilatory drive in carotid body–resected man

GEORGE D. SWANSON, BRIAN J. WHIPP, ROBERT D. KAUFMAN, KAMEL A. AQLEH, BENJAMIN WINTER, AND J. WELDON BELLVILLE
*Departments of Anesthesiology, Physiology and Medicine, University of California, Los Angeles, California 90024*

SWANSON, GEORGE D., BRIAN J. WHIPP, ROBERT D. KAUFMAN, KAMEL A. AQLEH, BENJAMIN WINTER, AND J. WELDON BELLVILLE. *Effect of hypercapnia on hypoxic ventilatory drive in carotid body-resected man.* J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 45(6): 971–977, 1978. – Steplike end-tidal hypoxic drives ($P_{ET_{CO_2}}$ = 53 Torr) lasting for 5 min were generated in a group of normal subjects and a group of carotid body–resected subjects when end-tidal $CO_2$ was maintained constant under eucapnic ($P_{ET_{CO_2}}$ = 39 Torr) and hypercapnic ($P_{ET_{CO_2}}$ = 49 Torr) conditions. The hypoxic ventilatory response of the normal subjects was prompt and significant in eucapnia and was enhanced in the hypercapnic state, evidencing $CO_2$-$O_2$ interaction. In contrast, the carotid body–resected subjects did not respond to eucapnic hypoxia but did demonstrate a small but significant ventilatory response to hypoxia against the hypercapnic background. This suggests that the aortic bodies in man may contribute a small component of the hypoxic ventilatory drive under hypercapnic conditions, although the possibility of neuromalike ending regeneration cannot be excluded.

steplike hypoxia; dynamic end-tidal forcing; aortic body function; carotid body resection; ventilatory control

PERIPHERAL CHEMORECEPTORS, the aortic and carotid bodies, are the exclusive mediators of hypoxic ventilatory drive in man and in experimental animals. Although the relative contribution of each group of chemoreceptors is somewhat variable among the species (2–5), the aortic bodies commonly subserve a more minor role as ventilatory chemoreceptors compared with the carotid bodies. According to the steady-state data of Wade et al. (17) and Lugliani et al. (10) and the analysis by Whipp et al. (20) of early transient ventilatory responses to hypoxic-hyperoxic transitions in carotid body–resected (CBR) subjects, it appears that, in man, the aortic body hypoxic drive is absent.

However, as hypercapnia is known to increase the peripheral chemoreceptor component of ventilatory drive at a given oxygen tension ($P_{O_2}$), and to increase the $P_{O_2}$ at which this drive becomes evident, the possibility exists that the aortic bodies might be functional ventilatory chemoreceptors in man, but that they have an eucapnic threshold below a arterial $P_{O_2}$ of 35–40 Torr (i.e., the lowest level at which the previous studies in man have been carried out). Consequently, with a background of hypercapnia, the aortic bodies might demonstrate ventilatory chemosensitivity in man in response to abrupt hypoxia. Alternatively, the aortic body ventilatory drive could be masked by a central hypoxic depression that may occur in steady-state experiments (7, 13).

In an attempt to assess these possibilities, we studied the ventilation response to an abrupt input of hypoxic inspired gas that results in a square-wave change of "alveolar" gas tension against a background of eucapnia or hypercapnia in normal subjects and in subjects who had undergone bilateral carotid body resection.

The study indicates that against a background of hypercapnia, a hypoxic ventilatory response can be discerned in subjects without carotid bodies, beginning at a time characteristic of aortic body stimulation. No such hypoxic response was evident during eucapnia.

## METHODS

Five subjects who had had both carotid bodies removed by a technique that does not disrupt barostatic reflexes (10, 22) were used in this study. These patients had a history of bronchial asthma but were in remission at the time of our studies. They were selected from a larger available group because their pulmonary function and gas exchange were within the normal range, except for evidence of a mild maldistribution of inspired air and a mild reduction of forced expiratory flow. For further details see Refs. 10 and 18. These subjects were naive to the purposes of this study. They had a mean age of 29 yr with a range of 16–45. Two of the five subjects were female and four of the five had participated in a variety of previous respiratory studies. The group of normal males used for controls in this study was composed of experienced subjects, in that they had previously participated in studies in our laboratory. However, they had no knowledge of respiratory physiology or the purposes of this study. The six normal subjects ranged in age from 22 to 34 with a mean age of 24 yr.

