Role of Carotid Chemoreceptors in Control of Breathing at Rest and in Exercise: Studies on Human Subjects with Bilateral Carotid Body Resection

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Heymans and his colleagues [22] were the first to find the chemoreflex ventilatory activities of the carotid body in the late 1920s, for which he was awarded the Nobel Prize in 1938. Comroe and Schmidt [8] further confirmed the above work by quantitative evaluation of the chemosensitivities of both aortic and carotid bodies. It is now known that contribution of both peripheral chemoreceptors to hypoxic hyperventilation reveals considerable species differences, i.e., among dogs, rats, cats, goats, and rabbits [7, 46]. Most of the animal studies, however, agree that the carotid body plays a dominant role in the peripheral chemorex activities [6, 9, 10].

In view of these observations, quantitative evaluations of the carotid body chemosensitivity in humans may be questioned with considerable interest. In Japan during the late 1940s and 1950s, a number of patients with bronchial asthma had therapeutic carotid body resections. The operations were done in the Department of Surgery of the Chiba University Medical School, where Dr. Nakayama, Professor of Surgery, developed a procedure for removing only the carotid chemoreceptors, preserving the baroreceptor function [40]. Nearly 20 years after these operations, we had the opportunity to study the control of respiration in these patients [27, 28, 29].

ROLE OF THE CAROTID BODY CHEMORECEPTORS AT REST

1. Method of evaluation: steady state vs. single breath response

Man has been shown to lose the ventilatory response to sustained hypoxia after removal or denervation of the carotid bodies [19, 23, 38, 47]. Therefore, the carotid bodies have been assumed to be responsible for all the peripheral chemosensitivity of the ventilation in man. However, evidence has accumulated that hypoxia may depress the central chemosensitivity [5, 24, 25, 32, 36, 41, 43, 44, 51]. Figure 1 schematically represents the hypoxic ventilatory responses in the normal

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as well as in the subject with bilateral carotid body resection (BR). Apparent loss of ventilatory response in the BRs could be because the residual hypoxic response (RHR) is counteracted by the hypoxic depression (HD). Accordingly, the actual ventilatory activities in the normal subjects may consist of three components, i.e., carotid body response (CBR), RHR, and HD.

The precise nature of RHR will be discussed later. To detect RHR in the BR subjects, we used the single breath test which was originally proposed by DEJOURS [12, 13]. The principle of this test is to evaluate the ventilatory response during the period in which the applied stimulus of the inhaled gas to the peripheral chemoreceptors does not yet reach the CNS. Therefore, the influence of hypoxic depression can be excluded. The number of modifications from the original single breath test were reported. Our method [17] was the single vital capacity (VC) breath test in which the amount of test gas is the VC volume. Accordingly, the magnitude of the test stimulus is great, enabling us to consider this method useful for detecting a weak peripheral chemosensitivity, which could be expected to be the case in the BR subjects.

2. Magnitude of the ventilatory activities

1) Hypoxic response. Figure 2A represents sustained hypoxic ventilatory responses of three different subject groups in terms of $\Delta V_{40}$ where BR and UR signify the subjects with bilateral and unilateral carotid body resection, respectively, and C is the control. $\Delta V_{40}$ is the increment of ventilation when alveolar $P_{O_2}$ ($P_{A0_2}$) decreased from normoxia (100 mmHg) to 40 mmHg with alveolar $P_{CO_2}$ ($P_{ACO_2}$) kept constant (isocapnic hypoxia). The magnitudes of $\Delta V_{40}$ in BR, UR, and control were $0.3 \pm 3.0$, $6.0 \pm 4.3$, and $17.8 \pm 8.2$ l·min$^{-1}$, respectively (mean $\pm$ S.D.). In accordance with previous findings [19, 23, 38, 47] and the schematical illustration of Fig. 1, $\Delta V_{40}$ of the BR subjects is not significantly different from zero, although considerable individual differences were seen. The
response of UR was about one-third of the control. Figure 2B shows the responses of the single VC breath test in the three groups. The magnitudes were 2.19±1.44, 10.9±7.15, and 22.46±6.90 l • min⁻¹ (mean±S.D.) in the BR, UR, and control groups, respectively. The response of BR is significantly larger than zero (p<0.01), which indicates that the subjects without the carotid bodies still exhibit the positive ventilatory response in the peripheral hypoxic chemosensitivity. The response of BR was about one-tenth the control and the response of the UR was about half of the control. Thus, the contribution of each carotid body was seen to have a graded influence on ventilatory activities.

