Anesthesiology 2002; 96:252

The Steep Dose–Response Curves of Anesthesia

To the Editor:—The critique by Eger *et al.*[1] on the article by Eckenhoff and Johansson[2] concerns combining the dose–response curves of several ion channels to make them steeper. The slopes of the *in vivo* studies are steep, whereas those of the *in vitro* studies are gradual. Both groups anticipate that when several binding sites among ion channels are combined, the dose–response curves may become steeper. The computation procedures were different. However, all dose–response curves become steep when plotted as quantal responses (hit or no-hit). In anesthesia, the animal responses are typically plotted as anesthetized or nonanesthetized (quantal response).

The Hill equation starts with the following form, where n molecules of an anesthetic A bind to the receptor R:

$$R + nA \rightleftarrows RA_n \quad (1)$$

The binding number n is designated as the Hill number, n_H. Hence, the Hill number should be an integer value. However, integer values are seldom found. The disagreement between n_H and the real binding number was recognized when Archibald Hill measured the oxygen binding to hemoglobin in 1913.[3] Hemoglobin has four oxygen binding sites, but the Hill number never reached three. This is because the first oxygen binding changes the binding affinity of the succeeding oxygen molecules.

The Hill equation does not count partially anesthetized intermediates:

$$RA_1 \cdot RA_2 \cdots RA_{n-1} \quad (2)$$

Therefore, n_H does not represent the binding numbers. Large Hill numbers indicate that unspecified multiple binding sites are acting with high cooperativity. Therefore, it is termed "cooperativity parameter."

Large Hill numbers are not limited to quantal responses. My colleagues and I[4] found large Hill numbers in brine shrimp, *Artemia salina*. These aquatic creatures swim at random with changing directions when placed in the artificial sea water. Their movement slows when anesthetics are introduced into the system. We digitized the swimming distances every 0.5 s for 30 s using a video camera and a computer system.[4] Despite the fact that the plot was produced by the averaged swimming distances in a unit of time, which is not quantal, we found large Hill numbers: enflurane, 11.9; halothane, 14.8; isoflurane, 13.5. The continuous response, identical to the channel studies, produced two-digit Hill numbers.

Regardless of quantal or nonquantal responses, the dose–response curves of living animals are extremely steep. So are the grouped dose–response curves of *in vitro* studies.[5] It indicates that anesthetics act at numerous sites with highly cooperative mode. The pressure reversal of anesthesia[6] shows that all systems are equally affected, including enzymes, channels, proteins, lipid membranes, and others. Anesthesia is a symptom complex and cannot be defined. It may be futile to designate a limited number of ion channels as the anesthetic action sites. All channels and all receptors may participate in anesthesia.

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Eliminating Blood Transfusions: Don't Forget Hypotensive Anesthesia

To the Editor:—In a recent reply to a letter to the editor,[1] Drs. Spahn and Casutt state that the "efficacy [of hypotensive anesthesia] has been challenged recently" and cited an article in which I was a coauthor.[2] I believe they have misrepresented the thrust of the paper, which was to demonstrate the safety of hypotensive epidural anesthesia in elderly higher risk patients. Although we found no significant difference in blood loss between groups (mean arterial pressure [MAP], 50 *vs.* 65 mmHg), this unexpected finding was addressed in the Discussion. I believe that this probably reflected "imprecision in the measurement technique." In a previous study in which blood loss was more carefully measured and surgical assessments of bleeding were recorded, there was a small but statistically significant difference in blood loss between 50 and 60 mmHg MAP during primary total hip replacement (THR).[3]

In primary total hip replacement, there is a clear relation between MAP and intraoperative blood loss. The results of four randomized studies[2,3,5,6] performed in the 1990s using epidural or spinal anesthesia clearly show that intraoperative blood loss is related to MAP with most of the benefits occurring when pressures are reduced within the normotensive range (MAP, 90–100 mmHg). Reduction in MAP below 60 mmHg produces less-dramatic benefits.