The subjects were tested in a semirecumbent position and breathed through a low-dead-space valve (Rudolph p320). Hypoxic steps of end-tidal $P_{O_2}$ were administered in eucapnia and hypercapnia ($P_{ET_{CO_2}}$ = 49 Torr). In eucapnia, the subject breathed room air for about 5 min before the hypoxic step ($P_{ET_{O_2}}$ = 53 Torr) was adminis-

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tered. In hypercapnia, the subject breathed approximately 5% $CO_2$ in 21% $O_2$ for 7–10 min before the hypoxic step was initiated. The hypoxic steps were only initiated after the ventilatory data were judged to be in a steady state for a minimum of 2 min. Thus, the data collection period consisted of 2-min normoxic control period, a 5-min hypoxic stimulation period, and finally a 5-min normoxic recovery period against a constant eucapnic or hypercapnic background.

To generate a steplike decrease in end-tidal $O_2$ from normoxic conditions to hypoxic conditions, the inspired $O_2$ concentration was abruptly dropped to zero from one or more breaths, and then slowly elevated so as to maintain the end-tidal $O_2$ at a predetermined hypoxic level. At the conclusion of the hypoxic step, the inspired $O_2$ was abruptly brought to a high inspired $O_2$ value for one or more breaths and then slowly returned to room air concentration so as to maintain the end-tidal $O_2$ at control normoxic conditions. The manipulation of the inspired gases, to achieve the desired end-tidal forcing function, was accomplished by the dynamic end-tidal forcing technique previously described (14–16). During the course of the experiment, the inspired $CO_2$ was manipulated to maintain isocapnic conditions in end-tidal $CO_2$ at either a eucapnic or a hypercapnic level.

Figure 1 shows a representative tracing of the inspired and expired $O_2$ pattern for a hypoxic step forcing. Note that when the hypoxic step is initiated, the inspired $O_2$ is lower than the end-tidal $O_2$ for several breaths. It typically required two to a maximum of four breaths to achieve the desired end-tidal $O_2$ hypoxic level. Thereafter the inspired $O_2$ was manipulated to maintain end-tidal $O_2$ constant. Similarly, at the conclusion of the hypoxic step, two to four breaths of greater than 21% oxygen were typically required to return the end-tidal $O_2$ to the control normoxic level.

The experimental apparatus is similar to that described for the previously published end-tidal forcing experiments (14–16). For this particular study, exhaled volume was obtained by an analog integration of the exhaled flow signal as derived from a linear mass flowmeter (Thermo Systems, 1051-1, linear from 0 to 500 l/min ± 0.5%). Carbon dioxide concentrations were measured by an infrared analyzer (Beckman LB-2); oxygen concentrations were monitored by a fuel cell analyzer (Applied Electrochemistry S-3A). Arterial $O_2$ saturation was estimated by ear oximetry (Hewlett-Packard 47201A, response time 3.0 s for 89%). The analog computer also generated interrupts indicating the beginning and the end of exhalation, which enabled the digital computer (Digital Equipment PDP-8/e) to register the breath-cycle timing sequence, sample the gas concentrations, and sample exhaled tidal volume. Minute ventilation was then computed digitally on a breath-to-breath basis.

To average the data from several subjects, the data from each subject were interpolated over 5-s intervals. The group means ± SE at each 5-s interval were determined for the normal ($n$ = 6) and the CBR ($n$ = 5) groups. The averaged variables include minute ventilation, end-tidal $O_2$, end-tidal $CO_2$, and arterial $O_2$ saturation as determined by ear oximetry. These group means and intersubject standard errors are shown at selected intervals in Figs. 2 and 3.

The average variables for the 2-min control period, for the final 4 min of the stimulation period and for the final 4 min of the recovery period were determined by computing the mean of the 5-s interval values for each period, respectively. These mean values were computed for each subject and were used in the Student's paired $t$ test for comparison of the levels between different periods. In addition, the group means for each period were computed and tabulated with a standard error that reflects both the intra- and intersubject variability. For example, in the control period (0–120 s), there are 24 5-s interval samples and 6 normal subjects, yielding a total number of samples ($n_s$ = 144) from which the intrasubject/intersubject standard errors were determined. The group mean for each period and the intrasubject/intersubject standard errors are tabulated in Table 1.

