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Preoxygenation

Best Method for Both Efficacy and Efficiency?

THE purposes of maximally preoxygenating a patient before the induction of general anesthesia and paralysis are to provide the maximum amount of time that a patient can tolerate apnea and for the anesthesia provider to solve a cannot-ventilate, cannot-intubate situation. This issue of ANESTHESIOLOGY contains an intriguing article by Baraka *et al.*[1] that describes a new method of preoxygenation that may be best with regard to both efficacy and efficiency.

Maximal preoxygenation is achieved when the alveolar, arterial, tissue, and venous compartments are all filled with oxygen. However, patients with a decreased capacity for oxygen loading (*i.e.*, decreased functional residual capacity [FRC], hemoglobin concentration, alveolar ventilation, cardiac output) or an increased oxygen extraction, or both, desaturate during apnea much faster than a healthy patient.[2,3] Consequently, in patients with oxygen transport limitations (who desaturate the fastest) and in any patient in whom difficulty in managing the airway is suspected (need to tolerate apnea the longest time), maximal preoxygenation is indicated. Moreover, because the development of a cannot-ventilate, cannot-intubate situation is largely unpredictable, the desirability/need to maximally preoxygenate is theoretically present for all patients. Along this line of thought, the American Society of Anesthesiologists Difficult Airway Algorithm,[4] which makes no mention of preoxygenation, should include a requirement for preoxygenation before the induction of general anesthesia whenever possible; obvious exclusion examples are very uncooperative adult patients and pediatric patients. Two major but preventable reasons why a patient will not be maximally preoxygenated are failure to achieve an alveolar fraction of oxygen ($F_{A_{O_2}}$) = 0.87 (i.e., failure to breathe fraction inspired oxygen tension [$F_{I_{O_2}}$] = 1.0 through a sealed system) and insufficient time of preoxygenation.

The major reason for failure to achieve an $F_{I_{O_2}}$ = 1.0 and an $F_{A_{O_2}}$ = 0.87 is a leak under the mask, allowing inspiratory entrainment of room air. Avoiding a leak between the mask and the face is the most important factor in obtaining maximal preoxygenation because it is the one factor that cannot be compensated for by an increased duration of preoxygenation, and relatively minor degrees of leak may be hard to appreciate.[5,6] Using the model of Farmery and Roe,[3] it can be shown that when preapnea $F_{A_{O_2}}$ is progressively decreased from 0.87 to 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, and 0.13 (breathing room air) for a healthy 70-kg patient, apnea times to arterial saturation of oxygen (Sa_{O_2}) = 60% are progressively decreased from 9.90 to 9.32, 8.38, 7.30, 6.37, 5.40, 4.40, 3.55 and 2.80 min, respectively. Clinical endpoints that indicate a sealed system are movement of the reservoir bag in and out with each inhalation and exhalation, respectively; presence of a normal capnogram and an end-tidal partial pressure of carbon dioxide ($P_{ET_{CO_2}}$) and tidal oximetry indicating appropriate inspired and end-tidal values.

The half-time for exponential change in $F_{A_{O_2}}$ with a step change in $F_{I_{O_2}}$ is given by $0.693 \times V_{FRC}/\dot{V}_A$ for a nonrebreathing system. With V_{FRC} equal to 2.5 l, the half-time is 26 and 13 s when $\dot{V}_A$ = 4.0 and 8.0 l/min, respectively. Thus, most of the oxygen that can be stored in the alveolar and arterial spaces can be brought in by hyperventilation $F_{I_{O_2}}$ = 1.0 for a short period of time and is the basis for the 4-deep-breath-within-30-seconds method of preoxygenation (termed the "4DB/30 sec method").

Indeed, three studies have shown that there is no significant difference between the arterial oxygen tension (Pa_{O_2}) achieved with 3–5 min of normal tidal volume ventilation of $F_{I_{O_2}}$ = 1.0 method of preoxygenation (termed the "traditional" [T] method) compared to the 4DB/30 sec method (table 1).[7–9] The similarity in Pa_{O_2} between the T and 4DB/30 sec methods of preoxygenation has led to the conclusion that the 4DB/30 sec method provides the same amount of preoxygenation as

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Table 1. Pa_{O_2} before and after Fast Track and Traditional Methods of Preoxygenation

