

## Lies, Damn Lies, and Statistics

*To the Editor:*—Mark Twain may have overstated his distrust of statistics, but the issue of interpretation of statistics comes to the forefront in the study by Arbous *et al.*<sup>1</sup> and the accompanying editorial by Warner.<sup>2</sup> As the results of the study are discussed, Arbous *et al.* jump from describing *associations* between outcomes and management factors, to cause-and-effect descriptions: “it was found . . . a checklist decreased the risk,” “the reversal of the effect of opiates and muscle relaxants seems to decrease the risk,” and so on. Warner embraces these ersatz “risks” as showing “anesthetic management processes to dramatically reduce perioperative mortality.”

When one looks at baseline characteristics of the study and control groups, there are, as the authors note, huge differences in the categories of urgent/emergent nature, time of day procedure performed, and American Society of Anesthesiologists physical status. In fact, 40% of the study cases were rated American Society of Anesthesiologists V—not expected to survive for 24 h, with or without surgery (regardless of anesthetic management). If we accept that a large proportion of the study cases carry greater risk by virtue of their physical status and the emergent nature of the injury or disease process, *and* that urgent/emergent cases generally account for all the outside working hour cases, differences in anesthetic management processes between the two groups seem more coincidentally associated than causative. Were equipment checks performed less frequently in the study group because of the emergent nature of the cases? Was the lower percentage of two providers at termination of a procedure simply a function of the

outside hour the procedure was performed? Was the lower reversal rate of opiates and muscle relaxants due to the fact that the study group was sicker, undergoing more complex procedures, and so remained intubated postoperatively? Did the study groups receive fewer narcotics and local anesthetics for postoperative pain because of their moribund (comatose?) or unstable condition?

This is not to suggest that anesthesia practice factors do not affect morbidity and mortality; some of the anesthetic practice factors in this study may one day be proven to be causative. But let us appreciate the method of this study for what it is: a tool to identify associations. Those associations then need to be further studied to identify them as causative or coincidental. Cars manufactured on Monday do not have more problems than others because that day of the week starts with the letter *M*. We need to look for truths, damn truths, and more than associations.

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## References

1. Arbous MS, Meursing AEE, van Kleef JW, de Lange JJ, Spooormans HHAJM, Touw P, Werner FM, Grobbee DE: Impact of anesthesia management characteristics on severe morbidity and mortality. *ANESTHESIOLOGY* 2005; 102:257–68
2. Warner MA: Perioperative mortality. *ANESTHESIOLOGY* 2005; 102:251–6

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## Anesthesia Management and Perioperative Mortality

*To the Editor:*—We read with great interest the recent article by Arbous *et al.*<sup>1</sup> regarding the effect of anesthesia management on perioperative morbidity and mortality. We agree with Dr. Mark A. Warner's observation in the accompanying editorial that this article is remarkable in several ways.<sup>2</sup> In particular, it reassures the reader that there are fundamental anesthetic management practices that may be a part of their practice or are readily introduced into their practice to improve patient outcome by reducing perioperative morbidity and mortality. These are practices that are generally recognized as important. An example of this is the protocol-based equipment check and checklist.

Checking equipment with a protocol and checklist is like Mom and apple pie. It is a practice that is universally recognized as important and, according to Arbous *et al.*, reduced the adjusted odds for anesthesia management risk factors for 24-h postoperative mortality and coma to 0.640 (with a 95% confidence interval of 0.432–0.948) relative to not checking the equipment, checking it without a protocol, or checking it with a protocol but no checklist.<sup>1</sup> This strikes readers as very plausible until they discover, in the Discussion, that equipment failure did not contribute to perioperative deaths.<sup>1</sup> The authors speculate that this risk factor may be a surrogate for characteristics of the anesthetic care team. If it is, surely just requiring protocol-driven equipment check and a checklist will not change the characteristics of the anesthetic care team and may lead to a false sense of security with respect to favorably affecting patient outcome.

