How and Why We Breathe

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Introduction

The human lung has evolved to be an efficient exchanger of the respiratory gases–oxygen and carbon dioxide. In this review, we will concentrate on the physiology and pharmacology of pulmonary ventilation–the process by which gases move into and out of the lungs–rather than on the mechanisms of gas exchange between the alveolar air and blood in the pulmonary capillaries. We will begin by discussing the mechanics of the lung and chest and the mechanisms by which spontaneous ventilation is controlled. On this basis, we will then review some of the methods for studying the control of ventilation and effects of commonly-used sedative, analgesic, and anesthetic medications on the control of breathing

Mechanics of the Lung

As you know, when the lungs are removed from the chest they tend to collapse, assuming a volume which is much lower than their usual resting volume or functional residual capacity (FRC). This tendency results from the additive effects of (1) elastic tissue within the lung parenchyma and (2) surface tension at the liquid / gas interface within the alveoli. The surface tension of water is what makes soap bubbles collapse; if the surface tension (T) is constant, the Laplace relation (P=2T/R) dictates that the the pressure is highest in the smallest bubbles; if in continuity with a larger bubble, the smaller bubble will empty completely. In healthy lungs, the tendency of alveoli to collapse is reduced by the presence of surfactant; since the surface tension (T) of surfactant *decreases* with decreasing alveolar size, the tendency of small alveoli to empty into larger ones is abated, and alveolar stability is ensured. In both neonatal and adult respiratory distress syndromes (RDS, ARDS) surfactant is depleted, and alveoli become unstable with an increased tendency to collapse.

The other factor determining the in-vivo resting volume of the lungs is the elasticity of the chest wall–including the rib cage, diaphragm, and mediastinum. In the absence of the inward pressure exerted by the lungs (as in bilateral, non-tension pneumothorax), the resting volume of the normal chest wall is about 750 ml larger than FRC. In the intact individual, where the volumes of the chest wall and thoracic cavity are essentially the same, the balance between the tendency of the lungs to contract and of the chest wall to expand determines the FRC. There are several physiological factors which help to determine the volume where this balance is achieved. Increased height, decreased weight, male gender, and upright posture all lead to an increase in FRC. Decreased muscle tone (as with anesthesia and paralysis) and abnormal chest wall geometry (as in kyphoscoliosis) decrease FRC. Emphysema, with the associated reduction in pulmonary elasticity, increases FRC.

As you might expect, the constant "tug of war" results in a negative pressure in the pleural space. (The pleural space tends to remain devoid of air because the sum of the partial pressures of gases in mixed venous blood is lower than atmospheric pressure; hence there is a pressure gradient favoring the absorption of gases from well-perfused cavities.) Interestingly, the actual intrapleural pressure varies depending upon the location of measurement (Figure 1). In an upright person, intrapleural pressures are least negative at the bases (because of the weight of the lungs, above) and most negative at the apices. This implies that when the lungs are at FRC, apical alveoli are more distended than basal alveoli (the more negative pleural pressure tends to hold them open). Paradoxically, these expanded alveoli can't expand much further–while their volume is large, their compliance is relatively low–so during spontaneous inhalation they don't expand very much. In contrast, alveoli at the bases, while less distended at FRC, are more compliant. Thus, spontaneous ventilation is

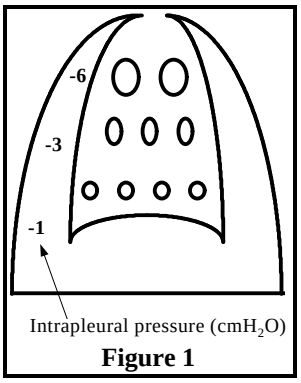

Figure 1

preferentially distributed to basal alveoli; this is particularly "convenient" since pulmonary blood flow, being gravity dependent, is also preferentially distributed to the basal lung. Similarly, in supine patients, spontaneous ventilation is preferentially distributed to the more posterior portions of the lung, where blood flow is also maximal.[1]

The relationship between the pressure generated by the muscles of ventilation and the volume of air which moves into the lungs is determined by the compliance of the respiratory system. Because the volume of the lungs and rib cage are coupled (in the absence of pneumothorax), overall respiratory system compliance (C_{TOT}) depends upon the compliances of both the rib cage (C_{RC}) and the lungs (C_L). However, the compliances are not strictly additive; rather they are related by the formula $1/C_{TOT} = 1/C_{RC} + 1/C_L$. In a normal adult, the $C_{RC} \approx 200$ and $C_L \approx 150$, so C_{TOT} is about 86 ml / cmH_2O.

