Dr. Severinghaus: You must know what the HCO₃⁻ is and normalize the data. There really isn’t any difference between the two methods. Proper normalization of the data make the differences go away. In fact, the Pco₂ and pH change faster with the steady state method than with the rebreathing method.

Dr. Edelman: Yes, but one difference that does not go away is that Read’s method is sensitive to changes in brain blood flow, whereas the steady state method is not. This creates the set-up for there to be a real difference in the response curves. While I can, I would like to ask Dr. Dempsey why, if he believes in the Tenney loop, he did not return his subjects to a hyperoxic state rather than a normoxic state.

Dr. Dempsey: Normoxia is the more physiologic state. Hyperoxia presents additional unquantifiable complications such as an effect on CO₂ transport and thus, possibly on brain ECF [H⁺]. Further, the important thing in these “post-hyperventilation” analyses is the abrupt relief of hypoxic conditions; and return to a normoxic state accomplishes this aim in the simplest manner.

Dr. Dempsey (in response to a question by Dr. Fitzgerald): We believed that in humans and dogs the major controller of CSF [HCO₃⁻] in respiratory alkalosis was plasma [HCO₃⁻]. Then we did longer (ie days) hyperventilation while holding plasma [HCO₃⁻] near normal and found that CSF [HCO₃⁻] decreased in a normal manner. We think, then, that “local” or “CSF-specific” factors—linked to or brain Pco₂—play a major role in CSF [HCO₃⁻] regulation, at least in chronic hypocapnia.

Dr. Kazemi: I think experiments of a few hours’ duration are too short to show the full effect on CSF [H⁺]. Also, where these H⁺ changes take place is important. Dr. Loeschke’s lab has shown that small changes in plasma [HCO₃⁻] cause small changes in [HCO₃⁻] at the brain surface but these changes in [HCO₃⁻] are not reflected immediately in bulk CSF.

Dr. Fitzgerald: Do [HCO₃⁻] changes affect CA++ and other important ions in the brain CSF? This question takes us back to Dr. Cameron’s point.

Dr. Hornbein: Things are getting more, not less complicated and I guess that’s as it should be. Perhaps we are placing too much emphasis on [H⁺] as the regulator of V. There are probably other ions and chemical stimulators which should be studied.

Central Nervous System and Chemoreceptor Factors in Control of Breathing*

Frederic L. Eldridge, M.D.

The respiratory control system at a conceptual level includes a set of receptors, some of which are chemoreceptors, which gather information about their environment and a complex array of neural connections which processes and sends the information to a set of effectors, the muscles, which produce ventilation. Although in the past most attention has been paid by respiratory physiologists to the chemoreceptor influences, it should be apparent that the neural elements of the system are crucial to its understanding. In this brief presentation, not even a superficial coverage can be made of all aspects of the system. Therefore, I have taken the liberty of selecting some topics which I believe are potentially important in the overall control of breathing, especially during conditions such as exercise or when a chemical stimulant is given.

Central Chemoreceptors

These are the well-known CO₂-H⁺ sensitive receptors located in the ventral medulla. It is apparent that they provide an important, presumably tonic, input to the respiratory control system. Although there are many studies of ventilatory responses to presumed changes in the stimuli affecting these receptors, we still don’t know their true input-output characteristics for, unlike the peripheral chemoreceptors, it has not been possible to measure directly their neural output. For reasons that will be expanded, satisfactory data about the quantitative characteristics of the chemoreceptors themselves are not likely to come from CO₂ studies that do not consider the local H⁺ ion environment and that use ventilation as the output measurement.

In this regard, it has been pointed out¹ that arterial Pco₂ is not necessarily a very satisfactory measure of the tissue Pco₂ or H⁺ ion concentration affecting the chemoreceptor milieu, which is clearly affected by cerebral blood flow and the cell’s own metabolism even when arterial Pco₂ is constant. Because many of the things we do to test respiratory control also affect cerebral blood flow, I believe that more attention will have to be paid to it in the interpretation of studies of respiratory control.

