Influence of low-dose anaesthetic agents on ventilatory control: where do we stand?

In this issue, Pandit and colleagues report the effects of subanaesthetic concentrations of sevoflurane on ventilatory responses to inspired carbon dioxide and sustained isocapnic hypoxia in healthy young volunteers. They concluded that sevoflurane at 0.1 minimum alveolar concentration (MAC) had little or no effect on both responses. Their data suggest that different anaesthetic agents have quantitatively and qualitatively different effects on ventilatory control. This could explain to some extent the finding that some agents, such as halothane, cause large reductions in ventilatory responses to hypoxia and hypercapnia, while others do not. The findings of Pandit and colleagues are in sharp contrast with the long-held belief stated in 1982 by Knill and Gelb that all halogenated anaesthetic agents at subanaesthetic concentrations abolish peripheral chemoreflex responses to (moderate) hypoxaemia (and hypercapnia).

Before we conclude that the influence of sevoflurane on ventilatory control is different from that of other inhalation anaesthetics, such as halothane and isoflurane, we need to take a closer look at the study of Pandit and colleagues. Their responses were obtained via a mouthpiece/noseclip arrangement, and their procedure allowed for watching television and reading a book, while verbal commands were used to check on the subjects, when necessary. These may seem of minor importance to most readers, but it is vital to realize the important influences that central nervous system (CNS) arousal state and behavioural stimuli have on the control of breathing. Chemical or metabolic control of breathing (i.e. control dependent on the chemical composition of arterial blood, as occurs during non-rapid eye movement (REM) sleep) and behavioural control of breathing (control that allows for adjustment of breathing to specific situations, such as speech, singing, reading, eating, surprise, pain, etc) interact in a complex manner, varying from inhibitory to excitatory interactions, depending on the nature of the non-chemical drives involved. An example of behavioural control of breathing is the fact that reading increases minute ventilation and the ventilatory response to hypoxia compared with the control state of relaxed wakefulness with closed eyes. Extrapolating these findings to the studies of Pandit and co-workers suggests that an additional non-chemical ventilatory drive, caused by reading, watching television, verbal command and possibly the mouthpiece, may have been introduced. Recently, we studied the ventilatory response to hypoxia during 0.1 MAC of isoflurane with open eyes (subjects were watching music videos) compared with closed eyes and the absence of external stimuli. A depressant effect of isoflurane was found only when the eyes were closed and external stimuli were absent. The additional drives caused by open eyes and auditory and visual stimulation interacted with the peripheral chemoreflex loop such that at 0.1 MAC of isoflurane, the hypoxic responses were increased to control levels (without isoflurane). A similar mechanism may have been active during the experiments of Pandit and co-workers, preventing depression of hypoxic and hypercapnic responses to become apparent. Without these additional drives, 0.1 MAC of sevoflurane causes 30–40% depression of the hypoxic ventilatory response. This is similar to that found for isoflurane.

The next important question is whether depression from low-dose anaesthetic agents is related to an effect at a specific site within the body or whether it is related to the state of sedation and light non-REM sleep they induce. When the state of sedation from low-dose sevoflurane inhalation is reversed to wakefulness (as judged by the bispectral index of the EEG) by applying acute pain, the ventilatory response to isocapnic hypoxia remains blunted. This indicates that inhalation anaesthetic agents, already at very low concentrations and independent of the CNS arousal state, impair ventilatory control. Anaesthetic wash-in studies, together with studies on the (dynamic) ventilatory response to carbon dioxide and acute acidosis, provide ample evidence that the site of action of low-dose inhalation anaesthetic agents is within the peripheral chemoreflex loop, most probably at the peripheral chemoreceptors of the carotid bodies. Evidently, at higher concentrations (>0.1 MAC), impairment of ventilation may be related further to effects at other sites, such as the CNS, upper airways and respiratory muscles.

The results of the studies on pain (with sevoflurane) and auditory stimuli (with isoflurane) illustrate the complexity of the interaction of anaesthesia–sedation, pain, arousal, behavioural stimuli and chemical control of breathing.
While pain and auditory and visual stimulation both caused arousal to the state of wakefulness and auditory and visual stimuli increased the gain of the peripheral chemoreflex loop during sedation with isoflurane, pain did not interact with the peripheral chemoreflex loop (i.e. pain did not change the peripheral gain). (Gain reflects ventilatory hypoxic and hypercapnic sensitivities.) Furthermore, the occurrence of natural sleep and rapid cycling between the different sleep stages, together with the sedation caused by anaesthetics or sedatives, influence of circadian variations, possible sex influences, underlying disease, age-related effects, etc, may also play important roles in the interaction of anaesthetics–sedatives and the control of breathing. These interactions remain poorly understood and merit further study.