Pondering this conundrum led to the recollection that these data have been published before, albeit in a different form.<sup>3</sup> Unfortunately,

this previously published report<sup>3</sup> was not included in the references of the current article,<sup>1</sup> nor were the results of the current article discussed within the context of the results of the previous report. In that previous report, the same authors similarly found that 769 patients died and 42 remained unintentionally comatose within 24 h after anesthesia among exactly the same number of patients (869,483) undergoing anesthesia between January 1, 1995 and December 31, 1996/January 1, 1997. However, unlike in the current report, they used rigorous and well-described criteria and a panel of experts to characterize only 119 of these deaths as somehow anesthesia related. In their former report, they identified anesthetic management factors contributing to the 119 deaths and comas that can be corrected to prevent these adverse events.<sup>3</sup> If the authors knew that 692 of the cases of death and coma in the two reports were not anesthesia related, how could they include them in a case-control study to identify risk factors for postoperative death and coma related to anesthesia management? How is it possible to draw conclusions regarding anesthetic management from cases in which anesthetic management has been determined to be unrelated to outcome? How do the results of the qualitative analysis of cases in which anesthetic management has been determined to be related to outcome<sup>3</sup> compare to case-control analysis of all cases, including those determined not to be related to anesthetic management?<sup>1</sup>

This communication is not meant to diminish in any way Dr. Warner's observation that the anesthetic mortality rate is not only high but also can and must be decreased.<sup>2</sup> Nor do we wish to minimize the importance of factors identified by Arbous *et al.* as contributing to

patient safety.<sup>2</sup> However, we do wish to disabuse practitioners and administrators of the notion that implementing these simple anesthetic management principles will affect the anesthetic mortality rate unless or until a more definitive study of their contribution to anesthetic-related mortality and coma has been reported.

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## Anesthesia Risk Factors Not Proven by Case-Control Study

*To the Editor:*—I applaud Arbous *et al.*<sup>1</sup> for attempting a large multicenter study to identify anesthesia care factors that may cause mortality. However, the design of the study could allow for misleading conclusions. Failure to have controls of similar case type resulted in the conclusions that two anesthesia personnel at emergence, reversal of neuromuscular agents, postoperative pain medication, and no anesthesiologist relief were associated with less mortality.

My previous experience at a trauma center is that patients who die often have long surgery at night when anesthesiologists change shift. After surgery, the patient is kept intubated and transported to the recovery room without need of additional anesthesia personnel. The neuromuscular agents are not reversed, and the patient is often too unstable to receive opiate pain therapy. Proper selection of control cases would show that this method of anesthesia care did not cause the death of the patient.

There is an old joke that oxygen is the most dangerous anesthetic, because all trauma patients who receive only oxygen for major surgery

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## Perioperative Morbidity and Mortality?

*To the Editor:*—While reading the article by Arbous *et al.*<sup>1</sup> and the accompanying editorial by Mark A. Warner, M.D.,<sup>2</sup> I was struck by a few important details and one important comment.

In a case-control study, it is of utmost importance that the controls be carefully matched to the cases to make any inference as to statistically significant differences between the two groups. In the article by Arbous *et al.*,<sup>1</sup> it is obvious that the cases are essentially American Society of Anesthesiologists class IV and V patients (69.8%) who underwent long, urgent operations (63.4%) often of major complexity (39.3%). These cases were individually matched only by sex and age with controls who were usually American Society of Anesthesiologists class I and II patients (78.4%) undergoing shorter elective operations (87.4%) that were almost entirely of minor or intermediate complexity (93.5%).

A small amount of effort might have controlled for these and more characteristics and given us a meaningful set of significant criteria to help anesthesiologists provide safer anesthesia to patients. As it is, the conclusions reached by the article are the equivalent of determining that the difference in taste between wine and vinegar has to do with the use of a cork and the size of the bottle.

In Warner's accompanying editorial,<sup>2</sup> the editor could very well have used this article to show the failings of case-controlled studies and the

## References

1. Arbous MS, Meursing AEE, van Kleef JW, de Lange JW, Spoorans HHAJM, Touw P, Werner FM, Grobbee DE: Impact of anesthesia management characteristics on severe morbidity and mortality. *ANESTHESIOLOGY* 2005; 102:257-68
2. Warner MA: Perioperative mortality: Intraoperative anesthetic management matters. *ANESTHESIOLOGY* 2005; 102:251-2
3. Arbous MS, Grobbee DE, van Kleef JW, de Lange JJ, Spoorans HHAJM, Touw P, Werner FM, Meursing AEE: Mortality associated with anaesthesia: A qualitative analysis to identify risk factors. *Anaesthesia* 2001; 56:1141-53

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die. It is no joke when the lack of proper controls in a study leads to conclusions that will be quoted to change proper anesthesia care. The editorial by Dr. Warner<sup>2</sup> was correct to state that case-control methodology does not prove that these are risk factors. This should have been stressed by Arbous *et al.*

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## References

1. Arbous MS, Meursing AEE, van Kleef JW, de Lange JJ, Spoorans HHAJM, Touw P, Werner FM, Grobbee DE: Impact of anesthesia management characteristics on severe morbidity and mortality. *ANESTHESIOLOGY* 2005; 102:257-68
2. Warner MA: Perioperative mortality: Intraoperative anesthetic management matters. *ANESTHESIOLOGY* 2005; 102:251-2

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importance of understanding the statistics before accepting the conclusions.