Peripheral Chemoreceptors

The input-output characteristics of the carotid body (CB) have been studied extensively²,³ and its responses to hypoxia and the CO₂-H⁺ stimulus are well known. Studies with hyperoxia or after ablation show that the CB has some input effect on respiration even during the breathing of air and is the main cause of the ventilatory response in acute metabolic acidosis.

My main point about peripheral chemoreceptor input is not really about the chemoreceptors themselves, but about their central neural responses. It is well accepted that because of the intermittent nature of breathing the
chemical stimuli reaching the CB oscillate around a mean; it has been shown that the neural output of the CB oscillates similarly as a result. In the past it had been assumed that if CB afferent impulses reached the brain they would have the expected excitatory effect, i.e., if they arrived during expiration they would be stored and remembered until the next breath where their effect would be manifested. Recent studies have shown this not to be the case. Stimuli given during inspiration cause only that inspiration to increase in magnitude and then only if given in the last half of inspiration; stimuli given during expiration affect only that expiration and have no effect on subsequent inspirations. These effects are probably due to neural gating of afferent signals by central neurones. Thus, there is a central neural mechanism by which the same signal from the carotid body has different effects on tidal volume and cycle durations, depending on its timing in relation to the respiratory cycle. Recent evidence indicates that this mechanism exists with the oscillations of CB output produced by actual ventilation. Thus, the existence of a constant mean level of a chemical stimulus and a constant mean CB output does not mean that the central effect and ultimate effect on peripheral output has remained constant.

Central Respiratory Controller

Although studied for many years, the mechanisms involved in rhythmicity and inspiratory-expiratory phase switching are not completely understood. Certainly feedback from the parabrachial nucleus (pneumotaxic center) and vagal stretch receptor signals are important mechanisms involved in switching; even carotid body input can affect it. Nevertheless, phase switching does occur even when many of the known feedbacks are absent. There is a general consensus that there is a central pattern generator which produces a motor program, itself under the influence of tonic input, temperature and perhaps feedback from the inspiratory neurones themselves. Under a given level of tonic input, this pattern generator sets a basic rhythm with a stereotyped output indicated by a fairly constant rate of rise of neural output activity, as represented by a phrenic nerve recording.

Recent work has suggested that vagal inflation receptors and other inhibitory influences on the central motor program, i.e., those associated with switching from inspiration to expiration, do not act directly on the inspiratory neurones. This conclusion is reached because a vagal input has no effect on the early part of inspiration—only the terminal portion of inspiration is affected. It is postulated by Bradley and colleagues and by von Euler and colleagues that a "threshold" must be reached in some intermediary pool of neurones, called the "off-switch" pool, before the inhibitory action resulting from the output of this pool can terminate inspiration. Various studies show that a number of other inputs, such as that from the parabrachial nucleus, from CO2 receptors, and perhaps the inspiratory activity itself can also act on this neuron pool, thus helping to terminate inspiration even in the absence of the vagal input.

Central Neural Feedback Mechanisms

Some part of the neural system has the property of maintaining an increased but slowly declining respiratory activity for some minutes after the cessation of a stimulus. Since the process occurs in decerebrate and decerebellate animals and is not affected by peripheral input, its locus must be in the medulla and pons. The most likely mechanism is that of maintenance of activity in neural circuits due to facilitatory feedback of neurons within the circuits. Once activated, the feedback process itself maintains the activity in the respiratory neurones; the slowly declining respiratory output during recovery from a stimulus reflects gradual decay of activity in the neuronal circuits. Such persistence of activity has been termed "reverberation," although the concept of "after discharge" shown to exist in the spinal cord by Sherrington could apply. Because the process is activated by a variety of stimuli, including those which are generally considered primary for respiration, and operates in animals and man, awake or anesthetized, it must be considered an integral part of the respiratory control mechanism. The process accounts for about 50% of the increase in respiratory output secondary to a primary stimulus. Thus, a significant part of the ventilatory response to any stimulus may be a function of this central neural mechanism and not just a function of the stimulus and its receptors.

