goscopes by other anesthesiologists failed to provide an adequate view of the larynx to permit intubation.

In summary, this new device has been well accepted and used successfully to facilitate tracheal intubations and, thus far, has not been associated with any complications. It appears sufficiently promising to justify further evaluations by other investigators.

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Interpreting Low-dose Anesthetic Effects on the Ventilatory Response to Hypoxemia: Facts, Findings, and Fanciful Formulations

To the Editor—In a recent editorial, Robotham considers how low-dose halogenated anesthetics may affect the ventilatory response to hypoxemia. ¹ In an admirable effort to reconcile "apparently conflicting reports" in the literature, he offers his own interpretations of research in this field. First, he concludes that, even though small doses of these agents may put a patient at risk for a depressed hypoxic response, a patient "who is otherwise healthy, responsive, and aroused by sensory stimulation, pain, or anxiety [as in anesthetic recovery] is much less likely to exhibit depression of respiratory drive to hypoxia." Second, he infers that, "[i]f emphasis added a behavioral state . . . ensues that results in the withdrawal of a central nervous system component [of] ventilatory drive, the presence of . . . 0.1 MAC doses may result in a reduced response. In my view, each of Robotham’s conclusions is open to serious question—as each rests upon a critical assumption that appears to be untenable.

The assumption underlying the first conclusion is that one can draw reliable inferences about a reflex of the "metabolic" ventilatory control system, such as the response to hypoxemia, in the presence of sensory stimulation that is known to incite the second ventilatory control system referred to as "behavioral" control.² In making this assumption, Robotham appears to have overlooked the distinctive anatomic and physiologic characteristics of each of these ventilatory control systems¹ and the considerable difficulty in identifying functional characteristics of one system when the other is simultaneously stimulated or uncontrolled.³

The metabolic control system arises from chemoreceptors that drive the brainstem controller to generate stable and automatic ventilation that defends metabolic homeostasis. The behavioral system, on the other hand, arises from multiple poorly defined neural inputs that activate a separate forebrain controller to superimpose highly irregular ventilation in conditions such as speech, sensory stimulation, anxiety, and REM sleep.⁴ The assumption that one can obtain reliable information about metabolic control when the unstable behavioral system acts simultaneously and independently has been refuted by authorities⁵ and seems intuitively unlikely. For example, would it be possible to infer the effects of opioid on automatic, metabolically controlled ventilation by administering opioid to the point of marked respiratory depression and then activating behavioral control by periodically speaking to the subject and reminding them to breathe? More pertinent to the issue at hand, would it be possible to infer the effects of low-dose anesthetic on the metabolic response to hypoxemia when the behavioral system is activated simultaneously by the combination of repeated nudges, an exciting movie, and speech—as in the research to which Robotham refers?⁶ Although behavioral control undoubtedly can be recruited in the clinical setting to stimulate ventilation and thereby protect a sedated patient from hypoxemia or a reduced response to hypoxemia, this does not imply that it modifies the ventilatory response to hypoxemia per se. Exactly how does Robotham reconcile his assumption with these well-founded concepts of ventilatory control?

The assumption underlying Robotham’s second conclusion is that the previously reported effect of low-dose halogenated anesthetic on the hypoxic response⁵⁶ is conditional upon the development of a new central nervous system (CNS) state, described variously as "sleep," "drowsiness," "reduced arousal," and "withdrawal of a CNS component of ventilatory drive."¹ ³ However, in making this assumption, Robotham appears to have overlooked the results of numerous investigations.

Several years ago, we observed that 0.1 MAC-equivalent states induced with methoxyflurane and with thiopental did not detectably

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affect the ventilatory response to hypoxemia, implying that the depressive effect of halothane, isoflurane, and enflurane on this response related to these particular agents rather than to a change in CNS state that would have been common to all. We also found that the effect of low-dose halothane could be reproduced within 30 s of its administration—before it produced a subjective sense of sedation in subjects and before it could have reached the brain to produce any CNS change. In addition, we observed that low doses of halothane and isoflurane did not produce the ventilatory effects of a state of sleep, i.e., a reduction of ventilation, an increase in PETCO2, and a reduced ventilatory response to added carbon dioxide. Further, research by Newton et al. and ourselves indicated that subanesthetic isoflurane (0.1 MAC) does not usually induce either the behavioral or the electrophysiologic changes of natural sleep. Finally, Isono has observed that subanesthetic halothane (0.2-0.4% inspired) in dogs reduces the hypoxic response more than does non-REM sleep alone and that there is no detectable difference in this effect whether animals are awake or in a state of spontaneous non-REM sleep, a state of substantial CNS depression. Thus, all available, pertinent evidence seems inconsistent with the assumption that the effect of low-dose halogenated agent is conditional upon a state of CNS depression—whether that state be natural sleep, sedation, or a modest "withdrawal of CNS ... ventilatory drive." What is the specific evidence in favor of Robotham's assumption? How does he reconcile it with all these inconsistent data?