Muscles of Respiration

During quiet breathing, inhalation is produced by contraction of two primary muscle groups: the diaphragm and the intercostals. About 60% of tidal ventilatory volume is contributed by the diaphragm[2], with the remainder being primarily contributed by the external intercostals. Since vital capacity (4-6 l in an adult) far exceeds normal tidal volume ($\approx$500 ml) it is apparent that individuals can survive indefinitely if they lack either one of these systems, provided the other is intact. This explains how patients undergoing cesarean section with a T-2 level of spinal anesthesia can breathe adequately using their diaphragms, alone, while patients with bilateral phrenic nerve block or cervical epidural anesthesia can breathe using only their intercostals.[3] Ideally, intercostal and diaphragmatic movements are coordinated; otherwise, the descending diaphragm can "suck in" the chest wall, resulting in paradoxical movement of the chest wall and abdomen with decreased effective gas exchange. Even during quiet breathing, exhalation may not be entirely passive; there is evidence that contraction of abdominal muscles may promote exhalation. During physical activity, or when there is an obstruction to airflow as in patients with asthma or obstructive airway disease, accessory muscles are recruited. Some of these, such as the scalenes and sternocleidomastoids, function during inspiration to elevate the chest wall and increase pulmonary filling. In contrast, the rectus abdominus acts during exhalation to increase airflow and to overcome the effect of intra- or extrathoracic airflow obstruction. Of course, adequate pulmonary ventilation requires that the airway be patent; cyclical activation of airway muscles including the genioglossus and tensor veli palatini muscles tend to open the airway during inhalation, particularly during natural sleep when the airway tends to collapse; inadequate function of this mechanism may contribute to obstructive sleep apnea.

Generation of the Respiratory Rhythm

Working our way back to the central nervous system, we now need to address the origin of the respiratory rhythm. In contrast to cardiac physiology where the location and function of pacemaker cells has been clearly established, the site and function of the respiratory pacemaker remains elusive. While it has been clearly established that the respiratory rhythm originates in the brainstem, the relative roles of the pons, medulla, and even peripheral mechanoreceptors has been a matter of debate for over a century. As might be expected based on the variety of muscles which contract and relax in phase with the respiratory cycle, there are many loci within the brainstem where cyclical neural activity can be detected. However, most of these regions represent outputs of the respiratory "generator" rather than components of the generator itself. Early attempts to localize the respiratory pacemaker were based on selective transection or ablation of neural structures. An early explanation, proposed by Hering and Breuer in the 1860's was that inspiration was self-limited by inhibitory vagal impulses arising from pulmonary stretch receptors. Subsequently, an interactive role of the pons and medulla was proposed, based on data from ablation experiments: After transection caudal to the pontine "pneumotaxic center", normal phrenic nerve respiratory activity is replaced by "apneusis", a respiratory pattern where inspiratory neurons continue to fire without expiratory interruption; this was interpreted as being related to "release" of the more-caudally located "apneustic center," and occurs only if the vagi have also been interrupted. Sectioning the brainstem below the pontine apneustic center results in a medullary "gasping" pattern of respiration, suggesting that respiratory rhythm generation occurs in the medulla, with "fine tuning" of the ventilatory pattern involving the pontine centers. Feedback via the vagus nerves also plays a role in the development of another

breathing reflex, of which all anesthesiologists are aware by feel if not by name: Head's Paradoxical Reflex occurs when an anesthetized patient "completes" a breath which is initiated by compressing the reservoir bag. It is "paradoxical" because unlike the Hering-Breuer reflex, pulmonary expansion causes further inhalation rather than initiating exhalation.

Part of the problem in further delineating the origin of respiratory rhythm is related to the fact that different types of experiments yield different results: If medullary cells inadvertantly become hypoxic, as a result of being being bathed in a nutrient medium in place of vascular perfusion with oxygenated blood, the normal, ramp-like phrenic nerve output is replaced by a pulsatile "gasping" pattern.