The authors also state that "a majority of surgical bleeding is venous bleeding." This may be true for some procedures, such as liver resection, but is not so for the majority of surgical procedures. We studied this in primary total hip replacement and found that central venous pressure had no relation to intraoperative bleeding ($r^2 = 0.005$).[3] Venous blood tends to be blue; arterial blood tends to be red. One merely has to look into most surgical wounds to realize that the

majority of bleeding is arterial. I agree with Klowden *et al.*[4] that it is time for the anesthesia community to stop criticizing hypotensive anesthesia and start practicing the technique.

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In Reply:—We appreciate the comment of Dr. Sharrock to our letter[1] and review article.[2] Four randomized studies are cited in which blood loss was reduced by hypotensive anesthesia.[3–6] In three studies with a total of 425 patients,[3,4,6] the reduction of blood loss was 13–130 ml without reduction of allogeneic blood transfusion. In one small study with 30 patients, blood loss was reduced by 500 ml, and also a reduction of allogeneic blood transfusion was observed.[5] In general, the blood sparing potential of hypotensive anesthesia is limited.

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Succinylcholine in the Intensive Care Unit

To the Editor:—The review by Gronert[1] is important because hyperkalemic cardiac arrest after succinylcholine is associated with significant mortality. Although only 18 cases of cardiac arrest associated with receptor up-regulation in the intensive care environment have been reported,[1,2] we believe that the incidence is much higher.

An intensive care unit postal survey conducted in the United Kingdom in 1998 revealed that 68.7% of respondents (intensive care unit clinical directors) would administer succinylcholine to patients typically at risk of critical illness polyneuropathy.[3] Therefore, despite the professional seniority of the respondents and the so-called textbook case of the patient at risk of critical illness polyneuropathy (prolonged intensive care unit stay after an episode of severe sepsis and complicated by failure to wean from ventilation), for more than two thirds of the respondents, succinylcholine was still the muscle relaxant of choice for emergency intubation.[3]

Succinylcholine is often administered to patients with receptor up-regulation in the context of respiratory failure to facilitate intubation. These patients often have multiple reasons to explain the development of cardiac arrest (*e.g.*, severe hypoxia and hypercarbia with high endogenous catecholamine secretion), and physicians simply may not recognize that succinylcholine has been the causative agent. In addition, of course, after a case report describing a rare event has been published, editors are reluctant to add other descriptive series to the literature.

This would suggest that hyperkalemic cardiac arrest associated with receptor up-regulation in the intensive care unit patient and succinylcholine administration may be underreported, and the mortality may be much higher than the reported 18.7%.[1] It is hoped that a review of this nature will serve to highlight the importance of this issue.

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In Reply:—Biccard and Hughes factually support their proposal. Overall evaluation implies that succinylcholine should not be used in intensive care unit patients with bed rest beyond 1 week (disuse atrophy aggravated by other factors) or with administration of nondepolarizers beyond 5 days (pharmacologic denervation).

Biccard and Hughes graciously ignored my failure to cite their reference.[1] Other work not cited further emphasizes the risk of altered skeletal muscle leading to sudden unexpected cardiac arrest at induction of anesthesia:

1. Hyperkalemic arrest and brain death occurred in a very ill 54-yr-old man given succinylcholine on his 35th hospital day, when recovery from quadriplegia of 14 months' duration was incomplete.[2] Plasma potassium was 9.8 mEq/l; he died 6 days after resuscitation.
2. Three obstetric patients with prolonged bed rest, given magnesium and ritodrine, had apparent hyperkalemic arrest when given succinylcholine. The mechanism is uncertain, but disuse atrophy was present, preanesthetic creatine kinase concentrations were increased, and membrane responses were perhaps altered by drug therapy.[3]
3. Hyperkalemic asystole occurred in a child with Becker dystrophy within 3 min of exposure to halothane (no succinylcholine), with 250,000 IU creatine kinase.[4] Brain death occurred eventually.

Inclusion of the succinylcholine-related data[1–3] in table 1 of my article[5] adds one denervation patient who died,[2] two surviving intensive care unit patients,[1] and three surviving miscellaneous category patients.[3] New totals for the category of receptor up-regulation: 70 patients, 78 arrests, 9 deaths, and mortality now 11.5% rather than 11.1%. Hopefully, this mortality can be avoided.