Spinal Integration

It has been demonstrated that the level of membrane potential in spinal motoneurones has a significant effect on their discharge frequency to a given central respiratory drive. Thus, phrenic or intercostal muscle activities (and tidal volume) can be affected by changes in membrane potential of the spinal motoneurones independently of central drive; even inspiratory (Tl) and expiratory (T2) durations can be affected. For example, it has been shown that CO2 directly depresses these neurones and our laboratory has shown (unpublished data) that stimulation of the calf muscles by squeezing can inhibit spinal motoneurones directly.

Thus, the spinal motoneurones are another location in the information transmission pathway which affect final respiratory output. Any interpretation of the response to a stimulus (eg, CO2) must therefore include the possibility of changes in their function.

Conclusion

I have tried, in this discussion, to point out some of the problems in interpreting a change in ventilation in terms of specific mechanisms when there are so many transformations of information at the various links in the neuronal chain from chemoreceptor to peripheral nerve. I therefore have not even touched on the additional problems involved in the transformation from neural signals.
to muscular work of breathing, and from that to ventilation.

Since he said it better than I could, my conclusion is a quotation from Dr. Eugene Robin's summary of a previous annual Aspen Conference, the 14th held in 1971:

"Fundamentally the control of ventilation is neuronal in nature. Therefore, ventilatory control must ultimately be described in acceptable neurophysiologic terms.

Because of the diverse connections, the problem of determining mechanisms of abnormal ventilatory control is quite complex. Given an abnormality in ventilatory response, the abnormality may reside in any segment of the total neuronal connections subserving a given function. For example, a blunted hypoxic drive could arise from direct abnormality of the carotid body itself; from changes in arrival time in afferent stimuli; from abnormalities of the afferent nerves; from increased inhibitory stimuli or decreased activating stimuli from a variety of central neurons; or from inadequacy of the peripheral ventilatory mechanism.

Classic approaches to the study of ventilatory control, say during exercise, which measure variables based on effector function such as ventilatory volume or gas exchange parameters, must be cautiously interpreted. At the very least, these studies will require reinterpretation in neurophysiologic terms."

Difficult as it may be to accept that a long-standing classic method is not adequate for its purpose, I believe that it is time to recognize that measurements of ventilatory responses alone are not likely to lead to any great understanding of the chemoreceptor or neural mechanisms involved in the control of respiration.

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Chemoreceptor Interaction during Medullary Perfusion

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Previously we have reported that hypocapnic vertebroarterial perfusates result in only a 33% reduction in ventilation within the first 2 minutes, if end-tidal carbon dioxide tension is maintained at hypocapnic levels.1 This slow response was attributed to a large CO2 compartment and a diminished cerebral blood flow,2 leading to a sustained high carbon dioxide tension in the chemoreceptive tissue. Mitchell et al3 have suggested that the central chemoreceptors are functionally located closer to cerebrospinal fluid than to cerebral capillaries. It is conceivable that a large cerebrospinal fluid compartment would serve to buffer rapid changes in chemoreceptor tissue PCO2, hence a prolonged time period may be required for chemoreceptor tissue PCO2 equilibration at a new low level of arterial carbon dioxide tension. Since blood flow is directly dependent upon the PCO2 of the arterial blood, the diminished local blood flow caused by the low arterial PCO2 may offset the increased ability of hypocapnic arterial blood to remove CO2 from the central chemoreceptor compartment. A second hypothesis is that peripheral chemoreceptor input becomes an important contributor to ventilatory drive in the absence of the central drive. Peripheral chemoreceptors can function independently to elevate ventilation in response to increases in PaCO2, especially if the change in PaCO2 is presented as a step function.3 A third possible mechanism is that ventilation may be sustained by a solely neural drive which persists despite cessation of chemical stimulation.3,4

The present studies attempt to resolve the extent to which each of the above three components (i.e., neural, blood flow-dependent, and peripheral chemoreceptor-dependent) may be involved in the slow decay in ventilation observed during hypocapnic medullary perfusion.

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