The respiratory neurons of the medulla are concentrated in dorsal and ventral respiratory groups. The dorsal respiratory group (DRG) is located near the floor of the 4th ventricle just ventrolateral to the nucleus-tractus solitarius, while the ventral respiratory group (VRG) is located adjacent to the nucleus ambiguus. Neurons of the DRG are primarily active during inspiration, and probably directly stimulate phrenic motor neurons. Most neurons in the VRG activate during exhalation, although some inspiratory phase neurons are present. Just rostral to the VRG is a region called the pre-Bötzinger Complex; cells in this region seem to be able to generate a "pacemaker" activity, related to voltage-dependent ion channels (much like cardiac pacemaker cells). It is not clear whether individual cells can function as respiratory pacemakers, or whether there needs to be a feedback loop between two pools of cells to sustain respiratory rhythm. Once the basic rhythm is established, the pattern of efferent nerve stimulation is modulated by neurons in the medulla and pons, with input from pulmonary stretch receptors *via* the vagus nerves. The integrated output of the respiratory center is then amplified by premotor neurons before being sent to the muscles of respiration *via* the spinal cord.

Regulation of Ventilation

Under normal circumstances, carbon dioxide is the primary chemical mediator of ventilatory control. At rest, even small increases in P_aCO_2 significantly increase alveolar ventilation. The CO_2 sensors are believed to lie near the ventral surface of the medulla, near the VRG; their cells appear to be sensitive to pH of the surrounding extracellular fluid. Because the blood-brain barrier is much more permeable to CO_2 than to ions such as H^+, changes in P_aCO_2 will rapidly change the pH within the receptors, while the effect of metabolic acidosis on central respiratory drive will be much slower and less pronounced. The relationship between P_aCO_2 and alveolar ventilation is shown as curve 'A' in Figure 2.

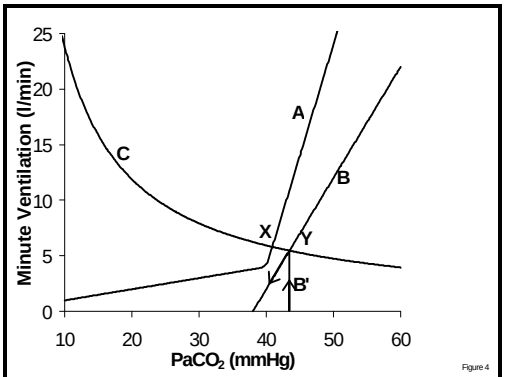

Figure 2

Of course, by itself, this relationship between P_aCO_2 and $\dot{V}_E$ does not uniquely determine an individual's P_aCO_2 or $\dot{V}_E$. For this we need a second relationship, based on conservation of mass, which results in an inverse relationship between the two variables, known as the CO_2 excretion hyperbola (Curve C)[4]. This is the graphical representation of the well-known phenemonon that increasing alveolar ventilation causes a decrease in P_aCO_2. The exact position of the hyperbola depends upon CO_2 production as well as barometric and water vapor pressures. The intersection of this "ventilatory response" curve and the CO_2 excretion hyperbola uniquely determines steady-state alveolar ventilation and P_aCO_2. In awake subjects, the CO_2 ventilatory response curve consists of two sections: When P_aCO_2 exceeds approximately 46 mmHg, the curve is essentially linear (corresponding to involuntary, medullary control of ventilation). Below 46 mmHg, the curve takes on a "hockey stick" appearance because of the effect of consciousness on respiratory control (following voluntary hyperventilation to a P_aCO_2 of 20 mmHg, awake individuals do not become apneic). On the other hand, in

spontaneously breathing anesthetized patients, even slight decreases in P_aCO_2 resulting from manual hyperventilation may completely abolish spontaneous ventilatory efforts; in this case the “tail” of the curve becomes linear (curve B); the intersection of the response curve with the abscissa becomes the "apneic threshold," below which spontaneous ventilation ceases. Interestingly, there is a hysteresis effect; once ventilatory drive is abolished by hyperventilation, it is necessary for P_aCO_2 to increase several mmHg above the apneic threshold before spontaneous ventilation will resume (line B’). The central ventilatory response to CO_2 is relatively slow; minute ventilation does not reach a new, steady state value until 4-5 min after a step change in P_aCO_2.