		Pa_{O_2} (mmHg) (mean ± SD)			
		Baseline, Room Air		After Preoxygenation	
Author	Weight of Patients	Fast Track	Traditional	Fast Track	Traditional (min)
Gold[7]	Normal	76.5 ± 5.3	75.8 ± 6.0*	339.0 ± 33.9	350.4 ± 35.8* (5)
Goldberg[8]	Morbid obesity	89.3 ± 13.5	87.4 ± 12.4*	397.5 ± 104.4	425.4 ± 81.1* (3)
Norris[9]	Cesarean section	102.5 ± 1.5 (SEM)	100.9 ± 3.1* (SEM)	404.2 ± 15.2 (SEM)	385.0 ± 23.6* (SEM) (3)

* No significant difference between fast track and traditional Pa_{O_2} values.

the T method. However, three studies have shown that patients preoxygenated using the 4DB/30 sec method desaturate faster than patients preoxygenated using the T method (table 2).[10–12] There are two possible reasons why the 4DB/30 sec method of preoxygenation results in faster desaturation than the T method.

First, if the half-minute volume of ventilation is much greater than the half-minute oxygen inflow rate, rebreathing of exhaled nitrogen must occur, which, in turn, will lower the $F_{I_{O_2}}$ less than 1.0.[10] However, simple calculation (and daily clinical observation of tidal oximetry) shows that the effect of nitrogen rebreathing in a completely oxygen-loaded standard anesthesia circle system is a minor factor causing submaximal preoxygenation. It is not surprising, therefore, that patients preoxygenated by the 4DB/30 sec method using an oxygen inflow rate of 35 l/min still desaturate to an Sa_{O_2} = 90%, much faster (212 ± 92 s) than patients preoxygenated using the T method (406 ± 75 s).[11]

Another reason why patients preoxygenated with the 4DB/30 sec method desaturate faster is because the tissue and venous compartments need more than 30 s to fill with oxygen; these compartments have the capability of holding a significant amount of additional oxygen above that contained while breathing room air.[13] In fact, if during breathing $F_{I_{O_2}}$ equal to 1.0, the alveolar arterial, venous, and tissue compartments are all considered, total whole-body oxygen stores can theoretically increase 1,200 and 800 ml from the end of the first half-minute (at 30 s) and first minute (at 60 s), respectively, to the end of the third minute (at 180 s) (fig. 1).[13] The 1,200 and 800 ml theoretically gained from the first half-minute and minute to the third minute, respectively, would be worth 3 to 4 min of oxygen consumption during apnea and can certainly account for the observed difference in rates of hemoglobin desaturation during apnea between the 4DB/30 sec and T methods of preoxygenation.

The article by Baraka *et al.*[1] is valuable because it not only confirms the previously observed differences between 4DB/30 sec and T methods of preoxygenation, but, more importantly, shows that an 8-deep-breath-in-60-seconds method of preoxygenation (termed "8DB/60 sec") results in a slower rate of hemoglobin desaturation (to Sa_{O_2} = 95%) during apnea than the T method. This is a surprising and clinically very important result because one would intuitively think that the 8DB/60 sec method would have results somewhere in between the 4DB/30 sec and T methods. However, because the authors used a relatively small volume Mapleson-D circuit (2.5 l) and a different oxygen flow rate in comparing 4DB/30 sec, 8DB/60 sec, and T methods, these results will require confirmation in a standard anesthesia machine circle system using the same flow rate for all conditions.

The authors hypothesized that the 8DB/60 sec method might result in a greater store of oxygen in the alveolar compartment compared to the T method by either causing an increase in flow rate into or the volume of the compartment. However, it is very unlikely that there was a significant difference in the amount of oxygen in the alveolar compartment (the product of $F_{A_{O_2}}$ × FRC) between the T and 8DB/60 sec methods of preoxygenation. Because the Pa_{O_2} values were nearly equal, the PA_{O_2} and $F_{A_{O_2}}$ had to be nearly equal for the two groups. Because all patients (who had no lung disease) were paralyzed and tracheally intubated and because the air-

Table 2. Time to Sa_{O_2} = 90% (or Sa_{O_2} = 93%) following Fast Track *versus* Traditional Methods of Preoxygenation

		Time to Sa_{O_2} = 90% (s) (mean ± SD)	
Author	Type of Patient	Fast Track	Traditional (min)
Gambee[10]	Normal	408 ± 108	534 ± 60* (3)
Valentine[11]	Elderly	212 ± 92	406 ± 75* (3)
McCarthy[12]	Elderly	222 ± 96 (to Sa_{O_2} = 93%)	324 ± 102* (to Sa_{O_2} = 93%)

* Statistically significant greater time to Sa_{O_2} = 90% (and Sa_{O_2} = 93%) between traditional *vs.* fast track methods of preoxygenation.

