Do Low-dose Inhalational Anesthetic Agents Alter Ventilatory Control?

Fifteen years ago, Knill and colleagues first reported that halothane at 0.05 and 0.1 MAC substantially depressed hypoxic drive.1,2 They subsequently reported that both enflurane and isoflurane also depressed hypoxic ventilatory drive at 0.1 MAC but that other inhalational agents did not.3,4 Only enflurane was observed to mildly depress hypercarbic ventilatory drive at 0.1 MAC,5 whereas isoflurane, though not depressing the response to a gradual increase in carbon dioxide, was observed to depress the normal peripheral chemoreceptor-mediated increase in ventilation to a single breath of 20% CO2.5 Considered in total, the studies suggest that subanesthetic (sedative) doses of halothane, enflurane, and isoflurane depress peripheral chemoreceptor responses to hypoxia and hypercapnia based on the rapidity of the effect6 and consistent with the direct measurements of chemoreceptor neural output by Davies et al.7 Because the response to hypercarbia is controlled predominantly in the central nervous system,8 the depressive effect of low-dose inhalational anesthetics on the minor contribution of the peripheral chemoreceptors to the total ventilatory response to hypercarbia would not appear to be of clinical concern. However, because the peripheral chemoreceptors produce increased ventilatory drive with hypoxia, if 0.1 MAC of the commonly used inhalational agents can markedly reduce this ventilatory response, it could contribute to the well recognized incidence of hypoxia in the postanesthetic state. Recently, Temp et al.9 challenged the findings of Knill and colleagues with respect to the effect of 0.1 MAC isoflurane on hypoxic drive, finding no effect. In this issue of Anesthesia, two reports add to our understanding of these apparently conflicting reports. Temp et al.,10 after modifying their protocol of exposure to hypoxia to more closely approximate the studies by Knill and colleagues, again report no effect of 0.1 MAC isoflurane on hypoxic drive. In contrast, Dahan et al.,11 using methodology similar to but not precisely the same as that of Temp et al., report that subanesthetic doses of halothane depress both hypoxic and hypercarbic peripheral chemoreceptor-mediated ventilatory drive, which is consistent with Knill and colleagues' prior studies.

The issue of interpreting apparently conflicting data in the literature with regard to the effects of a low dose of an inhalational anesthetic agent upon respiratory control can be considered at two levels: a general approach to the generic issue and evaluation of the specific issue. I was asked to undertake this task, not because I have any demonstrable expertise with regard to the specific issue of respiratory control (which I do not!), but because I have spent a considerable portion of my research career trying to resolve similar apparent conflicts in systems physiology, e.g., why do "opposing camps" of investigators find either increases or decreases in left ventricular volumes when stroke volume decreases during inspiration?12 Observations and conclusions that appear at first to be diametrically opposed can be explained rather than assuming one observer is correct and the other is not. Serious technical errors in methodology, obviously, must be excluded; however, when reports from different laboratories with excellent records of careful investigation appear to conflict, the answer frequently is that each is "correct" within the parameters of their respective investigative protocols and that a broader understanding is derived by defining the key variables that produce the apparently contrasting results.

Scientific investigators need to control as many variables as possible to isolate critical variables as potentially mechanistically involved in a given response. This is not necessarily what the clinician wants measured. For the scientific investigator, it is the defining of precise stimulus-response relationships with controlled independent variables (e.g., variation in arterial hemoglobin oxygen saturation in the presence or absence of 0.1 MAC of an inhalational agent) that is used to study the outcome variable (e.g., minute ventilation). For the clinician, it is whether the patient will increase ventilation in response to potentially harmful mix of hypoxia and hypercarbia, averting harm or, at least, giving an indication that a problem may exist.

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EDITORIAL VIEWS

Three general areas of input need to be considered in evaluating the etiology of ventilatory drive: 1) metabolic-chemical factors, typically including $P_{O_2}$, $P_{CO_2}$, and $pH$, are well appreciated determinants; 2) behavioral factors, which include a range of diverse and often difficult to quantify changes in states of central nervous system arousal, sleep, sedation, anxiety, or mental activity, such as reading or speech, can alter drive; and 3) postural factors, in which ventilatory drive is altered, for example, to facilitate a prolonged Valsalva maneuver during lifting, straining, or changes in body position. It may be crucial to appreciate that, when active, behavioral and postural factors can override the metabolic-chemical control system, although the latter normally sets limits. Most studies of ventilatory drive attempt to control both behavioral stimulants and postural factors by keeping them to a minimum to focus on the metabolic-chemical factors.