## RESULTS

The technique for maintaining a constant end-tidal $CO_2$ tension ($P_{CO_2}$) during the test was successful as shown in Table 1. Note that the end-tidal $P_{CO_2}$ is not significantly different when the stimulation period is compared to the control period and the recovery period.

The mean hypoxic response characteristics in the normal subjects, against a eucapnic background, indicate a rapid ventilatory response that results in a steady-state plateau within approximately 45 s after the initiation of the hypoxic stimulus (Fig. 2$A$). In contrast,

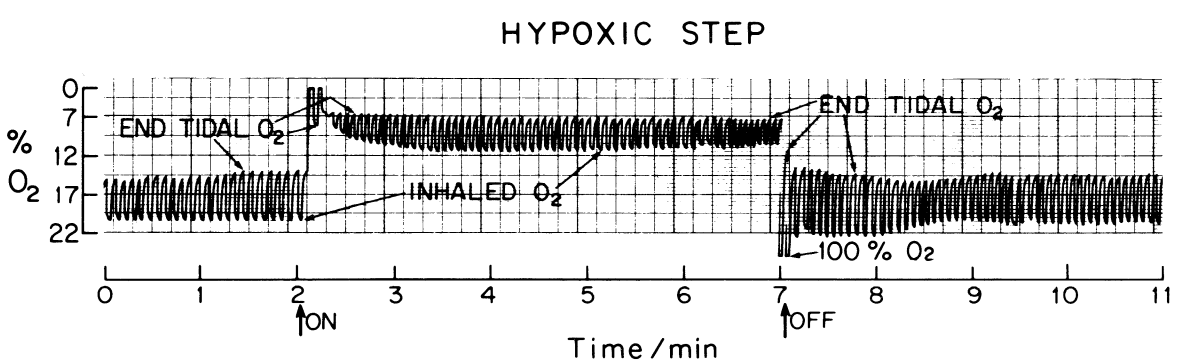


FIG. 1. Manipulation of inhaled $O_2$ to achieve a steplike end-tidal $O_2$ transition, using dynamic end-tidal forcing technique. Note two breaths of 100% nitrogen at beginning of step and two breaths of 100% $O_2$ at its termination. See text for further discussion.