2) Hypercapnic response. In contrast to the marked depression in ventilatory hypoxic responses, the BR groups revealed substantially well-maintained hypercapnic ventilatory responses in both hypoxia (end-tidal $P_{CO_2}$ 60 mmHg) and hyperoxia (Fig. 3). The ordinate in this figure is the slope of the steady state CO₂ response curve ($S$) obtained by a linear regression analysis between ventilation and $P_{ACO_2}$. The $S$ values in BR, UR, and control were 0.71±0.12, 0.83±0.32, and 0.01±0.53 l • min⁻¹ • mmHg⁻¹ (mean±S.D.), in hyperoxia and 0.83±0.36, 1.06±0.48, and 1.33±0.66 l • min⁻¹ • mmHg⁻¹ (mean±S.D.) in hypoxia, respectively. The average $S$ value of BR is about 70% of the control.

Ventilatory response to CO₂ is known to be mainly determined by the central chemosensitivity, and animal experiments with carotid body resection already demonstrated well-preserved CO₂ sensitivities [7, 8, 9]. Our results have confirmed that this is also the case in humans, and at least 30% of the CO₂ response may originate from the peripheral chemosensitivity.

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3. Nature of the residual hypoxic response (RHR) observed in the subjects with bilateral carotid body resection (BR)

1) Aortic body. Since the aortic bodies remain intact, RHR may be related to their activities. We have reported earlier [28] that the ventilatory response to the single VC breath test in two patients whose carotid bodies had been removed one month previously showed responses similar in magnitude to the responses in our BR group. This suggests that the weak RHR observed in the BR could have existed soon after the carotid body resection. On the basis of this assumption, it may be inferred that the carotid body plays the role of about 90% and the aortic body about 10% of the total peripheral chemosensitivity and that hypoxic depression at $P_{O_2}$ 40 mmHg is about as great as the ventilatory activity of the aortic body.

2) Glomus pulmonale. KRAHL [31] pointed out the possible chemosensitive activity of the glomus pulmonale in the pulmonary circulatory system, which histologically has the same branchial origin as the aortic and carotid bodies. However, no definite functional activities of this particular organ have been proven.

3) Regeneration of the carotid body chemosensitivity. MITCHELL et al. [39] were the first to find the nerve impulse responses to hypoxia in the central end of the sinus nerve one year after nerve section in the cat, suggesting regeneration of the sensory terminal. Similar observations were also reported in the rabbit [2] and the pony [4]. In a recent review, EYZAGUIRRE and ZAPATA [14] stated that apposition between cut nerve terminals and the carotid body cell is necessary for regeneration of the chemoreception, and some inductive influence from the glomus cells seems to play a role in this process. Whether or not such a process actually takes place in humans is difficult to assess. However, in one patient we noted partial recovery of the ventilatory response to the single VC breath test 2 months after bilateral carotid body resection [28]. Therefore, possible involvement of
regeneration in the RHR cannot be completely excluded.

4) Activation of the aortic body chemosensitivity after carotid body resection. SMITH and MILLS [45] observed substantial recovery in the peripheral chemosensitivity after sinus nerve section, in the cat amounting to 70% at 93–111 days and 100% at 260–315 days postoperatively. This recovery disappeared when the cervical vago-sympathetic nerve trunk was cut. Therefore, the aortic chemosensitivity was assumed to be activated by the sinus nerve section.

It must be noted, however, that regeneration or activation of the peripheral chemosensitivity reported in the animal experiments is very great in magnitude, 30–100% of the control ventilatory activity. The RHR seen in humans by our studies is at most about 10%. Therefore, the possible role of the regeneration or activation process mentioned above may not be so crucial in determining the peripheral chemosensitivity in human subjects.

5) Natural selection. This might possibly have facilitated the survival of those denervated patients who either possessed aortic response or regenerated chemosensitivity. We experienced that two older patients (61 and 71 years) with chronic obstructive pulmonary disease and life-long asthma, whom we studied shortly after surgery [29]; both died during sleep about one year after their bilateral glomectomy.

4. Difference in chemoreceptor activities between carotid and aortic bodies

Experimental studies of the peripheral chemoreceptors have been conducted mainly on the carotid bodies, because the aortic bodies, located in the thoracic cavity, are relatively difficult to approach. However, recent studies disclosed the characteristic features of this organ.

1) Quantitative comparison of carotid and aortic chemoreceptor nerve activities. LAHIRI et al. [33] compared the nerve discharges from the carotid and aortic bodies. In response to both hypoxic and hypercapnic stimulations of a given magnitude, discharge frequencies from the carotid body are 3 to 5 times greater than those from the aortic body. This indicates that the difference in ventilatory activities originated, at least in part, from the difference in afferent nerve discharges from both the chemoreceptor organs.