For any individual, the CO_2 ventilatory response curve is not fixed: its slope and displacement are critically dependent upon a second, peripheral ventilatory control system, whose sensors are located in the carotid bodies. While these sensors primarily respond to decreases in P_aO_2, they also respond to decreases in pH and (during hypoxia) to increases in P_aCO_2. As oxygen saturation decreases, the slope of the ventilatory response to CO_2 increases, producing a family of CO_2 response curves (the so-called "Oxford Fan", Figure 3). Therefore, when measuring hypercarbic ventilatory response, it is necessary to maintain a constant degree of hypoxic stimulation. This is usually achieved by using high inspired oxygen concentrations, effectively "turning off" the hypoxic drive mechanism. Of course, the slope and/or displacement of the hypercarbic ventilatory response are affected by many of the drugs used by anesthesiologists; changes in these variables are sensitive indicators of the effects of drugs on ventilatory control. In contrast, measurements of resting ventilation and P_aCO_2 are relatively insensitive to the effects of drugs on ventilatory control. As shown in figure 2, a drug which causes a 50% decrease in the ventilatory response to CO_2 may cause resting P_aCO_2 to increase by only 2 or 3 mmHg with a correspondingly small decrease in resting minute ventilation. These changes are likely to be completely obscured by normal intra and inter-subject variability as well as by the acute hyperventilation associated with obtaining an arterial sample.

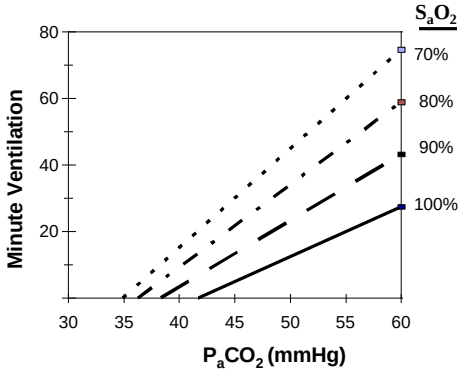

Figure 3

The interactions between central and peripheral ventilatory control mechanisms are summarized in Figure 4. Note that an increase in $PaCO_2$ increases the output of both the CNS respiratory centers and the peripheral chemoreceptors. In contrast a *decrease* in PaO_2 increases the output of the peripheral chemoreceptors (hence the ‘minus’ sign), while it decreases the output of the CNS respiratory centers (hypoxic ventilatory decline).

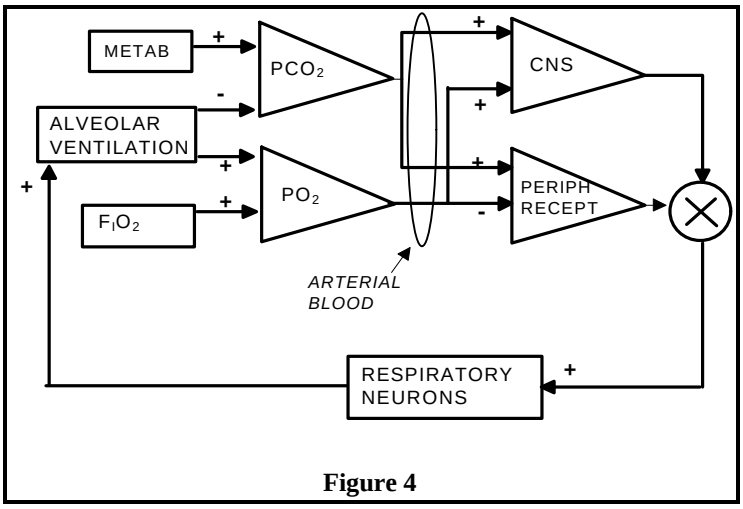

Figure 4

EFFECTS OF SPECIFIC AGENTS ON VENTILATORY CONTROL

Narcotic Analgesics

The effects of narcotics on hypercarbic ventilatory drive have been extensively studied. However, there is still controversy regarding whether their primary