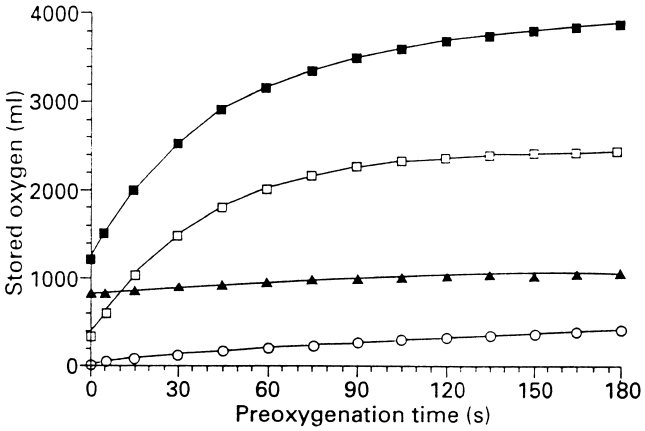

Fig. 1. Variation in volume of oxygen stored in the functional residual capacity (□), the blood (▲), the tissue (○), and the whole body (■), with duration of preoxygenation. (Reprinted with permission from Campbell and Beatty.[13])

way was exposed to atmospheric pressure at the beginning of the apnea period, the FRC for the two groups should have been nearly equal. Thus, the amount of oxygen in the alveolar compartment cannot provide the explanation for the different rates of hemoglobin desaturation.

Given that the half-time for decreases in Pa_{CO_2} with step increases in minute ventilation is 3 min, the 8DB/60 sec method (hyperventilation for 1 min) could result in a significant decrease in Pa_{CO_2} and an increase in *p*H. A significant decrease in Pa_{CO_2} and an increase *p*H could result in a significant change in blood compartment oxygen transport variables, such as the position of the oxyhemoglobin dissociation curve, oxygen consumption, cardiac output, and blood and plasma volumes, which, in turn, could alter the rate of hemoglobin desaturation. Thus, the answer as to why the 8DB/60 sec method resulted in slower hemoglobin desaturation than the T method may reside in the blood compartment rather than in the alveolar compartment. Future areas of useful research will be to determine how oxygen transport parameters, the overall well-being of the patient, and rates of hemoglobin desaturation to levels lower than an Sa_{O_2} equal to 95% are effected by the 8DB/60 sec method of preoxygenation. Obviously, if the 8DB/60 sec method of preoxygenation clears the system used and the physiologic hurdles, then it will fulfill efficacy and efficiency criteria for being the best method of preoxygenation.

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Anesthetic Preconditioning

Not Just for the Heart?

THE observation that brief episodes of ischemia in the heart, occurring before a subsequent longer interruption of blood flow, provides protection against dysfunction and necrosis has been termed *ischemic preconditioning*.[1] The protection is well described in a variety of animal models as well as in clinical settings, and it is not a trivial effect. In models of stunned myocardium in which dysfunction persists for hours or days after ischemia/reperfusion, preconditioning can virtually prevent contractile dysfunction. In models of infarction, the necrotic area within a region at risk can be reduced by 60–75%. Clinically, this can mean the difference between sustained inotropic support in the postoperative period or considerably greater functional capacity in patients after discharge. The study by Novalija *et al.*[2] in this issue of ANESTHESIOLOGY continues the series of rather remarkable studies demonstrating that brief exposure to a volatile anesthetic, in this case sevoflurane, can mimic a brief ischemic insult and thereby precondition the myocardium, decreasing reperfusion damage and dysfunction.

