and after sinus nerve cold block, implying that the central chemoreceptor feedback alone is adequate to maintain ventilation. However, when the central contribution is removed, the peripheral component is unmasked.

Peripheral chemodenervation did not alter the transient changes in respiratory frequency seen during hypocapnic perfusion. Afferent chemoreceptor input augmented tidal volumes during the perfusion. This supports the hypothesis of Misericocchi that peripheral afferent input influences primarily the per breath output of the respiratory centers, whereas central chemosensitive afferent input influences both the rhythm generator and the respiratory centers.

In the present study, augmentation of medullary blood flow accelerated the decrease in ventilation. This suggests that cerebral blood flow determines the rate of removal of CO₂ from some central compartment. If blood flow to this compartment is restricted, as in hypocapnia, then the response of the chemoreceptors will be slowed. Since all the present experiments started with the same initial activity, no change in the course of recovery would be expected with variations in blood flow if the ventilatory output were solely sustained by a slow decline of neural activity initiated by identical levels of hypercapnia in the medulla. Although there may be a neural component contributing to the maintenance of ventilation, it does not appear to be the rate-limiting factor in these experiments. On the other hand, if neural reverberations alone sustain ventilation, then not only does the peripheral input determine the extent of the reverberations, but an additional input from the central chemoreceptors must also influence the rate of decay of these reverberations.

In summary, the greater decrease in ventilation observed in denervated animals compared with intact animals during normal flow hypocapnic perfusions suggests that there is a substantial carotid chemoreceptor contribution to the ventilatory drive during recovery from CO₂ breathing. The faster decrease in ventilation seen during high flow hypocapnic perfusions than during normal flow hypocapnic perfusions in intact dogs appears to be due to a faster removal of CO₂ from the medullary chemosensitive tissue. Whether all or part of the remaining time course of ventilatory decline is due to purely neural factors cannot be determined from these experiments. However, we favor a large neural component for the latter.

References


Role of Brain Blood Flow in the Control of Breathing: Effects of Flow Limitation*

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It is widely accepted that Pco₂, H⁺ and Po₂ levels of the brain play a critical role in the control of breathing. Although brain blood flow (BBF) plays a key role in setting the levels of these parameters, little is known about the effects of its limitation, especially in unanesthetized subjects. We have studied acute reductions of BBF for two major reasons: 1) our previous studies have shown that brain hypoxia can stimulate or depress ventilation depending upon the degree of limitation of O₂ delivery to the brain and the concomitant Pco₂; thus, BBF reduction which is likely to alter both does not readily allow our prediction of its effects on ventilation; 2) this study seemed likely to shed light on clinical problems, such as the atypical ventilatory responses of certain acutely ill patients to chemical stimuli or the reported enhancement of ventilatory responses to CO₂ in diffuse cerebrovascular disease, since both groups might have impairment of BBF. Six goats were prepared with chronic arterial and cerebral venous (sagittal sinus) catheters. BBF was measured and controlled via chronic exteriorized (common carotid-internal maxillary) arterial shunts with obliteration of extracerebral branches. At four levels of BBF we measured ventilation (Ve), blood gas tensions, ventilatory responsiveness to CO₂ by the rebreathing method (ΔVe/ΔPco₂) with simultaneous measurement of both PaCO₂ and PVco₂, and ventilatory responsiveness to hypoxia by transient inhalation of nitrogen (ΔVe/ΔSaO₂). As BBF was reduced, PVo₂ decreased and PVco₂ increased. Ve increased when BBF was reduced to 50% but further reductions caused apnea. PaO₂ and PaCO₂ did not change significantly. ΔVe/ΔSaO₂ was enhanced by moderate (70%) BBF reduction, but was depressed by further reduction to 50%. ΔVe/ΔPco₂ was also enhanced by reduction to 70% if PaCO₂ were taken as the stimulus

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Termination of Inspiration Through Graded Inhibition of Inspiratory Activity

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Termination of inspiration by volume feedback represents a crucial determinant of the respiratory pattern. Previous reports have emphasized the all-or-none characteristics of inspiratory termination, pointing out that inhibition of peripheral inspiratory activity occurs only when a volume threshold is reached, whereupon an abrupt and, presumably, irreversible inhibition ensues. Yet, in spontaneous breathing a progressive inhibition precedes complete cessation of phrenic efferent discharge. To elucidate the role of this so-called "terminal inhibition" in inspiratory-expiratory (I-E) transition, we have altered the volume-time trajectory and noted changes in peripheral inspiratory activity.

Experiments were carried out on barbiturate-anesthetized, paralyzed cats ventilated by a servorespirator that maintained tracheal pressure proportional to an average phrenic efferent signal (100 msec bin width). Single breath tests were performed by changing respirator gain or by substituting a ramp signal. Inhibition of inspiratory activity was detected by comparing the average phrenic neurograms for the test breath with that for an inspiration in which lung volume remained at FRC.

By suddenly changing respirator output during the phase of "terminal inhibition" we found that the duration and magnitude of phrenic inhibition can be continuously modulated and that the inhibitory process can be reversed even when there has been a 50% reduction in phrenic activity. In other words, I-E transition is not an all-or-none switch. On a volume-time plot (Fig 1, inset), the locus of points for first detectable inhibition inscribes a curve (dashed line) displaced downward a constant vertical distance from the traditional $V_r/t_i$ plot (thick upper line). Lying between these two are similar curves plotted for constant fraction reductions in phrenic discharge (5%, 10%, 20%, 25% iso-inhibition lines). The resultant family of curves constitutes an inhibitory band, and the position of the volume-time trajectory in the band predicts the intensity of phrenic inhibition at any instant. Furthermore, the relation between lung volume (above FRC) and phrenic inhibition at any particular time can be derived as shown in Figure 1, lower curve. Increases in lung volume have no effect until the volume associated with the first detectable inhibition is reached. Therefore, inhibition increases alinearly with volume, ie, once a substantial inhibition is produced, further volume increments result in progressively greater increments in inhibition.

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