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# *"The Proper Study of Mankind Is Man"*—Rather, Men and Women Undergoing Anesthesia and Surgery*

STARTING in 1997, Hahn *et al.*[1–4] introduced and developed the concept of volume kinetics, which describes the peak effects and clearance of intravenously infused fluids in terms similar to those used in pharmacokinetics to describe the peak effects and clearance of drugs. Stanski,[5] in an editorial accompanying the landmark article by Svensen and Hahn in ANESTHESIOLOGY in 1997,[1] commented that the volume kinetic approach could "allow for more rational design of intravenous fluid paradigms." Toward that end, Hahn *et al.* have examined several key questions in volunteers[6–8] and in experimental animals.[9–12] One of the least expected observations, obtained in sheep, was that isoflurane anesthesia seemed to be associated with extravascular accumulation of infused crystalloid.[9] However, in this issue of ANESTHESIOLOGY, Ewaldsson and Hahn[13] convincingly demonstrate that, in humans, neither isoflurane nor propofol anesthesia is associated with extravascular fluid accumulation. The authors infer from their data that volume kinetics are powerfully influenced by hypotension,[13] an inference that merits examination in the context of previous volume kinetic studies.

In pharmacokinetics, an exogenous substance is introduced, blood or other fluids are repeatedly sampled, and the resulting temporal pattern is analyzed to determine important kinetic variables. In contrast, volume kinetics examines the clearance of endogenous substances, *e.g.*, water, that already are present in considerable quantities. For such studies, an endogenous tracer is necessary, the best being the blood concentration of hemoglobin, which is an obligatory intravascular tracer. To confidently calculate volume kinetic variables, the blood concentration of hemoglobin should be repeatedly measured before, during, and after fluid infusion in a relative steady state. High-probability solutions to the kinetic equations necessitate that changes in potentially confounding physiologic and pharmacologic influences be minimized for a sufficient time interval to construct clearance curves. In practice, time intervals of 180 min after the beginning of an intravenous infusion have provided sufficient data for reliable kinetic analyses.

Such time intervals of relative stability can be achieved easily in certain types of volunteer and animal studies. For example, in volunteers, isotonic crystalloid solutions were rapidly cleared,[1] colloid solutions were less rapidly cleared,[1] and crystalloid solutions produced higher peak volume expansion and more delayed clearance in hypovolemic than normovolemic volunteers.[6] During intervals of relative stability in preeclamptic parturients, crystalloid solutions were more rapidly cleared than in normal volunteers.[14] In experimental animals, isoflurane anesthesia was associated with similar clearance of infused crystalloids from blood but markedly delayed urinary excretion, implying greater extravascular retention.[9,15] As in volunteers, hemorrhage in sheep both increased peak expansion and delayed clearance from blood.[12] *Pseudomonas* bacteremia, which in sheep mimics many characteristics of clinical sepsis, unexpectedly did not influence volume kinetics.[16] In sheep, continuous infusion of $\alpha$-adrenergic agonists dramatically accelerated, whereas $\beta$ agonists delayed, clearance of infused crystalloids.[17]

However, the clinical circumstances of anesthesia and surgery usually preclude 180 min of steady state conditions, the influences of surgical stress and surgically induced fluid shifts are difficult to separate from the influence of anesthesia, and blood loss confounds kinetic analyses based on measurements of the blood concentration of hemoglobin. Nevertheless, volume kinetic studies have been performed in patients undergoing surgery. During laparoscopic cholecystectomy in women undergoing sevoflurane–narcotic anesthesia, induction of anesthesia, before fluid infusion, was associated with 4.2% plasma dilution (equivalent to intravascular volume expansion); subsequent fluid infusion was associated with calculated kinetic variables that were similar to those acquired in female volunteers, despite marked inhibition by anesthesia of the infusion-associated diuresis seen in volunteers.[18] In contrast, in men undergoing prostatectomy during enflurane anesthesia, crystalloid fluids seemed to produce greater volume expansion than in unanesthetized volunteers.[19] In a heterogeneous group of patients undergoing elective surgery of variable magnitude during subarachnoid block or sevoflurane–narcotic general anesthesia, volume expansion was greater in patients undergoing general anesthesia, but urinary elimination was similarly reduced in both groups.[20] Men undergoing short urologic procedures

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* Alexander Pope: Essay on Man. Epistle ii. Lines 1, 2. 1733.