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Aprotinin and Reduced Epinephrine Requirements in Orthotopic Liver Transplantation

To the Editor:—We read with interest the recent article by Molenaar *et al.*[1] regarding aprotinin potentially reducing the need for vasopressors during orthotopic liver transplantation. We commend the authors for their work, but have several comments and questions. Although we accept the finding of a statistically significant difference in epinephrine requirements in the aprotinin treated groups, we question the clinical significance of a 50-μg difference in a liver transplant population. We also disagree that the authors demonstrate this reduced vasopressor requirement to be independent of the decreased transfusion requirements in these groups. This article reports a subgroup of a previously published, larger study.[2] Perusal of the original article shows that the time of the greatest difference in blood transfusion requirements was the postreperfusion period, the time at which the current authors found their greatest intergroup differences in epinephrine requirements. The authors contend that because central venous pressures 5 min before and 30 min after reperfusion and hemoglobin values 5 min after reperfusion were equivalent between the groups, intravascular volume and fluid resuscitation were also similar between groups. We believe that during liver transplantation, central venous pressures may not accurately reflect fluid status, particularly after reperfusion. Pulmonary capillary wedge pressure might be a more appropriate measure in this setting. Regarding hemoglobin, it is well-recognized that blood loss may not be reflected in the hemoglobin concentration. Finally, the equivalence of values at a few time points does not exclude short-term fluctuations, such as blood loss requiring pressor support, before transfusion.

Regarding the design of the study and the analysis of the results, we would be interested to know what selection criteria were used to identify this subgroup from the original study population. Second, we would be interested to know which variables were log transformed to ensure normality. Third, we note from table 3 of Molenaar *et al.*[1] that the requirements for epinephrine in the placebo group are extremely skewed, suggesting one or two high-requirement outliers, and wonder if this may have influenced the final analysis.

Finally, the authors postulate that their results are explained by aprotinin-mediated inhibition of the kallikrein-induced release of bradykinin, despite achieving adequate doses for inhibition only in the high-dose group. Ironically, the high-dose group experienced the same magnitude of hypotension at recirculation as the patients who received placebo. Observing that the low-dose group was normotensive immediately after reperfusion, the authors suggest that kallikrein inhibition can be obtained at lower concentrations than previously reported. This may be excessively speculative in the absence of appropriate measures of kallikrein activity. Other potential mechanisms of action for aprotinin[3] include actions on ischemia–reperfusion injury, which may be of relevance during liver transplantation.

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In Reply:—We thank Drs. Jankowski, Findlay, and Plevak for their interest in our work and the editor for giving us the opportunity to respond to their remarks and questions. In our response, we will follow the same order as in the letter by Jankowski *et al*.

We fully agree that a reduction of 50 μg epinephrine alone is not the main indication for administering aprotinin to patients undergoing orthotopic liver transplantation (OLT). The main objective of using aprotinin during OLT is to reduce transfusion requirements. However, aprotinin may have additional benefits. It is beyond doubt that aprotinin is an inhibitor of kallikrein. As discussed in our article, there is substantial evidence that activation of the kallikrein–kinin system plays a role in the hemodynamic changes after graft reperfusion in OLT. In our study, we have shown that aprotinin improves hemodynamic stability. This indirectly adds clinical evidence to the current literature that activation of the kallikrein–kinin system is involved in the hemodynamic changes during OLT. As we have suggested, further evidence could come from the measurement of plasma kallikrein–aprotinin complexes.

At this stage, we cannot completely rule out that differences in blood loss have also contributed to the observed differences in vasopressor requirement between the placebo and aprotinin groups. However, we have no arguments to believe that the correction of blood loss was less adequate in the placebo group and thus could entirely explain the use of more epinephrine to maintain adequate perfusion pressure. Jankowski *et al.* suggested that pulmonary capillary wedge pressure might be a more appropriate reflection of the fluid status. Therefore, we have performed a retrospective analysis of pulmonary capillary wedge pressure in our patients at 5 and 30 min after reperfusion. No significant differences in mean pulmonary capillary wedge pressure values were found at these time points, confirming our conclusions about fluid status. Our position is also supported by a recent abstract from Jankowski's own group, reporting similar findings in a placebo-controlled study in patients undergoing OLT.[1] In this abstract, significantly more vasopressor and inotropic infusions were reported in the placebo group, compared with the aprotinin group. The authors concluded that aprotinin may result in more stable hemodynamics during OLT and that part of this effect could be *independent* of its effects on blood loss.[1]