Assuming that behavioral and postural factors are controlled and equivalent in two studies, what general principles may be important in defining observed differences in the ventilatory response to respiratory gas tensions? First, there is a substantial interaction in the acute ventilatory response to both hypoxia and hypercarbia, such that an increase in $P_{CO_2}$ of even a few millimeters of mercury can substantially increase the minute ventilation to the same hypoxic challenge. Therefore, even if the hypoxic challenges were equal, very small differences in $P_{CO_2}$ between studies could account for substantial differences. Thus, semantic precision in defining ventilatory response to hypoxia or hypercarbia depends on methodologic precision. The control states in Temp et al.'s and Dahan et al.'s papers with regard to minute ventilation and end-tidal carbon dioxide (both adding carbon dioxide to the inspired gas) demonstrate higher averaged minute ventilation for similar or smaller end-tidal carbon dioxide values reported in Knill and colleagues' studies. Could differences in measurement techniques of end-tidal carbon dioxide account for these observations? If a lower end-tidal carbon dioxide in Temp et al.'s subjects accounts for the different response to hypoxia, it would not account for the elevated baseline minute ventilation. Another factor or factors must be present in their studies.

Second, the mechanisms producing the normal ventilatory response to hypoxia reflect a time-dependent, initial peripheral chemoreceptor-driven increase in ventilation, followed by a slower onset of central depression over a brief period. The central nervous system-derived depression, usually ascribed as occurring within 5–10 min, has been reported to begin within 30 s.\textsuperscript{13} Thus, in response to inducing isocapnic hypoxia, one would find an initial increase in ventilation, which then decreases over time as central hypoxic depression begins to have an effect. Both Temp et al. and Dahan et al. address these temporal issues and conclude that this issue cannot explain the "apparently conflicting" results.

Other differences in methodologies involve the rate at which the hypoxia is induced and the method of controlling the end-tidal carbon dioxide. Temp et al. address the former, repeating their observation of no effect of 0.1 MAC with a change in oxygenation closer to Knill and colleagues' methodology. Most importantly, Dahan et al., using a methodology similar to that of Temp et al., with regard to rate of hypoxic challenge and breath-to-breath forced control of end-tidal carbon dioxide, find that 0.05 and 0.1 MAC halothane result in the same findings as those of Knill and colleagues, depressing the hypoxic ventilatory response and the peripheral chemoreceptor component of the hypercapnic ventilatory response.

To randomize awake and treatment presentations, Temp et al. needed to study subjects on different days, whereas both Dahan et al. and Knill and colleagues, by ordering presentations so that the control condition was always first, could complete all aspects of the study in a single session. This is important because it is well accepted that measurements of ventilatory drive in the same subject can vary markedly from one day to another, making differences among treatment states difficult to demonstrate. This accepted finding is compatible with a hypothesis that the central nervous system arousal/behavioral state of subjects on different days may be a major determinant of ventilatory drive. Thus, Temp et al.'s technique addresses the problem of true randomization in their study design, but they are confronted with an expected higher variability in their measurements, making it more difficult to find statistical differences, particularly with a small number of subjects. Based on the above information, and barring measurement or technical error, it seems highly likely that 0.1 MAC of the commonly used inhalation agents can depress hypoxic drive, but some factor in Temp et al.'s methodology ablates this depression.