If these questionable assumptions are put aside and the findings of all relevant research considered, interpretations of this research become relatively straightforward. When studied in conventional conditions of metabolic control, low doses of halogenated agents reduce the hypoxic response substantially, as has been observed and confirmed both qualitatively and quantitatively by at least three independent laboratories. The effect appears not to be due to a change in CNS state or to an action on CNS structures but rather to a preferential and potent action at the site of the peripheral chemoreceptors, as has been demonstrated for subanesthetic and/or anesthetic doses of halothane by two independent laboratories and inferred for low-dose isoflurane by a third. When attempts are made to investigate this effect in conditions of superimposed behavioral control, apparent changes appear highly variable amongst individual subjects and, when averaged, inconsistent with what is observed in conditions of metabolic control. These "apparently conflicting" findings turn out to be neither surprising nor obviously meaningful with respect to anesthetic effects on the hypoxic response when one considers the following points: (1) the ventilatory response to hypoxemia is a reflex of the metabolic and not the behavioral control system, (2) low-dose halogenated anesthetics reduce this ventilatory response primarily, if not solely, by an action on the peripheral chemoreceptors, which are components of the metabolic and not the behavioral control system; (3) behavioral control superimposes variable ventilation that, within broad limits, is independent of metabolic control; and (4) certain neurologic diseases affect the behavioral and metabolic aspects of breathing differently or even selectively, and drugs undoubtedly can do the same (e.g., example of opioid effect given above).

References


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In Reply.—My respect for the quality of Knill's intellectual insights, body of work, and tenacity in defending his views was exceeded only by my trepidation in undertaking the task of writing the editorial in question. So that the readership will understand that the vigor of our discussion reflects true academic debate, it is worth noting that Knill and I were fellows together in Toronto, sharing the same office space and debating issues of clinical physiology in the same fashion then as now. Approximately 5 years ago, Knill and I discussed (over beverages at the airport before a ASA meeting) the lack of any subsequent studies attempting to replicate his pioneering work. It is ironic that the first such studies, by not reproducing his results, have led to a revival of interest in the subject. With the above in mind, the last sentence of my editorial was a direct formal invitation to Knill to fire away. As is usual when he debates this subject, Knill's response has stimulated and provided me with the opportunity to better define what I intended to communicate and to revise a few words that, despite my efforts to the contrary and as he pointed out, lacked the necessary precision.

Knill's response reinforces my perception that a major problem relates to the semantics of scientific terminology and the endpoints therein defined. As stated in the third paragraph of the editorial, what a scientific investigator seeks in an experiment and what crucial information a clinician wants from experimental results may not be the same. Although more knowledge of the individual components contributing to an integrated physiologic response should be the goal for clinical decision-making, the bottom line always remains what is the net result. For the anesthesiologist with respect to the subject at hand, the information desired is, "Does the patient increase or decrease minute ventilation under the given set of conditions?" The terminology now becomes confusing because, despite "increased hypoxic drive" emanating from the peripheral chemoreceptors, it is an experimental and unfortunate clinical reality that, as hypoxia becomes increasingly severe, mammals ultimately stop breathing because of hypoxic central nervous system (CNS) depression. Knill reemphasizes, and I agree, that both metabolic-chemical factors and higher CNS behavioral states will affect ventilation. As Knill and I agree, precision can be derived by defining ventilatory control as having these component "drives." Each of these components, to be measured independently, requires rigid control of the variables that may influence other drive pathways. Defining hypoxic drive demands that behavioral and postural factors be controlled independently, because hypoxia is a chemical stimulus and thus alters ventilation through chemoreceptors, located predominantly in the carotid body. With neural pathways and the respiratory musculature functional, a change in "hypoxic drive" is defined by measurements of minute ventilation. Changes in minute ventilation then would be expected to reflect changes in chemoreceptor output.

This is where the fun begins. Is hypoxic drive absent if a subject is pharmacologically paralyzed such that, despite increased chemoreceptor output in response to progressive hypoxia, minute ventilation remains unchanged? Knill argues that the obvious problems with such a construct form the basis for the strictly controlled scientific investigation of mechanisms of respiratory control and that these problems should equally apply to the study of background behavioral factors. However, the clinician in me wants to know what is the resultant effect on integrated ventilatory output in each situation (the presence or absence of neuromuscular blockade or changes in levels of CNS stimulation) because my acute management decision will be based on changes in ventilation, not solely on changes in chemoreceptor output. Thus, to be more precise, perhaps a different terminology should be applied to studies of ventilatory control that seek to define the net result of changes in multiple interacting input stimuli, e.g., hypoxia and auditory stimulation, from studies that seek to define the contributions of the individual component parts.

The simplest solution might be calling the net sum of chemical and behavioral input, the ventilatory output, and the component parts, drive pathways. Given such an understanding, I would agree with Knill that, by scientific convention, hypoxic drive should be defined with a standard "basal" behavioral state and that he could agree that altering that behavioral state could affect the ventilatory output. Thus, chemical and behavioral drives can interact in either positive or negative reinforcing fashion, with the net sum of the component drives reflected in the integrated effect on ventilatory output. I attempted to hie closely to this line of reasoning in the editorial by using the terms "ventilatory response" or "exhibit depression of respiratory drive" to reflect the integrative endpoint of minute ventilation as determined by multiple interacting input factors.

Much of Knill's critique is based on his reconstruction of my logic to ascribe assumptions that he reasons I must have made. In fact, neither assumption was made. The first assumption postulated is that I drew reliable inferences about the metabolic ventilatory control system's response to hypoxia in the presence of sensory stimulation that is known to independently affect ventilatory control. I agree with Knill that the metabolic and behavioral systems as described by Plum are "almost completely separate anatomically," but as Plum also notes, they "are normally closely integrated physiologically" and "some cerebral effects appear to influence mainly metabolic functions of respiration." Indeed, Knill subsequently concedes that "behavioral control undoubtedly can ... stimulate ventilation and thereby protect a sedated patient from hypoxemia or a reduced response to hypoxemia...." However, I may disagree with his subsequent phrase of that sentence that "this does not imply that it modifies the ventilatory response to hypoxemia per se." If he has