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during epidural anesthesia retained a relatively high proportion of infused volume intravascularly.[21]

Together, these studies demonstrate the difficulty of separating the effects of volume kinetics during anesthesia and surgery. The magnitude of surgery and the hemodynamic responses to anesthetic and surgical manipulations varied substantially, with the most striking effects being differences in blood pressure. In the women undergoing cholecystectomy, induction of anesthesia was associated with hypotension so that blood pressure was substantially lower than baseline when fluid infusion began as surgery started; data collection for volume kinetic analysis continued for at least 2 h after completion of surgery, during which time blood pressure returned toward preanesthetic values.[18] In the comparison of general and subarachnoid anesthesia, a 60-min, 20-ml/kg fluid bolus was initiated 20 min before anesthetic induction.[20] Data were collected only until the end of the infusion, during which time blood pressure was 30–40 mmHg below the preinduction baseline in both groups, with the greater reduction occurring in the group receiving subarachnoid blocks. In men undergoing urologic surgery during epidural anesthesia, greater reductions in blood pressure were associated with greater intravascular retention of fluid.[21]

The study published in this issue of ANESTHESIOLOGY was well designed to minimize the influence of surgical manipulation and partially isolate the influence of anesthesia while providing sufficient time to collect samples for kinetic analysis.[13] Thyroid surgery, which is associated with little soft tissue manipulation, lasted a mean of 143 min—sufficient time to complete most kinetic analyses. Anesthetic management was randomized to permit comparison of the effects of isoflurane and propofol. Although no control data were collected in unanesthetized patients, published data from unanesthetized subjects were available for comparison. The greater intravascular retention of fluid, in comparison to unanesthetized subjects in previous studies,[1] was associated with hypotension during both propofol and isoflurane anesthesia. Fractional plasma dilution was greater than in previously studied, unanesthetized volunteers, in association with reductions of 30–40 mmHg in both anesthetized groups.

These data should encourage advocates of crystalloid fluid therapy. Intravascular volume expansion produced by crystalloid fluids was increased during anesthesia in humans, and excess interstitial accumulation of fluid did not occur. Why do these data seem to conflict with data in sheep? One possibility is that because the sheep in the previously cited studies[9,15] did not have development of hypotension, the effects of anesthesia *per se* were evident. Perhaps anesthesia is associated with intravascular fluid retention if hypotension is prominent and with extravascular fluid retention if blood pressure is maintained at a higher level. In the surgical patients in the current study, the reduction in blood pressure seems to have provided the dominant influence. Further studies are necessary to determine the influence on volume kinetics of "typical" clinical anesthetic management, in which blood pressure is maintained closer to preoperative baseline than in the current study.

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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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formed the first known experiment on biologic rhythms. He investigated the behavior of heliotrope, a plant with leaves that open during the day and close at night. He found that the leaves continued to open and close even when lighting levels were constant. This indicated that the force driving the plant's rhythms was internally generated. The first observations of circadian rhythms in humans were made in 1866, when William Ogle noted that fluctuations in body temperature varied in synchrony with day and night.

These biologic rhythms have been observed in cells, tissues, organs, and human beings. At a given moment, a disruption in an organism is maintained at a certain value by a cascade of reactions. However, during a fixed period, the levels of biologic values are not constant, with variations of up to 50% sometimes observed. Without being opposed, homeostasis and biologic rhythms are in fact complementary and enable physiologic functions to adapt to an external environment.

The most important rhythm in chronobiology is circadian rhythm, which refers to the 24-h daily biologic cycle. However, many other important cycles are also studied, including ultradian (a cycle that is shorter than 1 day) and infradian rhythms (a cycle that may last weeks, months, or seasons). Circadian rhythms have been reported in heart rate, blood pressure, temperature, plasma concentrations of hormones and electrolytes, functions of the kidneys, the lung, the gastrointestinal tract, and the liver. The onset and symptoms of various diseases such as asthma and coronary ischemia are also not constant and exhibit temporal changes.[1]

Temporal change of pain has been found in patients with migraine, arthritis, and biliary colic pain.[2] Variability in pain perception and sensitivity to analgesic therapy have long been noted.[3] A 15–40% day–night difference for morphine consumption was noted in patients undergoing surgery.[4] In surgical patients, the need for fentanyl was 30% less in a group of patients undergoing elective cholecystectomy performed earlier in the morning as compared with a late group. Numerous studies reported that the duration of action of local anesthetics exhibited temporal changes with a maximal analgesic effect during afternoon.[5]