2) Latency to chemical stimuli and dependency on COHb content and Ht value in the peripheral chemosensitivities. Despite the anatomically closer location to the lung or the heart of the aortic than the carotid body, the latency of chemoreceptor nerve discharges in response to hypoxic and hypercapnic air inhalation was found to be much longer in the former than the latter [35]. Such difference can be ascribed to the highly vasculatized and abundant blood flow in the carotid body vs. the relatively restricted blood perfusion in the aortic body. The aortic body is found to sensitively respond to increasing COHb and anemia whereas the carotid body does not [21, 34]. This difference is claimed to be explained by the perfusion characteristics of both chemoreceptor organs, as mentioned above.

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ROLE OF THE CAROTID BODY IN EXERCISE

Five BRs and 12 control subjects with similar limitations in their pulmonary functions were compared during a bicycle ergometer exercise [26].

1. Ventilation response to incremental work rate in the subjects with and without the carotid body

Figure 4 illustrates the significant depression of hyperpnea in the BR subjects during exercise. Further analysis revealed that a less respiratory frequency response was mainly responsible for this diminished ventilation in the BRs. In reflecting this decreased ventilatory response, alveolar and arterial $P_{CO_2}$ in the BR were also significantly higher than the control. On the other hand, no difference was noted in heart rate and blood pressure response between the two groups, suggesting the well-preserved baroreceptor function as claimed by Nakayama in his operational procedure [40].

2. Possible role of the carotid body in exercise hyperpnea

The ventilatory responses to hypoxia and hypercapnia have been reported to be slightly different, in that the frequency is preferentially stimulated by hypoxia [20, 42]. The failure of the BR subjects to increase the rate would therefore be consistent with the concept that the tachypnea of exercise depends in part on the carotid chemoreceptor drive.

Exercise in the BR subjects was presumably below the "anaerobic threshold (AT)" defined by Wasserman et al. [48]. We measured blood lactate before and after work in three of the five BRs. Its rise was $1.2 \pm 0.6$ mM (mean $\pm$ S.D.), a relatively small change. At this level of work, Lugliani et al. [38] and Wasserman et al. [49] reported that ventilation in the BR was not different from the control.

![Fig. 4. Comparison of exercise hyperpnea in the subjects with bilateral carotid body resection (BR) and the control (C). Ventilation at rest is not statistically different in both groups; however, ventilatory responses to exercise loading were significantly less (*p < 0.05) in the BR than the C subjects. Each column represents mean $\pm$ S.E.](image-url)
group, which seemed to conflict with our findings. The difference between their studies and ours lay in the subjects examined. Forced expired volume in 1 sec (FEV₁₋₀) was moderately depressed in our subjects, normal in Wasserman's, and only slightly lower in Lugliani's. The existence of flow limitation in the pulmonary function may have resulted in the manifestation of the depressed exercise hyperpnea in our subjects.

The ventilatory response to carotid chemoreceptor stimuli has been reported to be intensified by exercise in humans and dogs [1, 50]. Thus, despite the fact that we are dealing with levels of exercise below the AT, we might expect that the BR subjects, with no carotid afferent nerve traffic, show less exercise hyperpnea.

When normal subjects undergo exercise at a moderate intensity below AT, ventilation increases without appreciable changes in the blood gas composition [37]. Numerous efforts have been made to explain this mechanism. In 1960 YAMAMOTO [52] proposed that increased CO₂ production by exercise will make greater arterial Pₐ₉ oscillations in synchronization with the respiratory cycle, and thus will stimulate ventilation even with mean arterial Pₐ₉ unchanged. This is usually called the oscillation hypothesis, a topic which has become a matter of strong controversy among exercise physiologists [11, 16]. Those who support this hypothesis consider the carotid body as the receptor for sensing the Pₐ₉ oscillation because this organ is known to respond to pH change [18, 30]. The depressed exercise hyperpnea in our BR subjects may very well be evidence to support this oscillation hypothesis.

Excision of the carotid bodies also interrupts the reflex arc involving the cervical sympathetic control of the carotid body blood flow. A few investigators claimed that this sympathetic activity intensifies the carotid body chemosensitivity, and is thus possibly responsible for ventilatory response to exercise [3,15]. However, more recent studies seem to agree with the fact that this sympathetic activity mainly controls the by-pass flow in the carotid body and does not influence the chemoreception [14].

SUMMARY

Control of ventilation at rest and in exercise was studied in subjects whose carotid bodies were bilaterally resected (BR) for the treatment of bronchial asthma some 30 years ago. Ventilatory activities of the carotid body were estimated to be responsible for about 90% and about 30% of the hypoxic and hypercapnic responses, respectively. The BR subjects still revealed a weak hypoxic chemosensitivity, called residual hypoxic response (RHR). The nature of RHR was discussed in detail.

Exercise hyperpnea was found to be depressed in the BR subjects when compared with the subjects with similarly impaired pulmonary function. This result
appears to support the oscillation hypothesis in explaining exercise hyperpnea.

Key words: carotid body, chemoreceptor, hypoxia, hypercapnia, exercise.

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