The preconditioning protection observed with brief ischemia seems to be mediated by release of adenosine—it can be duplicated by adenosine administration,[3] prevented by blockade of adenosine receptors[4] and by inhibition of 5′-nucleotidase,[5] which is responsible for generation of adenosine. Adenosine binds to its receptor (A1 and possibly A3), and *via* a G-protein–linked process, increases protein kinase C (PKC) activity. The resulting phosphorylation of the adenosine triphosphate (ATP)-sensitive K channel (K_{ATP}) results in the channel being less sensitive to inhibition by ATP.[6] Physiologically, the K_{ATP} channel opens when intracellular ATP stores are depleted, permitting K^+ to flow out of the cell, thus restoring the resting membrane potential and decreasing activity. This channel plays an important role in regulating the tone of vascular smooth muscle by causing hyperpolarization and relaxation when oxygen delivery results in decreased ATP production. In the heart, the K_{ATP} channel is not normally active, but its sensitivity to inhibition by ATP is decreased with PKC activation. When K_{ATP} channel activity is increased, the cardiac action potential shortens, accompanied by a mild negative inotropic action and remarkable protection against a subsequent sustained ischemic or hypoxic insult. Preconditioning can also be elicited by activation of a variety of ligand receptors (endothelin, δ-opiate, α-adrenergic) that increase PKC activity, as well as by drugs such as K_{ATP} channel openers (*e.g.*, nicorandil or cromakalim). Of special relevance to anesthesiology, brief exposure to a volatile anesthetic can activate cardioprotection against a subsequent prolonged ischemia that is identical to ischemic preconditioning in that it can be inhibited by blocking K_{ATP} channels or adenosine receptors.[7–12] Similar effects of ischemia and isoflurane and sevoflurane in preconditioning have also been demonstrated in isolated human atrium.[13,14]

Although initially attributed to K_{ATP} channel effects on the sarcolemma, the remarkably profound protective effect exceeds the modest electrophysiologic changes. Furthermore, preconditioning actions are observed in the absence of alterations in electrophysiologic behavior.[15–17] However, in addition to their location on the myocyte membrane, K_{ATP} channels are located in the mitochondrial inner membrane, where they seem to regulate mitochondrial volume as well as the massive electrical and proton gradient that powers ATP synthesis. Preconditioning can be initiated by the opening of mitochondrial K_{ATP} channels and prevented by their blockade.[18,19] The model that emerges is one in which surface receptor activation turns on PKC activity, resulting in activation of mitochondrial K_{ATP} channels to pro-

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vide protection to myocytes.[17,20] PKC activity is actually mediated by a large class of ubiquitous phosphorylating enzymes that have varying requirements for activity (G proteins, phospholipids, diacylglycerol, and increased intracellular Ca^{2+}). A recent study suggests that a particular isoform (PKC-δ) is the type that is translocated to the mitochondria to activate K_{ATP} channels located there.[21] Evidence is accumulating to document the functional role of K_{ATP} channels in mitochondria, suggesting that channel activation leads to a decrease in the voltage gradient and a decrease in Ca^{2+} accumulation.[20,22,23] However, the exact pathway by which mitochondria and cells are protected remains to be defined.

Although demonstrating the cardioprotective effect of sevoflurane, the more newsworthy result in the article by Novalija *et al.* may be that this protection occurs not only in cardiac myocytes, but also extends to the endothelium of the coronary vasculature. A study dating back to the early 1990s demonstrated that a brief episode of ischemia also protects the functional integrity of the endothelium, demonstrating that the vasodilating capacity of the coronary vasculature was retained in hearts that were ischemically preconditioned.[24] The ischemic preconditioning of the endothelium also seems to be mediated, at least in part, by adenosine receptors and K_{ATP} channels.[25] In addition, further studies have demonstrated that structural integrity of endothelial cells is better maintained after preconditioning.[26] It is interesting that these structural studies of endothelial cells subjected to ischemia/reperfusion show marked mitochondrial swelling, an effect not observed in preconditioned endothelium.[26] In addition, the structural evidence of protection seemed to last for up to 1 month. Further studies are required to demonstrate more precisely how volatile anesthetic preconditioning compares with ischemic preconditioning of both myocytes as well as the endothelium.

One of the major features of endothelial protection by brief ischemia or anesthetics is the ability to generate nitric oxide and mediate vasodilation.[2,25] The presence of nitric oxide is not only important for regulating vascular tone, but also for its ability to prevent leukocyte adhesion and migration into reperfused tissues. Endothelial nitric oxide production can prevent recruitment of polymorphonuclear leukocytes (neutrophil) into ischemic regions.[27–29] Because neutrophil accumulation and infiltration clearly contributes to the postischemic "no reflow" phenomenon, contractile dysfunction, and myocardial necrosis, prevention of their accumulation by maintained endothelial integrity is critically important. In addition, ischemia can induce expression of a variety of cell surface markers (P-selectin, intercellular adhesion molecule-1) and inflammatory mediators (tumor necrosis factor-α) that also contribute to neutrophil accumulation.[30] If endothelial protection by anesthesia includes the prevention of the expression of the cell adhesion molecules such as P-selectin, the endothelial protection provided by the anesthetics during ischemia may have profound implications with regard to maintaining vascular integrity during the stressful period of reperfusion. Although there are conflicting data concerning the role of free radicals as well as the exact cellular biochemical pathways involved, the studies with regard to anesthetics suggest that there may be remarkable protection provided by these agents.