effect is on the slope or the displacement of the CO_2 ventilatory response curve. These discrepancies, in fact, may be explained by the conditions under which the response is measured. Using the steady-state technique, Bourke et al.[5] found that 0.2 mg/kg of morphine i.v. shifted the CO_2 response curve 8 mmHg to the right, without affecting its slope. In contrast, we observed that a single 0.5 mcg/kg dose of remifentanil acutely decreased the slope of the ventilatory response to CO_2 by 72%. It seems that in awake patients, narcotics are more likely to shift the CO_2 response curve to the right, while in sedated or anesthetized patients they tend to decrease the slope of the ventilatory response. Changes in the slope of the curve may have more serious consequences than parallel displacements–particularly when they occur quickly. Because fentanyl and remifentanil reach the ventilatory control centers quickly, they acutely depress and may even stop spontaneous ventilation, particularly if patients are asleep. Because P_aCO_2 does not rise quickly enough to re-stimulate ventilation, patients are likely to become apneic, especially if sedated or anesthetized . As expected, administration of naloxone completely reverses narcotic-induced depression of ventilatory control.

The administration of opioids into the epidural and subarachnoid spaces has become an accepted means of postoperative pain control during the last few years. Clergue, et al[6] found that intrathecal morphine can cause a 20-40% decrease in the slope of the CO_2 response curve. The depression, which peaks between 7 and 11 hours after morphine administration, is associated with rostral spread of the anesthetic to the medullary ventilatory control centers. The propensity of subarachnoid and epidural morphine to produce delayed respiratory depression has been attributed to the fact that it is hydrophilic: morphine remains dissolved in the CSF rather than binding to tissues. However, the shorter-acting, lipid soluble narcotics may also cause respiratory depression when injected epidurally. When administered into the epidural space, both fentanyl (3 μg/kg)[7] and alfentanil (15 μg/kg)[8], produce a more profound and long-lasting depression of the CO_2 response slope than observed when equal doses are administered intramuscularly. Of course, it has been known for decades that naloxone can completely antagonize opioid-induced respiratory depression. However, unless opioid antagonists are titrated slowly, there is a risk of rebound hypertension and tachycardia as the desirable analgesic effects are concomitantly reversed.

Anesthetic Induction Agents

Because of their short duration of action, the respiratory depressant effects of induction agents such as thiopental are best studied using the dual isohypercapnic technique. In both normal volunteers and patients with COPD, thiopental 3.5 mg/kg decreases the slope of the ventilatory response to CO_2 by 25-30% within 2 minutes; the hypercarbic response returns to normal within 5 minutes after injection.[9] This acute change in the CO_2 response curve explains the apnea which follows induction of anesthesia with thiopental; spontaneous ventilation resumes as the CO_2 response curve returns to normal (and P_aCO_2 increases) increasing respiratory drive.

Propofol, too, is a potent respiratory depressant. Following rapid injection of propofol 2.5 mg/kg, ventilatory response to CO_2 decreased by 50%. Interestingly, subjects took longer to recover from both the sedative and respiratory depressant effects of the propofol as compared to an equipotent dose of thiopental (4.0 mg/kg). Furthermore, following propofol, respiratory depression was evident between 15 and 20 min after injection, at a time when level of consciousness had returned to normal. Nieuwenhuijs et al.[10] demonstrated that insofar as its effect on CO_2 response is concerned, propofol primarily depresses the central chemoreceptor CO_2 response, with minimal effect on the peripheral chemoreceptors. In contrast, we demonstrated that during moderate ("conscious") sedation with propofol, hypoxic ventilatory drive (which is mediated by the peripheral receptors) decreased by 80%, at a dose of 85 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The discrepancy may be related to the relatively modest contribution of the peripheral chemoreceptors to CO_2 responsiveness as compared to their primary role in hypoxic response.

Sedatives

When given alone, oral diazepam causes minimal respiratory depression, explaining its relatively high margin of safety. Oral midazolam may cause mild respiratory depression, particularly when combined with other sedative or analgesic medications; this may be related to its more rapid onset of action.[11] When given intravenously, midazolam

causes significant respiratory depression. When midazolam is titrated to a level of "moderate sedation" the ventilatory response to CO_2 decreases by approximately 25% in healthy volunteers. The ventilatory response to hypoxia also decreases by about 25% during moderate sedation with midazolam. Both of these effects are reversed by flumazenil 0.5 mg. The ventilatory depressant effects of midazolam are potentiated by concomitantly administered opioids. During a low-dose alfentanil infusion, addition of midazolam decreased the ventilatory response to CO_2 by approximately 40%, resulting in a 60% decrease from baseline. When flumazenil was administered, the component of the respiratory depression associated with midazolam was completely reversed, with the residual respiratory depression being that attributable to the alfentanil, alone (Figure 5).[12] This implies that non-anesthesiologists who administer a combination of an opioid and midazolam for moderate or deep sedation can administer flumazenil to reduce (though not eliminate) respiratory depression while minimizing the risks of rebound hypertension and tachycardia which would accompany administration of naloxone.