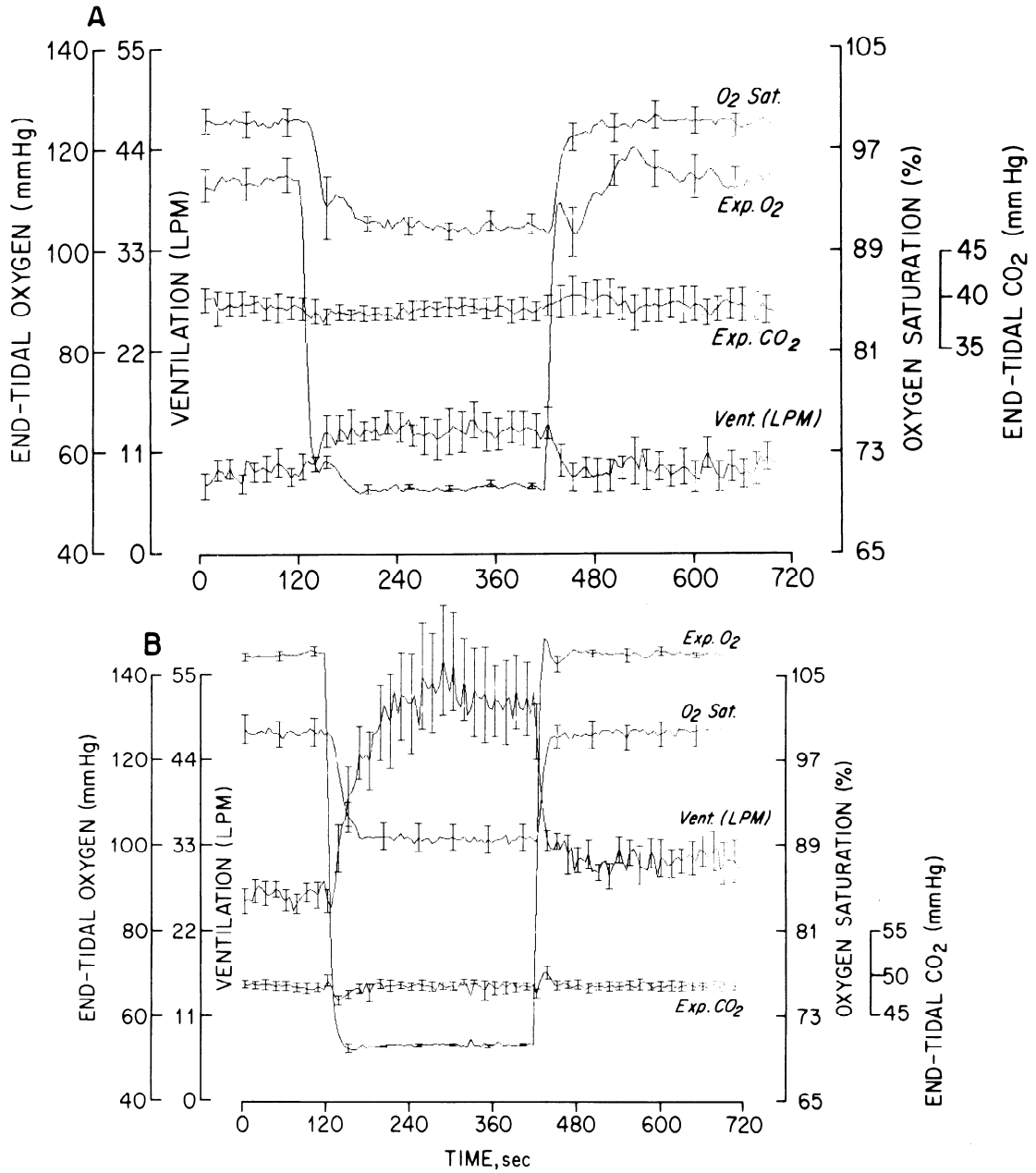


FIG. 2. Ventilatory response (mean ± SE) for normal subjects to a hypoxic steplike change in end-tidal $O_2$ (± SE). *A*: response in eucapnia ($P_{ET_{CO_2}}$ = 39 Torr); *B*: response in hypercapnia ($P_{ET_{CO_2}}$ = 49 Torr). $P_{ET_{CO_2}}$ (± SE) is shown. Arterial $O_2$ saturation (± SE) is assessed by an ear oximeter (see METHODS) that has a standard internal calibration. Thus saturation scale reflects this calibration and not an absolute calibration to each patient. Intersubject (5 carotid body-resected subjects and 6 normal subjects) standard errors are computed from interpolated data at specific times shown.

the hypoxic ventilatory response characteristics in hypercapnia (Fig. 2*B*) indicate that, although the response begins rapidly the ventilation pattern is slower, and when the paired comparisons of the values during the 3rd and 5th min (during the stimulation period) were tested, two of the six subjects and the group mean exhibited a slight overshoot that was statistically significant ($P < 0.05$). Ventilation then falls quickly on the return to normoxia but exhibits a residual hyperpnea.

The mean results for the CBR subjects are shown in Fig. 3. Note that a steplike hypoxic change was achieved in this group that is similar to that achieved in normal group. In contrast to the normal response, the CBR group (Fig. 3*A*) shows no significant hypoxic ventilatory response in eucapnia, tested statistically by paired differences. However, in hypercapnia a slight hypoxic ventilatory response is apparent (Fig. 3*B*), increasing ventilation by approximately 2 l/min to a value that is significantly different ($P < 0.05$) from the control value (Table 1). This is more evident in Fig. 4, where the ventilation scale is expanded.

## DISCUSSION

The step decrease in end-tidal $P_{O_2}$ was used in an attempt to present an abrupt hypoxic signal that propagates the arterial blood to the peripheral chemorecep-

tors and to brain tissue. Although end-tidal $P_{CO_2}$ underestimates arterial $P_{CO_2}$, and end-tidal $P_{O_2}$ overestimates arterial $P_{O_2}$ at rest, the changes in end-tidal values should reflect the changes in arterial gas tension in normal lungs. This can be assessed by the pattern of the arterial blood signal arriving at the ear, characterized by the arterial $O_2$ saturation change. Figures 2 and 3 show the relative timing between the end-tidal $O_2$ change and the saturation response at the ear. Note that after a circulatory delay only minor temporal distortion is apparent (9).