The good news for anesthesiologists is that volatile agents that we routinely use seem to provide a significant protective effect, not only on the myocardium, but on the vascular endothelium. If endothelium in other vascular beds shows similar degrees of protection, then the use of volatile anesthetics may provide important protection for a far wider variety of tissues. Over the next few years we can look forward to more detailed explanations of the pathways of anesthetic preconditioning, as well as the extent to which other tissues share the beneficial effects observed in the myocardium. Considerable effort will no doubt be expended to develop pharmacologic means to maximize protection, perhaps seeking other drugs that can provide the similar kind of protection provided by volatile anesthetics. In the mean time, we can be assured that at least certain anesthetic agents seem to precondition and protect, but much work remains to be performed to define fully the extent of protection.

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The Legal System and Patient Safety: Charting a Divergent Course

The Relationship between Malpractice Litigation and Human Errors

TO sustain a claim of medical malpractice, a plaintiff must show a pre-existing duty on the part of the physician and then a breach of that duty that causes the plaintiff damages.[1] The duty arises most commonly when a physician–patient relationship is formed and requires the physician to provide patient care that a similarly situated practitioner in good standing would provide in the same clinical circumstances.[2] Care falling below this standard represents a breach of duty; if the breach causes the patient injury, the physician is liable for damages. Plaintiff claims of a breach of the standard of care and causation generally must be supported by expert testimony.[3] However, in this issue of ANESTHESIOLOGY, Edbril and Lagasse[4] report data that indicate adjudication of medical malpractice claims may not follow these legal precepts. They find that upon review of anesthesia care by anesthesiologists provided in an academic setting, substandard care was unrelated to litigation risk and adverse malpractice adjudication. Thus, the standard of care defined by anesthesiologists, as mandated by the legal system, does not seem to comport with litigation risk and malpractice adjudications against anesthesiologists.

This study adds to the growing literature indicating that the legal system may not be adjudicating malpractice claims according to the legal rule. Using data from the Harvard Medical Practice Study, Brennan *et al.*[5] found that malpractice liability was only correlated with severity of patient injury, not negligence. Furthermore, in their seminal work from the American Society of Anesthesiologists closed claims study, Cheney *et al.*[6] found that more than 40% of patients who were provided appropriate, nonnegligent care as defined by neutral anesthesiologists still collected payments from these anesthesiologists. But physicians also disagree with jury verdicts that hold for the defendant physician. Liang[3] reported that a homogeneous sample of neutral anesthesiologists in an academic center disagree with jury verdicts, even in some cases in which juries found no defendant anesthesiologist negligence. Radiologists have shown similar behavior.[7] These findings are compelling because it has also been reported that lay persons, without medical or legal knowledge, are statistically better able to predict jury verdicts than anesthesiologists, who are legally informed as to the standard of care through their clinical training.[8] Even studies that report that the tort system assesses negligence appropriately find that non-negligent physicians are still required to pay malpractice judgments against them.[9,10] Thus, one major goal of the medical malpractice tort system—to provide efficient and appropriate physician incentives to render nonnegligent care to minimize patient injury—seems to be unfulfilled by the traditional tort system.

Furthermore, Edbril and Lagasse report that anesthesia care deemed negligent by the study's reviewers did not result in patient suit or malpractice system compensation. This result, too, is consistent with results from the Harvard Medical Practice Study, which reported that very few negligently injured patients are compensated by the tort system.[11–13] Hence, the other major goal of the malpractice system— compensation of patients who are negligently (as defined by the legal standard) injured—also seems to be unfulfilled. These conclusions raise the possibility that the billions of dollars spent on the malpractice system annually[14] may not be an effective allocation of social resources to minimize patient injury, maximize patient safety, and compensate injured patients.[3]

Edbril and Lagasse suggest that to combat these legal system weaknesses, a peer-review process should be used to assess provider negligence. However, this approach has significant difficulties. Hindsight bias plays a tremendous role in *ex post* review of clinical circumstances[15–17]; thus, negligence may be overestimated. In-