Jankowski *et al*. asked about the criteria that were used to select the subgroup of patients included in our study. They are correct that these patients were part of a larger, multicenter project. The selected center was the largest center participating in the EMSALT study and therefore enrolled the largest subgroup. No preselection or subselection was performed. The reason why we performed the study in this center only is explained by a combination of factors. First, all patients in this center received pulmonary artery catheters, which, in some European centers, is not standard practice during OLT. Second, the limited number of anesthesiologists and the uniform practice with respect to control of hemodynamics, as described in the article, contributed to the decision to perform this study on intraoperative hemodynamics and vasopressor use in one center only.

The following variables were found to be nonparametrically distributed and therefore log transformed to perform two-way analysis of variance with correction for repeated measures: cardiac index, systemic vascular resistance index, and mean pulmonary artery pressure. By definition, median values and the Kruskall-Wallis test are not influenced by outliers. Therefore, the skewness of our data on epinephrine requirement did not affect our analysis.

Our conclusion that concentrations of approximately 100 KIU/ml may be sufficient was not based on differences in blood pressure after reperfusion, as was suggested by Jankowski *et al.*, but on the lack of difference in vasopressor requirement between the regular and high-dose groups. We disagree with Jankowski *et al.* that we have ignored other mechanisms of action that could be involved as well. In the Discussion of our article, we mentioned that aprotinin ameliorates the systemic inflammatory response and the release of proinflammatory cytokines in patients undergoing cardiopulmonary bypass. However, whether these or other effects are clinically relevant in liver transplantation and contribute to a reduction of ischemia–reperfusion injury is still unclear. Unlike the effect of aprotinin on the kallikrein system, a positive effect of aprotinin on ischemia–reperfusion injury in liver transplantation has been debated.[2] Although graft survival may be improved, we have not been able to demonstrate a significant reduction in peak concentrations of aspartate aminotransferase and alanine aminotransferase after transplantation in patients who received aprotinin, compared with placebo.[3] This subject deserves more research.

I. Quintus Molenaar, M.D., Bruno Begliomini, M.D., Gerardo Martinelli, M.D., Hein Putter, Ph.D., Onno T. Terpstra, M.D., Ph.D., Robert J. Porte, M.D., Ph.D.* *University Hospital Groningen, Groningen, The Netherlands. r.j.porte@chir.azg.nl

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BIS Monitoring: There's More to It Than Awareness

To the Editor:—We read with interest the recent article by O'Connor *et al.*[1] regarding the lack of cost effectiveness of the Bispectral Index (BIS)® monitor (Aspect Medical Systems, Natick, MA) when used to prevent awareness during general anesthesia. In arriving at their conclusion that the BIS® monitor is an expensive way to prevent awareness during anesthesia, the authors admonished that

their cost effectiveness analysis was justified only if the BIS is used solely to reduce the risk of awareness. Also of interest, in the same issue of the Journal, is the article by Röpcke *et al.*,[2] which examines the concentration–response relation of desflurane to the electroencephalogram as measured by the BIS during surgical stimulation. This article, along with many others,[3–6] clearly shows that the BIS has a much broader application in anesthesia practice than solely to prevent awareness.

To use the BIS® monitor only for the purpose of preventing awareness would be comparable with using a blood pressure monitor to prevent hypertension: it is too limited in scope and too narrow in its focus. Blood pressure monitoring allows one to gauge the response of the sympathetic nervous system to anesthesia, surgery, and other intraoperative factors. It is useful over a wide range of values in helping the practitioner to make decisions regarding the care of the patient. The value provided by the monitor must be interpreted in the context of the clinical situation. Similarly, the BIS® monitor measures the response of the frontal electroencephalogram to anesthetics as influenced by surgical stimulation and other conditions. Analogous to the blood pressure measurement, any given BIS value must be interpreted in the light of the clinical scenario. One cannot make an appropriate interpretation if the value is taken out of context of the patient's condition.