In the CBR subjects, who have a mild maldistribution of alveolar gas, a steady decline in arterial saturation was apparent during the hypoxic step (Fig. 3*A*) in contrast to the abrupt plateau in normal subjects (Fig. 2*A*). This decline was more dominant in particular subjects. A continued decrease in arterial $O_2$ saturation in this group is likely to be consequent to the influence of the lung regions with long time constants for washin of hypoxic gas. Because the continued decrease in $O_2$ saturation was not present against the hypercapnic background (Fig. 3*B*), the high $P_{CO_2}$ may have caused bronchodilatation in the constricted regions, as described previously by Widdicombe (21). Furthermore, the presence of hypercapnia influenced the level of arterial desaturation obtained for the same hypoxic

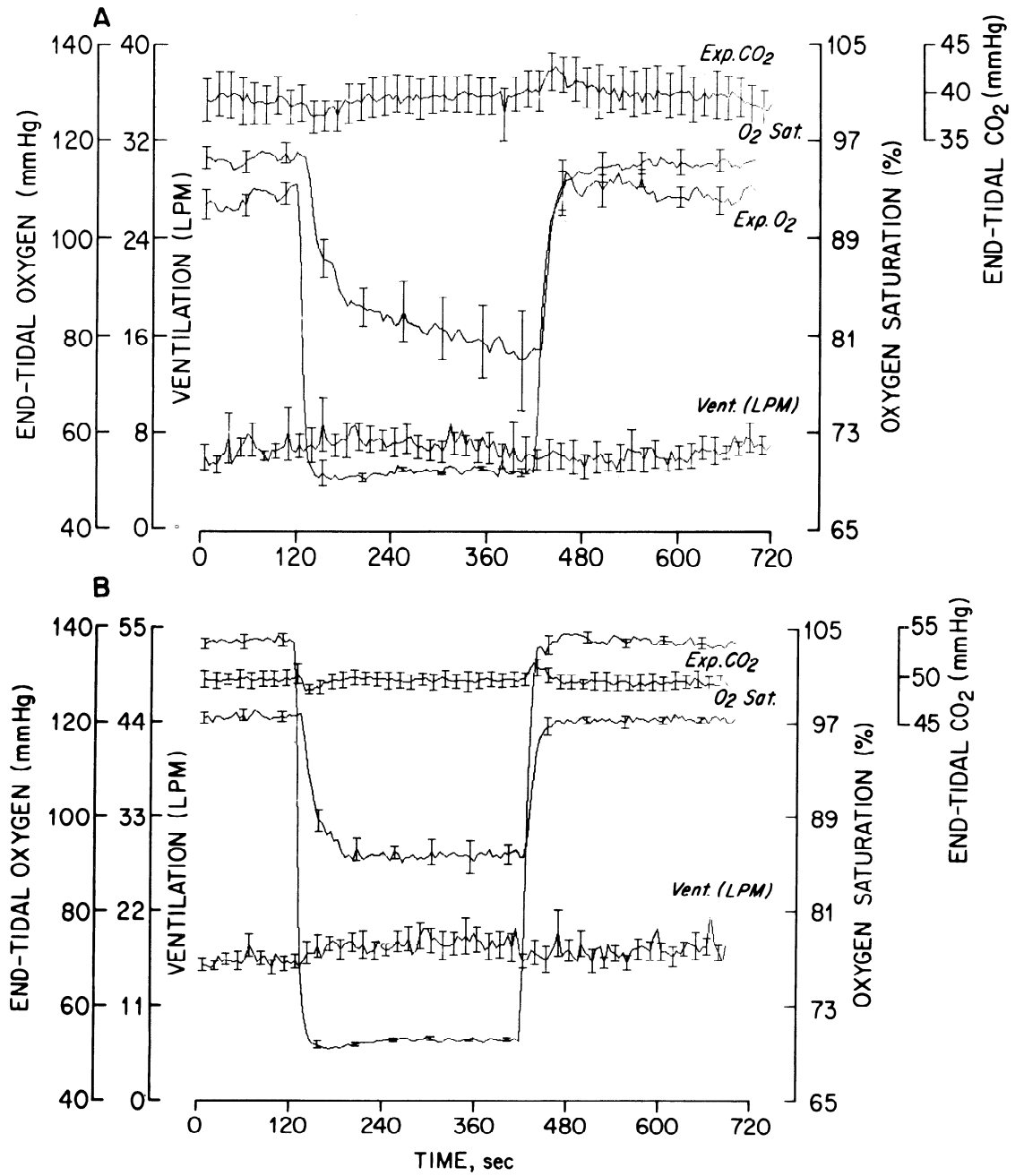


FIG. 3. Ventilatory response (mean ± SE) for carotid body-resected subjects to a hypoxic steplike change in end-tidal $O_2$ (± SE). *A*: response in eucapnia ($P_{ET_{CO_2}}$ = 39 Torr); *B*: response in hypercapnia ($P_{ET_{CO_2}}$ = 49 Torr). $P_{ET_{CO_2}}$ (± SE) is shown. Arterial $O_2$ saturation (± SE) measured by an ear oximeter is also shown. All standard errors shown are intersubject.