My comment comes from reading the editorial views expressed by Dr. Warner. We anesthesiologists enjoy the comparison between what we do and what commercial pilots do. Pilots can boast of a 6-sigma mortality rate, a feat few of us in anesthesia can claim. We steadfastly defend the use of ancillary anesthesia providers who are present alone during the greatest part of the anesthetic period. I wonder if any commercial pilot would even consider turning over the aircraft controls to the flight attendant, even though the plane is on auto pilot at 30,000 ft altitude, with the proviso "just call me if anything goes wrong."

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## References

1. Arbous MS, Meursing AEE, van Kleef JW, de Lange JJ, Spoorans HHAJM, Touw P, Werner FM, Grobbee DE: Impact of anesthesia management characteristics on severe morbidity and mortality. *ANESTHESIOLOGY* 2005; 102:257-68
2. Warner MA: Perioperative mortality: Intraoperative anesthetic management matters. *ANESTHESIOLOGY* 2005; 102:251-2

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## Impact of Anesthesia Management Characteristics on Severe Morbidity and Mortality: Are We Convinced?

*To the Editor:*—We read with great interest the article by Arbous *et al.*<sup>1</sup> Although we commend the authors for designing an ambitious and creative study to address this important topic, we do have several reservations about the study design, interpretation of the results, and hence the conclusion.

Because anesthetic mortality and serious morbidity are rare events, the use of a case-control design is very appropriate. Case-control studies usually include several controls for every case to increase the power of the study and to increase the likelihood that the conclusions will be valid.<sup>2</sup> In this study, the investigators used only one control per case (807 cases *vs.* 883 controls). A higher number of controls would have increased the probability that the controls were a representative sample of the entire cohort.

The main outcome in the study was death or coma within 24 h of surgery, an important and indisputable outcome measure. The limitation of this outcome is that many patients who experience perioperative complications die within days to weeks rather than within 24 h of surgery.<sup>3</sup> Intraoperative management factors may impact their postoperative course and their eventual demise.

We understand that the investigators chose to limit the matching of controls only to age and sex to prevent bias and also to allow them to examine all factors affecting mortality in a multivariate model. The possible flaw with this approach in the context of their study is that American Society of Anesthesiologists (ASA) physical status classification is such a powerful confounding factor that it could have undermined their multivariate model. Most of the patients who died (> 90%) had an ASA physical status of III-V. Fewer than 30% of the control patients had an ASA physical status of III-V (table 1).

This brings into question whether there were enough ASA physical status III-V patients in the control category to validate a multivariate calculation for other factors relating to mortality. This could have been addressed in two ways: The study could prospectively have enrolled only ASA physical status III-V patients, or many more control patients could have been included.<sup>4</sup>

In addition to presenting odds ratios for rare events, it is important to present the number needed to harm. For example, the investigators presented an odds ratio of 10:1 for preventing death by adopting a universal practice of reversing muscle relaxants. We made some assumptions and calculated that the number needed to harm for the entire cohort might be 1 in 25,000. This means that 25,000 people on average would have to have muscle relaxation not reversed to result in one additional death. The odds ratio for preventing death by having

**Table 1. Distribution by American Society of Anesthesiologists Physical Status Classification**

Group	ASA I or II	ASA III-V	Total
Dead (cases)	68	739	807
Alive (controls)	692	191	883
Total	760	930	1,690

ASA = American Society of Anesthesiologists.

two anesthesia providers present for all inductions and emergences was 10:6. This may translate to an even larger number needed to harm than for not reversing muscle relaxants. The cost of providing two anesthesia providers for every anesthetic—no matter how minor the surgery and no matter how healthy the patient—would be staggering and may not result in many lives saved. A similar study focusing only on patients with an ASA physical status of III-V might be more useful in identifying which anesthetic management factors are most important in decreasing the likelihood of death among the sickest patients presenting for high-risk surgery.

Despite our reservations, we appreciate the study of Arbous *et al.* and believe that it raises important issues. In particular, we believe that separating anesthetic from surgical death is a false distinction. This study highlights the contention that multiple aspects of perioperative care and management may impact on postoperative outcome. This is a seminal study that is likely to be extensively quoted. It is important to highlight some of its limitations and to avoid overinterpretation of the findings.