We have previously shown that 10 $\mu$g intrathecal sufentanil for early labor analgesia exhibited a 30% variation in duration over the course of the day, with the shortest duration of analgesia at midnight (78 min) and the longest at noon (128 min).[6]

A study by Pan *et al.*[7] in this issue of *Anesthesiology* continues the series of studies demonstrating that the duration of action of anesthetic agents is sensitive to the time of day, although analgesic requirements during the full 24-h period were not documented. The authors found a 27% reduction of spinal fentanyl in its duration of action in the early night period (8 PM to 2 AM: 69 ± 5.0 min), compared with daytime (12 noon to 6 PM: 92 ± 6.0 min). The possibility that patient perception of labor pain differs throughout the day was advocated but not found in the studies of Debon *et al.*[6] and Pan *et al*. Therefore, variation in the production of pain mediators or temporal change in opioid receptor affinity/receptor number during the 24-h period could participate in circadian changes observed in these clinical studies.

It has been also shown that biologic rhythms influence the pharmacology of anesthetic agents such as local anesthetics, hypnotics, and muscle relaxants.[8] The real question is whether these circadian effects are of actual clinical importance in anesthesia and, if so, when and in which patients. Possibly, several domains of our practice of anesthesia or intensive care could be affected by chronobiology.

Many drugs used to treat critical care patients show temporal change. Studies have demonstrated that the pharmacokinetics of aminosid and certain antibiotics are altered by the time of day in critical care patients.[9] Therefore, the right treatment given at the wrong time can be ineffective or create a crisis of escalating toxicity. Conversely, even a weak treatment, if given at the right moment, could prove surprisingly effective. However, although the clinical benefits of taking into account the time of day that a medication is administered have been clearly demonstrated in asthmatic and cancer patients, they have yet to be demonstrated in intensive care unit patients, and studies are required in the intensive care unit setting.

The implication of chronobiology in the practice of clinical anesthesia is probably of less importance except for the treatment of postoperative pain. Nonsteroidal antiinflammatory drugs, opioids, and $\alpha_2$ agonists are widely prescribed to cure postoperative pain.[10] Many reports have shown that these drugs have a circadian component. The use of patient-controlled analgesia makes it possible to adapt to temporal variations of pain on nyctemeral rhythm, and for many of us, this method of administration represents a fortuitous introduction of the notion of chronobiology in anesthesia. The work of Pan *et al.* further encourages us to use self-controlled means of administration for obstetric analgesia or for postoperative pain relief.

On the other hand, it is difficult to foresee the overall influence of circadian effects on general anesthesia. We use several drugs to anesthetize a patient, and each drug has a particular chronobiologic profile that is not necessarily in tune with the others. It is therefore difficult to predict the overall effect of circadian changes on the course of anesthesia. One can consider that in the future, only the use of a monitor to detect the depth of anesthesia will make it possible to integrate the notion of chronobiology.

Finally, the domain in our specialty that is the most concerned with chronobiology is without a doubt that of clinical and experimental research.[11] Much research has

been done to understand how patient characteristics such as sex, age, weight, and recently, genetics relate to the pharmacokinetics and pharmacodynamics of anesthetic agents. Chronobiology should be considered as any other variable in pharmacokinetic studies of drugs used in the practice of anesthesia. It would be of interest to verify the impact of biorhythms on the pharmacokinetic models currently proposed in anesthesia.

Between the study that Munson *et al.*[12] published in 1970 and that of Pan *et al.*[7] in 2005, few clinical or experimental studies on chronobiology were published in the principal anesthesiology journals, whereas many studies have been published in the journals of other specialities. When one notes the marked differences observed in the studies by Pan *et al.* and Debon *et al.* (30% difference), one wonders whether most of the previously published studies should not be reevaluated. Considering that there are many other possible confounding factors in every study that can affect the conclusion, this recommendation must nevertheless be qualified without being excluded.

To conclude, the impact of time of the day remains relatively unknown in studies devoted to anesthesia. Although its current impact on the routine of anesthesia is minimal, it is likely that chronobiology will provide major contributions to the pharmacology of anesthetic agents currently used for anesthesia. The value of the studies by Pan *et al.* and Debon *et al.* is to emphasize that this impact is important and must not be ignored in future clinical or experimental research.

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