end-tidal $O_2$ level. For the normal subjects, this is in the direction predicted by the Bohr shift. For the CBR subjects, the average level of desaturation was diminished in a background of hypercapnia, again suggesting that hypercapnia is causing a more even distribution of ventilation-perfusion in the CBR group.

TABLE 1. *Average data for normal and carotid body-resected subjects*

| | Control, 0–120 s* | Stimulation, 180–420 s | Recovery, 480–720 s | Stimulation–Control | Stimulation–Recovery | Recovery–Control |
|---|---|---|---|---|---|---|
| *Normal subjects, Eucapnia* | $n = 6$ $n_s = 144$ | $n = 6$ $n_s = 288$ | $n = 6$ $n_s = 288$ | | | |
| $P_{ET_{CO_2}}$ | 39.4 ± 1.0 | 38.9 ± 0.7 | 39.4 ± 1.3 | −0.5 | −0.5 | 0.0 |
| $P_{ET_{O_2}}$ | 113.6 ± 3.3 | 52.9 ± 0.3 | 114.6 ± 3.2 | −60.7† | −61.7† | 1.0 |
| $S_{O_2}$ | 99.1 ± 1.2 | 90.9 ± 0.6 | 98.9 ± 1.0 | 8.2† | −8.0† | −0.2 |
| $\dot{V}_E$ | 8.9 ± 0.9 | 13.2 ± 1.4 | 9.2 ± 1.1 | 4.3† | 4.0† | 0.3 |
| *Normal subjects, Hypercapnia* | $n = 6$ $n_s = 144$ | $n = 6$ $n_s = 288$ | $n = 6$ $n_s = 288$ | | | |
| $P_{ET_{CO_2}}$ | 48.5 ± 0.4 | 48.5 ± 0.4 | 48.4 ± 0.4 | 0.0 | 0.1 | −0.1 |
| $P_{ET_{O_2}}$ | 144.2 ± 0.9 | 53.1 ± 0.02 | 144.4 ± 0.9 | −91.1† | −91.2† | 0.2 |
| $S_{O_2}$ | 99.4 ± 1.1 | 89.4 ± 1.1 | 99.5 ± 1.1 | −10.0† | −10.0† | 0.1 |
| $\dot{V}_E$ | 26.5 ± 1.2 | 50.7 ± 4.5 | 30.7 ± 1.5 | 24.2† | 20.0† | 4.2† |
| *CBR subjects, Eucapnia* | $n = 5$ $n_s = 120$ | $n = 5$ $n_s = 240$ | $n = 5$ $n_s = 240$ | | | |
| $P_{ET_{CO_2}}$ | 39.1 ± 1.8 | 39.5 ± 1.7 | 39.6 ± 1.9 | −0.4 | −0.1 | 0.5 |
| $P_{ET_{O_2}}$ | 107.8 ± 1.9 | 52.1 ± 0.2 | 109.3 ± 1.9 | −55.7† | −57.2† | 1.5 |
| $S_{O_2}$ | 95.4 ± 0.8 | 81.4 ± 2.2 | 95.0 ± 0.9 | −14.0† | −13.6† | −0.4 |
| $\dot{V}_E$ | 6.5 ± 0.7 | 7.0 ± 0.9 | 6.3 ± 0.8 | 0.5 | 0.7 | −0.2 |
| *CBR subjects, Hypercapnia* | $n = 5$ $n_s = 120$ | $n = 5$ $n_s = 240$ | $n = 5$ $n_s = 240$ | | | |
| $P_{ET_{CO_2}}$ | 49.4 ± 0.7 | 49.4 ± 0.7 | 49.2 ± 0.6 | 0.0 | 0.2 | 0.2 |
| $P_{ET_{O_2}}$ | 137.2 ± 0.8 | 52.8 ± 0.1 | 137.4 ± 0.9 | −84.4† | −84.6† | 0.2 |
| $S_{O_2}$ | 97.5 ± 0.3 | 85.8 ± 0.6 | 97.3 ± 0.2 | −11.7† | −11.5† | −0.2 |
| $\dot{V}_E$ | 16.3 ± 0.4 | 18.3 ± 1.0 | 17.7 ± 0.8 | 2.0† | 0.6 | 1.4 |