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### References

1. Arbous MS, Meursing AEE, van Kleef JW, de Lange JJ, Spoormans HHJM, Touw P, Werner FM, Grobbee DE: Impact of anesthesia management characteristics on severe morbidity and mortality. *ANESTHESIOLOGY* 2005; 102:257-68
2. Miettinen OSM: The "case control" study: Valid selection of subjects. *J Chronic Dis* 1985; 38:543-8
3. Harrison G: Death due to anesthesia at Groote Schuur Hospital, Cape Town—1956-1987: Part I. Incidence. *S Afr Med J* 1990; 77:412-5
4. Lagasse RS: Anesthesia safety: Model or myth? A review of the published literature and analysis of current original data. *ANESTHESIOLOGY* 2002; 97:1609-17

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*In Reply:*—I clearly appreciate Dr. Robertson's Mark Twain reference and his amplification of the limitations of case-control studies. However, I fear that his impressions of the article by Arbous *et al.*<sup>1</sup> and my editorial<sup>2</sup> are based on isolated statements contained within them. The isolated quotation of statements without appreciation or notation of full context can be misleading. Indeed, my editorial notes that "... a case-control methodology can be used to seek possible but not proven [emphasis added] risk factors." Further, "... the findings in [the Arbous] study support many plausible assumptions." Although I am likely biased, my statements do not seem to qualify as lies, much less as damn lies.

Drs. Avram and Krejcie are, as usual, absolutely correct that all statistical associations found using case-control methodology must be practically assessed in context and then subjected to more rigorous

scrutiny in prospective studies to ascertain their validity. I thank Dr. Schmidt for supporting these contentions.

Finally, and to be perfectly candid, I do not know how to respond to Dr. Ivester's comment on aircraft personnel. My editorial had nothing to do with distinctions between types of anesthesia personnel. Therefore, his comment does not seem pertinent to the current issues unless he disagrees with my statement that "... immediate availability of anesthesiologists to help when needed ... should be seriously considered when seeking opportunities to improve the perioperative outcomes of anesthetized patients." I personally believe that this statement is quite appropriate, important, and relevant to good patient care.

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## References

1. Arbous MS, Meursing AEE, van Kleef JW, de Lange JJ, Spoormans HHAJM, Touw P, Werner FM, Grobbee DE: Impact of anesthesia management characteristics on severe morbidity and mortality. *ANESTHESIOLOGY* 2005; 102:257-68

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*In Reply:*—We would like to express our thanks for the critical assessments of our article “Impact of Anesthesia Management Characteristics on Severe Morbidity and Mortality.”<sup>1</sup> All five letters address the same issue: Can causal associations be addressed in case-control studies, and should controls be fully matched to cases?

Observational studies have a record of successful contributions to medicine in establishing causal relations and increasing knowledge on pathogenesis, etiology, prognosis, and diagnosis (smoking and lung cancer, asbestos and mesotheliomas, long-term propofol infusion and cardiac failure).<sup>2,3</sup> For a rare outcome such as death after anesthesia, a case-control study is a particularly efficient research design.<sup>4-6</sup> Our study, with the extensive collection of information on each anesthetic procedure of cases and controls, was not a fishing expedition, nor did the statistical analysis dredge for associations. It was based on previous knowledge of potential anesthesia management-related determinants of postoperative mortality that had previously been qualitatively addressed but rarely quantified, and on common sense. The risk factors that, in our study, were significantly and independently associated with postoperative mortality and severe morbidity confirm what many anesthesiologists suspect and support our previous knowledge. Like any study, whether observational or interventional, ours only increases the causal probability of previous views and decreases the size of the confidence interval. Consequently, intervention studies will need to confirm what we have found.

The second issue to be addressed is the marked lack of understanding of the principles of the case-control design as expressed in the letters—in particular, the erroneous view that confounding bias is reduced (as completely as possible) by matching of controls to the cases. Three questions should be addressed: (1) Should we have fully matched the controls; (2) can the risk factors in anesthesia management as observed in our study be explained by the fact that the cases were sicker, more frequent emergency cases outside working hours, and so on; and (3) is there evidence for important residual confounding? The answer to all of these questions is no.<sup>7-12</sup>

Controls in a case-control study should represent those at risk of becoming a case; they provide estimates of the background frequency of an exposure (such as anesthesia management-related factors) in individuals who are free of the outcome. Fortunately, cases and controls are different. There are several factors that cause someone admitted to surgery to become a case or stay a control. What is the consequence of attempts to match as completely as possible? A major part of the thus highly selected group of controls would comprise patients who should belong in a museum for being alive. Importantly, it would not have been possible to correct in the multivariate analysis for the matched factors, and it would be unclear which bias we had introduced of unknown factors by matching on a few known factors.

