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Upper Airway Collapsibility

An Emerging Paradigm for Measuring the Safety of Anesthetic and Sedative Agents

EASTWOOD *et al.*[1] have contributed an article to this issue addressing the upper airway at various levels of propofol anesthesia. Ventilatory depressant properties of anesthetic agents can be characterized by their effects on resting carbon dioxide concentrations and the ability to alter the normal ventilatory response to hypoxia and hypercapnia.[2] However, in most clinical situations, the presence of hypercapnia as a result of ventilatory decline is not harmful, especially during administration of supplemental oxygen.[3] In fact, the most serious complication that results from the administration of agents that depress consciousness is upper airway obstruction because, if undetected or inadequately treated, it rapidly results in hypoxemia.[4]

Several decades ago, researchers studying obstructive sleep apnea syndrome developed a model to measure upper airway collapsibility during sleep.[5] By considering the cartilage-free upper airway as a classic Starling resistor, the pressure within or contiguous with the airway can be artificially altered, and by measuring corresponding peak flows during conditions of flow limitation, a critical pharyngeal closing pressure (Pcrit) is derived.[6] Pcrit reproducibly describes the inherent collapsibility of a subject's airway and has been used to measure the impact of an intervention such as weight loss,[7] uvulopalatopharyngoplasty,[8] or administration of continuous positive airway pressure.[9]

The Pcrit measurement has been used previously to characterize upper airway collapsibility in sedated[10] and anesthetized[11] patients. However, in this issue of the Journal, Eastwood *et al.* [1] take this methodology to a new and more clinically meaningful level by demonstrating the dose–response relation between the depth of propofol sedation and Pcrit. The dose response for upper airway collapse is one of several important components that describe the safety of a sedative agent (*i.e.*, therapeutic margin) and may determine the choice of sedatives by practitioners without training in general anesthesia.

This Editorial View accompanies the following article: Eastwood PR, Platt PR, Shepherd K, Maddison K, Hillman DR: Collapsibility of the upper airway at different levels of propofol anesthesia. ANESTHESIOLOGY 2005; 103:470–7.

I believe there are two perspectives to consider when interpreting this data. The first is the actual Pcrit values obtained and the ability to compare these values against those obtained with other anesthetics or sedatives at the same depth of unconsciousness. The range of Pcrit values reported for propofol is between those reported for isoflurane[11] and midazolam,[10] indicating that its relative propensity to preserve upper airway patency (*i.e.*, safety) is greater than for isoflurane but less than for midazolam. That is, at similar depths of sedation, propofol is more likely to cause upper airway obstruction than midazolam. This underscores the recent American Association of Nurse Anesthetists–American Society of Anesthesiologists joint statement cautioning that use of propofol for sedation should be restricted to practitioners with training in general anesthesia.* I do not believe I would be taking great risk of criticism by stating that when it comes to upper airway obstruction, propofol is not a typical sedative!

The second perspective is the percent change in Pcrit relative to the change in level of unconsciousness. For Eastwood's group as a whole, the mean Pcrit increased from −0.3 mmHg at the lowest propofol plasma concentration studied (2.5 μg/ml) to +1.4 mmHg at the highest concentration studied (6.0 μg/ml). Although statistically significant, this is hardly a clinically relevant difference and is less than the span of pressures seen within one respiratory cycle in most anesthetized adults. As a reference, remember that this lower concentration of propofol is associated with a wide range of states of consciousness, from awake to deeply sedated, and the higher concentration of propofol is usually associated with a state of deep sedation.[12] This relative change in Pcrit between a span of sedative states may serve as a marker of an agent's safety. Future investigations with additional anesthetic and sedative agents will reveal these types of differences.

An important limitation of the measurement of upper airway collapsibility in sedated or anesthetized patients is the lack of a consistent and reliable pharmacodynamic indicator of the depth of unconsciousness. In our study on the effect of midazolam on Pcrit, we used a standardized sedation score.[10] Eastwood *et al.* used target plasma concentrations of propofol and Bispectral Index scores, which exhibited reasonable consistency but poor precision. The comparison of Pcrit values between different agents must rely on a standardized level of unconsciousness so that one is comparing "apples with apples."

Another limitation of this methodology is the subjective identification of flow-limited breaths, which indicate

* AANA-ASA Joint Statement Regarding Propofol Administration. American Society of Anesthesiologists Web Site. Available at: http://www.asahq.org/news/propofolstatement.htm. Accessed May 31, 2005

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upper airway narrowing. To date, investigators using the Pcrit method have identified flow-limited breaths by their characteristic flow wave appearance consisting of a flattened plateau during inspiration. More objective, mathematically based methods that use inspiratory flow and airway pressure values have recently been described[13] and may prove more consistent in future trials.

The use of the genioglossus electromyography also deserves comment. Sleep apnea researchers believe that a major factor contributing to the loss of pharyngeal patency in patients with obstructive sleep apnea is the dysfunction of certain patency reflexes, such as the negative-pressure reflex. The negative-pressure reflex describes the activation of pharyngeal dilator muscles in response to the application of pharyngeal negative pressure. This has been most widely studied in the genioglossus muscle because the body of the muscle is easily accessible to electromyographic needles.[14] Contraction of the genioglossus causes extrusion of the tongue, and alleviation of upper airway obstruction at the level of the oropharynx. However, magnetic resonance imaging studies have demonstrated that upper airway obstruction during sedation with propofol also occurs at the level of the soft palate and epiglottis.[15,16] Therefore, reflex activation of the genioglossus during the application of negative pressure likely serves as a surrogate for other pharyngeal dilator muscles at distant locations within the upper airway. Nevertheless, the effect of a sedative or anesthetic agent on the negative-pressure reflex may prove useful as a measure of safety in future studies.

The effects of standardized levels of anesthetic and sedative agents on upper airway patency are an important step in advancing safety for nonintubated, sedated patients. Sleep apnea researchers have extensively investigated a myriad of factors that affect upper airway collapsibility.[17] In comparison, upper airway studies during sedation or general anesthesia are in their infancy, and we should follow their leads.

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Timing Is Everything

The Pendulum Swings On

IN his *Introduction to Experimental Medicine* in 1865, Claude Bernard noted that the physical state and chemical composition of the internal environment remains essentially constant. This idea was taken further by W. B. Cannon, who introduced the word *homeostasis*. Homeostasis is the maintenance of constant conditions in a biologic system by means of automatic mechanisms that counteract influences on disequilibrium.

On the other hand, chronobiology is a field of biology that examines time-related phenomena in living organisms. One century before Claude Bernard's work, Jean Jacques d'Ortous de Mairan, a French astronomer, per-

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