Values are means ± SE; SE's reflect the intersubject/intrasubject variability for each period. $n$, Number of subjects; $n_s$, number of samples; $P_{ET_{CO_2}}$ and $P_{ET_{O_2}}$, end-tidal $CO_2$ and $O_2$ tension, in Torr; $S_{O_2}$, arterial $O_2$ saturation, in %; $\dot{V}_E$, minute ventilation, in l/min; CBR, carotid body-resected. * Time frames of the control, stimulation, and recovery periods are indicated in seconds. † Significantly different ($P < 0.05$) by the Student's paired $t$ test.

The characteristics of the carotid body and aortic body in man suggest that the response to an abrupt hypoxic stimulus should be fast. Thus, we would expect a rapid ventilatory response and a rapid return to control for an abrupt hypoxic stimulation and also following its removal. Therefore, the response characteristics for the normals in eucapnia (Fig. 2*A*) are to be expected. Furthermore, when the carotid body pathway is interrupted, no significant hypoxic ventilation response is evident, as indicated by the lack of CBR-subject response in eucapnia (Fig. 3*A*).

Inasmuch as a significant transient ventilatory response to the hypoxic stimulus is not evident, it does not appear that a slowly developing central hypoxic depression is masking the faster aortic body stimulation (7). Thus, as previously reported (10, 17) the aortic body does not appear to stimulate ventilation under moderate hypoxia and eucapnia.

The addition of inspired $CO_2$ to establish a hypercapnic background modified the hypoxic response in both the normal group and the CBR group. In the normal subjects, the magnitude of the hypoxic response is markedly increased, evidencing $CO_2$-$O_2$ interaction. Although not physiologically significant in our study, the peak and slight decay over the 5 min of hypoxic stimulation that occurred in two of the subjects suggest that there may be a slowly developing central hypoxic depression, which gradually competes with the peripheral hypoxic stimulation (7, 19), although the eucapnic hypoxic pattern does not suggest this. Alternatively, the peripheral chemoreceptors may exhibit slow adaptive features similar to those observed in studies conducted in cats (2).