The question of whether the BIS® monitor is cost effective in general must await the determination of its overall usefulness. The BIS® monitor is the first broadly applicable clinical tool to measure and transform the electroencephalogram into a readily interpretable form that correlates with anesthetic dosage and measures the individual patient response to anesthetics. Given the current growth of information about pharmacogenomics[7] and the importance of individualizing dosages and drugs, any device that allows us to monitor the unique response that each patient has to varying anesthetic doses will be useful. We hope that articles such as that by O'Connor *et al.*[1] with their rather narrow focus will not provide the justification for those readers who would hastily dismiss, without further investigation, the potential of new devices such as the BIS® monitor.

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Pulse Oximetry and BIS Monitoring

To the Editor:—Although it is not discussed by O'Connor *et al.*[1] in their recent article, the scientific literature about pulse oximetry is perhaps more pertinent to the use of Bispectral Index (BIS) monitoring than screening preoperative chest films, the straw man they erect in their argument. Specifically, the studies by Moller *et al.*[2,3] of more than 20,000 patients failed to show an effect on "cardiovascular, respiratory, neurologic or infectious" outcomes (including death) or length of hospital stay from the use of pulse oximetry. However, in responses to a questionnaire administered to anesthesiologists taking part in the study, 80% of anesthesiologists said that they felt more "secure" using pulse oximetry, and 18% said that pulse oximetry had helped them to manage a particular incident during an anesthetic procedure. In their editorial accompanying these studies, Orkin *et al.*[4] comment, "While aids to vigilance cannot independently engender greater safety (*i.e.*, improved outcome) their use provides comforting backup to clinical observation, allows dedication of attention to other matters and reassures our fallible reasoning with online data during critical periods of the anesthetic."

Bispectral Index monitoring, like pulse oximetry, is an "aid to vigilance." By itself, it cannot prevent or treat awareness during anesthesia. However, a quick glance at the BIS® monitor (Aspect Medical Systems, Natick, MA) to confirm that it is overwhelmingly likely that the patient is asleep during a period of tachycardia or increased blood pressure permits the anesthesiologist to quickly focus her or his attention elsewhere. The comment of O'Connor *et al.*[1] that "there are cases of awareness in the Aspect database" is clarified, in this context, by the fact that there are no cases of awareness in the Aspect database with a BIS measurement lower than 65.[5] Should BIS monitoring be made a standard of practice in anesthesia? The arguments for and against are no more powerful than they are for pulse oximetry.

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In Reply:—We are pleased that neither Drs. Spackman and Abel nor Dr. Gage disagree with the fundamental conclusions of our article—that the more rare awareness is, the more difficult it is to prove that the BIS® monitor (Aspect Medical Systems, Natick, MA)—or any other depth of anesthesia monitor—prevents it, and the more expensive it is to use for this purpose. Dr. Gage's reference to the study that failed to demonstrate a benefit to the use of pulse oximetry is further evidence of how difficult conducting such studies in the clinical setting can be.

We are wary of the pulse oximetry analogy for a variety of reasons, not the least of which is that reasoning by analogy can be treacherous. The value of analogy depends critically on underlying similarity, and analogies may mislead if the similarity is not present. Pulse oximeters measure a well-defined physiologic variable; their performance can be calibrated with other instruments available to practitioners. No such calibration exists for the BIS® monitor. Pulse oximeters are used in a fashion different from the BIS® monitor. The majority of the use of pulse oximetry in the operating room is to detect hypoxia; only rarely is it used to titrate other therapies (such as fraction of inspired oxygen, positive end-expiratory pressure, and others). The BIS® monitor, when used as advocated, is used to titrate the anesthetic itself, trading between deeper levels of anesthesia and lower drug acquisition costs, improved recovery, and fewer side effects. To realize these benefits, practitioners deliberately conduct an anesthetic that provides a state that is closer to awake than to asleep, and that may paradoxically increase the risk of awareness in the patient. Of course, it is difficult to prove or disprove this conjecture for the reasons we explored in our article.

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