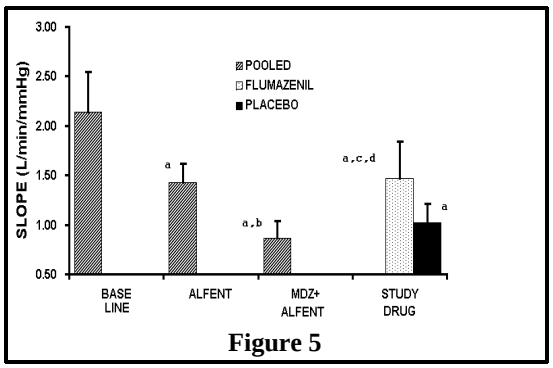

Figure 5

Diphenhydramine, of course, is an anti-H1 antihistamine which has significant sedative, antiemetic, and antipruritic properties. Because of its perceived safety, it is commonly prescribed to treat side-effects of neuraxial opioids including pruritus and nausea. As its use in this setting has become routine in some centers, it is important to know whether concomitantly administered diphenhydramine might potentiate the respiratory depression associated with the neuraxial opioids. Interestingly, when administered alone, diphenhydramine had no effect on the ventilatory response to hypercarbia (during hyperoxia) or to or to hypoxia (during normocarbia). However, Diphenhydramine caused a 66% increase in hypoxic ventilatory drive, when $P_{ET}CO_2$ was maintained at 54 mmHg, indicating that it significantly augmented the interaction between hypoxic and hypercarbic ventilatory control mechanisms. Unfortunately, the experimental design did not allow a determination of whether this augmentation was mediated centrally or peripherally.[13] A follow-up study determined that diphenhydramine 0.7 mg/kg partially antagonized the respiratory depression associated with an alfentanil infusion, suggesting that diphenhydramine is unlikely to promote respiratory depression in patients who have received neuraxial opioids.

Inhalation Anesthetics

The inhalation anesthetics seem to affect the peripheral chemoreceptors more than the central components of ventilatory drive. Thus, as far back as 1976, it has been known that N_2O does not affect the ventilatory response to CO_2 while moderately depressing the response to hypoxia.[14] Shortly thereafter, Knill demonstrated that low doses of halothane (0.1 MAC) had minimal effect on the ventilatory response to CO_2, while decreasing the hypoxic response by 75%. 1.1 MAC halothane decreased the CO_2 response by about 60%, while completely abolishing response to hypoxia; in retrospect, the only response they observed was centrally-mediated hypoxic ventilatory decline.[15] In the ensuing years, these investigators demonstrated that enflurane and isoflurane have similar, selective effects on the peripheral chemoreceptors. In 1992, Temp et al. were unable to demonstrate a significant effect of 0.1 MAC isoflurane on hypoxic ventilatory drive.[16] The discrepancy, as demonstrated by van den Elsen in 1994, was related to the experimental conditions under which ventilatory drive was measured.[17] Knill's group studied subjects in unstimulated conditions, listening to soft music on the radio, while Temp's studies were performed with subjects watching Ken Burns's Civil War documentary on a TV monitor! The ventilatory depressant effects of inhalation anesthetics are of greatest concern during recovery from anesthesia, when ventilation is not artificially controlled and monitoring is less intense than during anesthesia *per-se*. Low residual anesthetic concentrations are unlikely to affect normal individuals whose ventilatory

control mechanisms are intact. However, patients whose central ventilatory drive is depressed, like those with COPD, may depend upon their peripheral chemoreceptors to maintain spontaneous ventilation; these individuals may be at particular risk for the ventilatory depressant effects of residual concentrations of inhaled anesthetics.

Many of the interventions which we routinely perform as anesthesiologists–i.v. sedation, general anesthesia, and regional anesthesia-- significantly affect the process of pulmonary ventilation. An understanding of the relevant anatomy, physiology, and pharmacology can enable us to keep our patients breathing safely in the perioperative period.

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