So where do we stand on the influence of halogenated inhalation anaesthetics on ventilatory control? Most studies indicate that impairment of responses mediated by peripheral chemoreceptors is seen when studying chemical control of breathing; 30–50% depression of the ventilatory response to acute hypoxia (arterial haemoglobin oxygen saturation approximately 80%) is observed when studies are performed at isocapnia (i.e. similar end-tidal PCO₂ values throughout control and drug studies). Non-chemical drives introduced during the studies may or may not counteract impairment of ventilatory chemoreflexes. At this point we would like to encourage those who plan to investigate the influences of anaesthetics and sedatives on ventilatory control to make use of objective measures of CNS arousal state during their studies, such as the bispectral index of the EEG. This may allow better interpretation and comparison of study results.

Finally, how do the above observations affect the postoperative patient? The main causes of postoperative hypoxic and/or hypercapnic episodes related to ventilatory control are: (1) inability to increase breathing (and hence oxygen uptake) as a result of a reduced ventilatory drive in a period when there is an increased need for oxygen; and (2) occurrence of upper airway obstruction. When hypoxia occurs (with or without hypercapnia), the most important sensors needed to increase breathing activity are the peripheral chemoreceptors of the carotid bodies. Furthermore, the arousal needed to overcome upper airway obstruction is partly mediated and dependent on effective functioning of the peripheral chemoreflex loop. The peripheral chemoreflex loop consists of the peripheral chemoreceptors, carotid sinus nerve, respiratory integrating centres in the brain stem, and the neuromechanical link between the brain stem and respiratory muscles. The integrity of each and all of these components is needed for an appropriate response to hypoxia. While low-dose inhalation anaesthetics affect the loop at the carotid bodies, non-halogenated anaesthetics and opioids, at (sub)hypnotic and analgesic concentrations, may interfere with the peripheral chemoreflex loop at other sites, for example within the brain stem. Non-respiratory stimuli, as occur in a busy postoperative care unit, may restore at least part of the impairment of the peripheral chemoreflexes and moderate hypoxia (haemoglobin oxygen saturation ~80%) may elicit sufficient response such that respiratory and upper airway muscle tone is increased. When non-respiratory stimuli are absent, for example as may occur on a quiet ward, during monitored anaesthesia care or during conscious sedation of a patient anaesthetized with a regional technique, moderate hypoxia is insufficient to elicit appropriate responses. Animal studies show that in such circumstances, much more severe hypoxia (<=80% saturation) is needed to activate the peripheral chemoreflex loop. This may be the cause of significant morbidity and mortality. Not all postoperative patients develop hypoxia–hypercapnia and subsequent complications. It is a major challenge to us all to identify patients at risk. Recent studies indicate that women have more depression of ventilatory responses than men from opioids (a phenomenon that has its origin within the peripheral chemoreflex loop). A recent study from the Netherlands on anaesthesia-related risk factors for perioperative morbidity and mortality revealed that older patients in particular are prone to fatal complications during spinal anaesthesia when combined with conscious sedation. Another group of patients at risk are those with obstructive sleep apnoea. Simply giving extra inspired oxygen to these patients, especially those with upper airway obstruction and impaired peripheral chemoreflexes, may complicate matters, as this impairs further peripheral chemoreceptor function and delays discovery and treatment: the pulse oximeter may give normal values while the upper airways are obstructed with the patient severely hypercapnic. Post-anesthesia care of these patients should involve intensive observation and measurement of respiratory-related variables and, when possible, measurement of arterial, end-tidal or transcutaneous carbon dioxide partial pressures.

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References
4 Knill RL, Gelb AW. Peripheral chemoreceptors during anesthesia: Are the watchdogs sleeping? Anesthesiology 1982; 57: 151–2


Sarton E, van der Wal M, Nieuwenhuijs D, Teppema L, Robotham JL, Dahan A. Sevoflurane-induced reduction of hypoxic drive is sex-independent. *Anesthesiology* 1999; 90: 1283–1293


Temp JA, Henson LC, Ward DS. Effect of 0.1 MAC isoflurane on two tests of the hypoxic ventilatory response. *Anesthesiology* 1994; 80: 739–50


Sarton E, Teppema L, Dahan A. Sex differences in morphine-induced ventilatory depression reside within the peripheral chemoreflex loop. *Anesthesiology* 1999; 90: 1329–1338