Figure 3*B* indicates a slight hypoxic stimulation

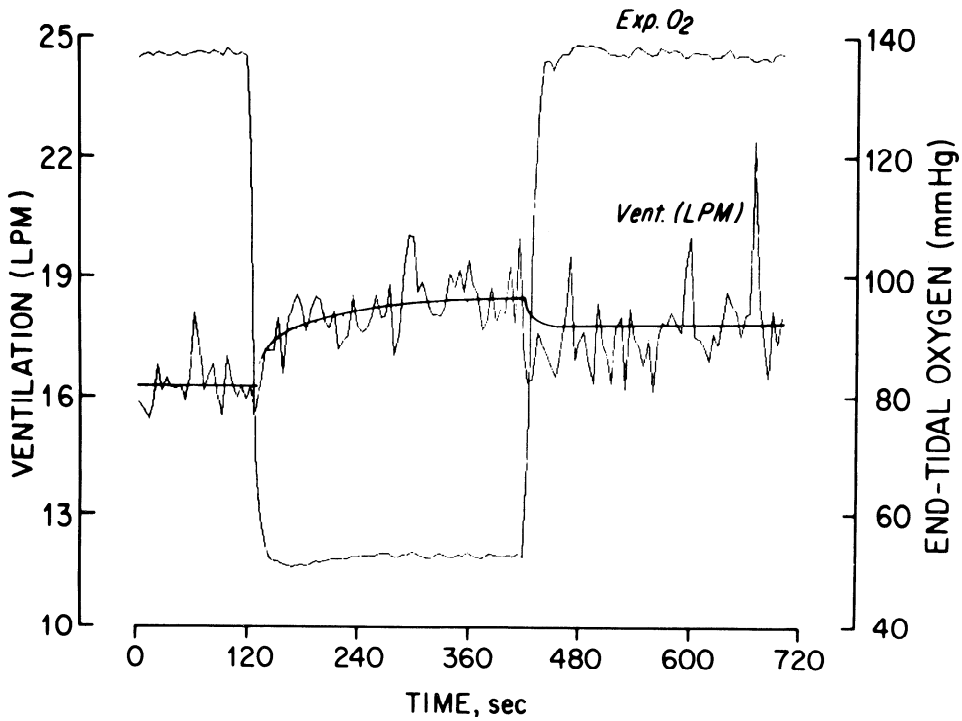


FIG. 4. Mean ventilatory response for carotid body-resected subjects to a hypoxic steplike change in end-tidal $O_2$. Same as Fig. 3*B*, but with the ventilation scale expanded.

under hypercapnia in the CBR group. This is more evident in Fig. 4, where the scale has been expanded. This ventilatory response is fast, as it is in the normal group (Fig. 2) and is compatible with an aortic body hypoxic response that is not evident in eucapnia. However, we are unable to discriminate between this mechanism or one in which the ventilatory response might be mediated by possible regeneration of fibers in the sectioned nerve of Hering into neuromalike endings as described in the cat by Mitchell et al. (12) or structures such as "miniglomera" described in the cat by Matsuura (11), although there is no evidence for their existence in man. It is interesting that in awake ponies (1) an acute hypoxic response was evident following carotid body denervation and became more marked within weeks. In the two ponies where the aortic bodies were denervated, the hypoxic response was abolished. Furthermore, these studies were performed under hypercapnic conditions, because the carotid body denervation led to chronic hypercapnia; thus the more likely mechanism is aortic body mediation.

Both the normal group and the CBR group demonstrate a residual hyperpnea under hypercapnic conditions during the normoxic recovery period. In the normal group the magnitude of the residual hyperpnea is 4.2 versus 1.4 l/min in the CBR group. This suggests that the magnitude of the residual hyperpnea is a consequence of peripheral chemoreceptor stimulation. A persistent hyperpnea after step termination of hypoxia was also observed by Dutton et al. (6). It is also similar to that observed in paralyzed cats after cessation of electrical stimulation of the carotid sinus nerve (8). Furthermore, a similar hyperpnea can be observed in man under isocapnic conditions after the cessation of voluntary hyperventilation (16). Thus the posthypoxic stimulation hyperpnea may be caused by similar mechanisms, although ventilation did not return to control during the 5-min recovery period (Fig. 2).

This residual hyperpnea contributes to the lack of a significant difference between the stimulation period and the recovery period for the CBR subjects under hypercapnia. However, the marked spikes shown in Fig. 4 for the recovery period also contribute. These spikes were contributed by one subject who had a tendency to sigh. If this subject is eliminated from the group, then the difference between the stimulation and the recovery periods becomes significant, even with a residual hyperpnea.

We have suggested that peripheral chemoreceptor stimulation initiates the residual hyperpnea. However, a central mechanism could also initiate this residual hyperpnea. If this were the case, then the same central mechanism might also be responsible for the stimulation period response of the CBR subjects. We cannot conclusively discriminate between a peripheral origin and a central origin of the stimulation period response, and of course both mechanisms could be involved. In favor of a peripheral chemoreceptor stimulation is the initial speed of the response at the initiation and the withdrawal of the hypoxic stimulation (see Fig. 4), suggesting a response too early to be central in origin.

It is therefore apparent from these studies that in eucapnia the carotid bodies are the exclusive mediators of the hyperpnea of hypoxia or that the aortic body contribution is too small to detect. Against a hypercapnic background, however, hypoxia induced a small hyperpnea in the CBR group with temporal characteristics of peripheral chemoreception. This hyperpnea is likely to originate in the aortic bodies, although the possibility of neuromalike ending regeneration cannot be excluded. The gain of this system is so low, however, that is unlikely to provide important modulation of respiratory drive.

We are grateful to Mr. Michael Williams for aid in computer programming and data analysis. Computing assistance was obtained from the Health Sciences Computing Facility, University of California, Los Angeles, supported by National Institutes of Health Special Research Resources Grant RR-3.

This investigation was supported in part by Research Grant HL-15659 from the National Heart, Lung, and Blood Institute.

Present address of G. Swanson: Dept. of Anesthesiology, University of Colorado School of Medicine, Denver, CO 80262.

Received 20 May 1977; accepted in final form 23 July 1978.

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