Sleep is an example of a behavioral state in which studies have demonstrated a variable\textsuperscript{14} or diminished ventilatory response to hypoxic challenge compared with awake human subjects.\textsuperscript{15} More than two decades ago, Forrest and Bellville suggested that sleep could
significantly enhance opioid-induced respiratory depression by affecting both baseline ventilation and the response to carbon dioxide. Temp et al. point out the potential importance of defining behavioral state with respect to sedation/sleep. Patients have long appreciated the similarity of general anesthesia to sleep, a comforting concept we use in preoperative consultations. Anesthesiologists implicitly appreciate that state of consciousness (open your eyes, time to wake up!) is important to control the upper airway and maintain an adequate respiratory drive in patients emerging from either inhalational or narcotic-based general anesthesia. Any parent can describe the state of “general anesthesia” their child exhibits when deeply asleep. They are completely limp, may exhibit partial upper airway obstruction, and are unresponsive to verbal or tactile stimulation, clearly “deeper” than 0.1 MAC reported by all the investigators. Patients with severe obstructive sleep apnea are hypopnoeal and can cycle between electroencephalogram- and electromyogram-documented sleep and arousal states within seconds. Dahan et al. accepted data in subjects who could be aroused easily at both 0.05 and 0.1 MAC halothane before and after the study period, but it is unclear whether the musical auditory stimulation prevented or facilitated a change in the subjects’ behavioral state during the study itself. These conditions were similar to Knill and colleagues’ protocol conducted in a quiet, dark room with or without music. Temp et al. maintained an “eyes open” awareness in their subjects throughout the hypoxic challenge with sensory stimulation, thus purposefully excluding a “drowsy,” depressed behavioral state. (Indeed, it would be hard to find a more cortically stimulating documentary than Ken Burns’s PBS series on the Civil War.) Thus, inquiry into similarities, differences, and interactions among anesthetics, hypoxic drive, and behavioral states might offer a logical avenue for exploration.

At the center of the “apparent conflicts,” it becomes clear that quantitative determination of respiratory control is difficult to perform methodologically, with numerous small but important factors, any one of which, if not controlled in the same manner in another study, can result in markedly differing results. Both Temp et al. and Dahan et al. thoughtfully discuss many of the factors relevant to this issue. However, are these very small differences, which may account for the differing results, clinically relevant? Severinghaus, reporting the results of a workshop in 1976, proposed a standard method for measuring ventilatory response to hypoxia and hypercapnia, noting, “This proposal is in no sense representative of consensus.” Fifteen years later, unanimous consensus clearly is not present among investigators who measure the effects of anesthesia on ventilatory drive. The elements recognized by the workshop as potentially affecting the measurement of ventilatory drive included instructions to the subjects as to how to breathe and minimization of extraneous stimuli, such as a full bladder, discomfort, whispering and conversation, anxiety, unexpected or threatening sounds, arterial puncture, and muscular movement.

Though this list offers potential explanations of differences among the various protocols used, one cannot help but be struck by the presence of each of the prescribed variables requiring control, as describing the normal conditions for a patient in a busy recovery room. This implies that ventilatory response to hypoxic or hypercarbic stresses in the clinical arena may be a tremendously dynamic response, for which rather subtle alterations in the patient’s environment and behavioral state may produce markedly different responses to the same hypoxic or hypercarbic challenge. The clinician is most concerned when the response is either physiologically harmful (producing cellular injury) or uncomfortable (producing dyspnea).

My interpretation of the literature to this point is that all the reported observations are correct and that a patient may be at risk with a depressed ventilatory response to hypoxia with even 0.1 MAC halothane, enflurane, or isoflurane. A patient in whom an anesthetic concentration of 0.1 MAC is present, but who is otherwise healthy, responsive, and aroused by sensory stimulation, pain, or anxiety, is much less likely to exhibit depression of respiratory drive to hypoxia. However, if a behavioral state then ensues that results in the withdrawal of a central nervous system component contributing to ventilatory drive, the presence of as little as 0.1 MAC may result in substantial depression of ventilatory response to hypoxia. An interaction between behavioral state and an anesthetic agent on hypoxic ventilatory drive appears to be a logical and possible explanation for the observed differences in the literature. Such interactions offer a reason for the ventilatory depression observed in those subjects “soothed” with quiet, darkness, and music, as opposed to those who were not depressed when stimulated visually or auditorily, by calling their name, or roused by touching. Thus, consistent with clinical experience, the patient who is “resting comfortably” in the recovery room may be at greater risk for complications of

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diminished ventilatory drive than the aroused, uncomfortable patient in pain awaiting administration of an opioid. How inhalational anesthetics, opioids, and behavioral states interact to alter ventilatory drive would appear to be both clinically relevant and deserving of study.

I would invite investigators with interest and expertise in this subject to refine my musing, clarify my misunderstandings, and test the resultant hypotheses.

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References