Two authors (Drs. Robertson and Schmidt) specifically raise the question of whether the difference we found in some anesthetic management factors between cases and controls could be explained by the fact that the cases were sicker, more frequent emergency cases outside working hours, and so on. Indeed, in this study, there should be concern that the condition of the patient (American Society of Anesthesiologists physical status classification) and the characteristics of the procedure (emergency, outside office hours) are potential confounders, because patient and procedure factors do influence anesthesia management and also affect outcome. However, rather than extensive matching, the proper way to address this issue in a case-control study is to measure the potential confounders and correct for them in the analysis. This is what we did. Indeed, introduction of important characteristics of patients and procedures did change the risk estimates related to anesthesia management factors, showing

2. Warner MA: Perioperative mortality: Intraoperative anesthetic management matters. *ANESTHESIOLOGY* 2005; 102:251-2

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that they are confounders of the relation. There was, however, a limit to the effect and the number of relevant confounders. In our view, therefore, residual confounding was not an important issue in our study.

Apart from anesthesia management, the American Society of Anesthesiologists physical status classification was obviously and not surprisingly the most important determinant of outcome. The number of patients with American Society of Anesthesiologists physical status III-V among the controls was large enough for proper adjustments in the analysis (23%).

In our study, we planned a qualitative analysis and a quantitative analysis. Both have been published, and they convey fundamentally different information rather than a simple duplication of the same findings as suggested by Drs. Avram and Krejcie.<sup>1,13</sup> It is interesting to compare both reports because they show marked agreement but also demonstrate that qualitative and quantitative analyses are complementary. The qualitative analysis looked at overall anesthetic management with all available information collected, as judged by a panel of anesthesiologists. In lengthy discussions, an opinion was formed about the extent of contribution of anesthesia to the fatal outcome. However, although on overall impression no major anesthesia management factors were found to have contributed to the death in 692 cases, they were included in the case-control study because they contain important information about anesthetic care (measured by an extended questionnaire and the anesthetic form) and reveal information that is difficult to extract in a qualitative analysis.

We hope to have addressed the letters to the editor to the satisfaction of the authors. We also hope that this response helps to support the important role of case-control methods in risk research and to a better understanding of its principles. This is not to neglect the point made by Dr. Warner in the editorial accompanying our findings.<sup>14</sup>

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## References

1. Arbous MS, Meursing AEE, van Kleef JW, de Lange JJ, Spoormans HHAJM, Touw P, Werner FM, Grobbee DE: *ANESTHESIOLOGY* 2005; 102:257-68
2. Rothman KJ, Greenland S: Causation and causal inference, *Modern Epidemiology*, 2nd edition. By Rothman, KJ, Greenland S. Philadelphia, Lippincott-Raven, 1998, pp 93-114
3. Cremer OL, Moons KGM, Bouman EAC, Kruijswijk JE, de Smet AGA, Kalkman CJ: Long-term propofol infusion and cardiac failure in adult head-injured patients. *Lancet* 2001; 357:117-8
4. Miettinen OS: Design of sampling of the base, *Theoretical Epidemiology*. Edited by Miettinen OSM. New York, John Wiley & Sons, 1985, pp 69-83
5. Miettinen OS: The “case-control” study: Valid selection of subjects. *J Chronic Dis* 1985; 38:543-8
6. Rothman KJ, Greenland S: Case-control studies, *Modern Epidemiology*, 2nd edition. By Rothman, KJ, Greenland S. Philadelphia, Lippincott-Raven, 1998, pp 93-114
7. Wacholder S, Silverman DT, McLaughlin JK, Mandel JS: Selection of controls in case-control studies: II. Types of controls. *Am J Epidemiol* 1992; 135:1029-41
8. Wacholder S, McLaughlin JK, Silverman DT, Mandel JS: Selection of controls in case-control studies: I. Principles. *Am J Epidemiol* 1992; 135:1019-28
9. Wacholder S, Silverman DT, McLaughlin JK, Mandel JS: Selection of controls in case-control studies: III. Design options. *Am J Epidemiol* 1992; 135:1042-50
10. Rothman KJ, Greenland S: Matching, *Modern Epidemiology*, 2nd edition. By Rothman KJ, