Volume 61, No. 2
August 1984

THE JOURNAL OF Anesthesiology
THE AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC.

EDITORIAL VIEWS

Anesthesiology
61:119–120, 1984

To Breathe or Not to Breathe

ONE OF THE MORE PREDICTABLE side effects of most of the anesthetics and anesthetic adjuvants we use currently is depressed breathing. The clinically relevant measure of this depression is elevation of the P_{CO_2} in alveolar gas or arterial blood, but in addition the response of ventilation to added carbon dioxide, $\Delta\dot{V}/\Delta P_{CO_2}$ is impaired. The extent of depression of $\Delta\dot{V}/\Delta P_{CO_2}$ is proportional to drug concentration; at least for inhalation anesthetics, comparison of ventilatory depression among them is possible utilizing multiples of MAC as a scaler.

Ventilatory depression does not necessarily equate with depression of ventilatory drive when drive is defined as the rate of respiratory motoneuron output during inspiration.[1] Rate of change of lung volume during inspiration (V_T/T_I) conveniently is used as a measure of ventilatory drive, yielding the following modification of the relationship between minute ventilation ($\dot{V}_E$), tidal volume (V_T), and frequency (f):

$$\dot{V}_E = V_T \times f = V_T/T_I \times T_I \times 1/T_{TOT},$$

where T_I is time for inspiration and T_{TOT}, the duration of the respiratory cycle. Anesthetic and sedative drugs may depress minute ventilation, yielding an elevation of P_{CO_2} through one of three mechanisms: 1) a decrease in drive, V_T/T_I; 2) a shortened time for inspiration, T_I; or 3) a slowing of respiratory frequency ($1/T_{TOT}$). Thus, two of the three mechanisms represent effects on timing rather than on drive. The use of tidal volume to assess drive presumes a direct relationship between respiratory motoneuron output and the movement of air with each breath. Interposed between neural output and air movement are the neuromuscular junction, the respiratory muscles themselves, and the mechanical properties of the chest wall, diaphragm, and lung. An anesthetic effect at any of these points may affect the volume of air being moved for a given neural output.[2] Only a limited amount of information currently is available concerning the way in which different anesthetic and sedative drugs influence the drive and timing relationships of breathing in humans, but the need to take into account these different ways by which resting P_{CO_2} may be elevated or $\Delta\dot{V}/\Delta P_{CO_2}$ depressed should be kept in mind.

Ventilatory response to stresses other than CO_2 also is diminished by anesthesia. For example, while the conscious individual exerts increased effort in response to an externally imposed airway resistance, under anesthesia this response to loading is lost.[3] And like the response to CO_2, the ventilatory response to hypoxia in both humans and other animals also is obtunded by anesthetics and many sedative drugs.[4] Indeed, Knill *et al.*[5] have shown that the response to hypoxia is more susceptible to depression by anesthetics than is the response to CO_2: at 0.1 MAC of halothane, hypoxic ventilatory response was diminished to 25% of control while $\Delta\dot{V}_E/\Delta P_{CO_2}$ was essentially unchanged. At 1.1 MAC, halothane completely eliminated any increase in ventilation to $P_{A_{O_2}}$ levels down to 40 mmHg, while CO_2 response was depressed only moderately. For those of us brought up on the belief that the hypoxic ventilatory response, mediated by way of the peripheral chemoreceptors, represents a last ditch defense mechanism that is relatively stalwart in its durability, the recognition of its susceptibility to anesthetic depression comes as a surprise.

In animals the ventilatory response to CO_2 is diminished only slightly by denervation of the carotid and aortic chemoreceptors, while the acute ventilatory response to hypoxia is eliminated. Therefore, the differences in anesthetic effect on hypoxic *versus* carbon dioxide ventilatory response in humans may reflect differing vulnerability to such drug depression of the two chemoreflex pathways—that for hypoxia emanating from the peripheral chemoreceptors and that for CO_2 being transmitted primarily from central chemosensitive areas located on the ventrolateral surface of the brainstem. Input from these re-

Accepted for publication January 25, 1984.

ceptors converges at or near the respiratory control centers located within the medulla. Thus a greater susceptibility to anesthetic depression of the hypoxic ventilatory response than the CO_2 response would involve a selective effect on the peripheral chemoreflex pathway somewhere prior to this convergence. In this issue, Knill and Clement present evidence obtained from carefully performed studies in volunteers to support the hypothesis that the primary target for this depression of hypoxic ventilatory response by subanesthetic concentrations of halothane is the peripheral chemoreceptor itself.[6] The authors have taken advantage of the shorter lung–carotid body than lung–brainstem transit time (about 5 *vs.* 14 s) and the 40 to 50 times greater blood flow per unit of mass of the carotid body (an organ representing only about 1/10,000,000 of our body weight) than the brain to separate anesthetic effects on peripheral *versus* central chemoreceptors. Observations during sudden exposure to subanesthetic concentrations of halothane reveal a rapid onset of depression of the hypoxic ventilatory response. The authors calculate that brain halothane concentrations will be too low in these first 30 to 60 s to contribute to this depression and therefore conclude that the decrease in ventilatory response to hypoxia is best explained by action primarily on peripheral chemoreceptors. This conclusion is consonant with observations obtained by direct recording of the effect of halothane on neural discharge from the carotid chemoreceptors in the cat, published in this journal two years ago.[7]

I find several aspects of this observation interesting. First, from the vantage of one with an affection for carotid bodies, I like the tidiness, care, and quality of this investigation performed on human subjects. Questions amenable to a relatively simple assessment and clear interpretation are not all that easy to pose and impose on people these days. The conclusion derived, that the depression of hypoxic ventilatory response by anesthetics occurs at the peripheral chemoreceptor itself, is not surprising and represents only a small step for mankind. But then mountains—as those with good hypoxic ventilatory responses know well—are climbed one step at a time.

The significance of this work to our anesthetic practice is simply that it heightens awareness concerning one possible cost of our pharmacologic trespass. Many of us have come to believe that ventilatory depression by anesthetic drugs is a manageable and therefore minor side effect. We base this view on the conviction that we can control ventilation and oxygenation during surgery if need be so that depression of breathing doesn't really matter. Our second premise is that the patient, once delivered to the postanesthetic domain, has so little residual drug effect left that they can ventilate adequately. Here perhaps we should be less certain. How sluggish may the recovery to normal P_{CO_2} be after anesthesia? We have a few hints, such as the study by Becker *et al.*[8] of CO_2 responsiveness following fentanyl anesthesia, which suggests a phasic recovery–depression–recovery phenomenon in the postanesthetic period. Hypoxic ventilatory responsiveness may be even slower to regain its original vigor. But does such depression matter? We can help prevent hypoxemia after anesthesia by adding oxygen to the air we breathe, thereby obviating the need to be concerned about the depressed hypoxic ventilatory response. What, though, about the patient's ability to defend against hypoxia secondary to mounting hypercapnia? Or airway obstruction? How much additional risk do we impose? Interestingly, curiously, these are questions for which we yet have no answers. So far as breathing is concerned, the immediate postanesthetic period would seem to be a time of high risk, for here, during emergence, patients often are perceived and monitored more as if they were in the world of the waking than that of anesthetic sleep.

So many of our choices and decisions concerning the drugs we use derive from our guesses concerning benefits *versus* risks related to side effects such as ventilatory (or circulatory, or neuromuscular) depression. Often our actions are based upon physiologic logic rather than on demonstrated functional significance of these events in the patients for whom we care.

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