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deed, Edbril and Lagasse's characterization that all adverse events are somehow a result of "error" seems to reflect this bias. Most researchers in this field would not characterize adverse events in this manner because even appropriate provider actions may result in untoward clinical results. This is best exemplified by Edbril and Lagasse's own definition of system error, including accidental occurrences that result from performing a technique properly, equipment failure despite proper use, miscommunication while following established protocol, inability to diagnose a disease process because of limitations of presently available screening and monitoring standards, inability to treat a disease process because of limitations in present standards of care, and inability to meet the demands for resources of equipment or personnel. These "system errors" accounted for 88% of the total errors reported, none of which are preventable. We do not believe these are errors at all and instead represent untoward events that are not preventable. We must emphasize that the human errors that resulted in a disabling injury as reviewed by Edbril and Lagasse form the basis of their report, not the system errors. Finally, it is difficult to determine whether such a peer-review system would result in cost savings relative to the current litigation system. Attorneys presently reject most requests for malpractice claim representation; reducing such barriers to facilitate plaintiff claim filing through peer review or other low-cost administrative mechanisms may consume and even surpass the cost savings from avoiding court.[14,18,19]

Other investigators have suggested the use of clinical practice guidelines.[20] The use of clinical practice guidelines is fraught with difficulty at the outset because these guidelines are not recognized legally as the standard of care.[20] Furthermore, guidelines, similar to a peer review process, assume there is a single standard of care for all clinical circumstances; this may be too narrow a viewpoint.[21] Significant discordance between evaluating physicians has been reported when assessing clinical scenarios,[7,8,22,23] reflecting the well-known variability phenomena in clinical care.[24,25] The standard of care consensus in the study by Edbril and Lagasse most likely reflects homogeneity of a single anesthesiology department, which was the sole source of reviewers. The vast majority of practice guidelines are also formulated by consensus rather than double-blind study and may conflict in their recommendations.[26] An excellent example of a clinical practice guideline with such problems is the pulmonary artery catheterization guideline published in ANESTHESIOLOGY.[27] This guideline does not provide objective evidence to support the benefits versus the risks of pulmonary artery catheterization, but merely lists the pros and cons regarding catheter use and clinical scenarios in which some practitioners have found them useful. Guidelines are also limited by the source from which they emanate,[28] which may reflect specialty turf battles rather than clinical indication or medical appropriateness. Finally, these guidelines are often outdated as soon as they are published and, in any event, are manipulated by local physicians and managed care organizations before being put into use.[29]

The reported results have significant implications for patient safety efforts. Instead of providing anesthesiologists with a clear incentive to provide nonnegligent care, the uncertainty of legal adjudication in practice may result in a heightened level of defensive medicine and paradoxically an *increased* risk of patient injury.[3,8,30] Although there is significant debate as to whether the legal system actually induces defensive medicine,[30] other mechanisms that instead induce physicians to proactively adopt behaviors that minimize patient injury and maximize patient safety would be a far better way to spend current malpractice system dollars.

To fulfill the goal of maximizing patient safety, a commitment to using these dollars to focus on evidence-based medicine and patient safety outcomes is essential.[31] A concurrent and necessary step would be to provide for immunity against legal discovery of data from internal and external safety reporting systems to encourage error reporting. Currently, legal incentives and potential discovery of this information in tort suits substantially chill reporting medical error.[30,31] In combination, open reporting of medical error and resources devoted to studying the issues so identified would provide significant progress toward systemically maximizing patient safety.[30] Similarly, accreditation organization support *via* data standardization, nonpunitive reporting approaches, and education would begin the process of broad, interprovider analyses that may yield insights into methods to maximize patient safety and minimize error.[30]

To accomplish the goal of compensation, one possible mechanism could be the use of a workers' compensation-type system for patient injury caused by medical error, with direct patient suits available only for situations of reckless provider actions. For the small minority of direct patient suits involving such actions, court-appointed experts representing the court, not the litigants, would be far more appropriate, eliminating financial bias from an expert's opinion. A similar system has recently been proposed for the aviation industry.[32] This approach

would focus on corrective action to improve patient safety, reduce the threat to clinicians of reporting errors, and still deter inappropriate, high-risk behavior.

Overall, Edbril and Lagasse's work highlights for the anesthesia community the significant weaknesses of the traditional tort system and the incentives it creates.[30,31] Their work also puts into stark relief the fundamental need for new methods to appropriately affect physician behavior so that the health delivery system can continuously improve in its efforts to provide safe, effective medical care while minimizing medical error and patient injury.[30]

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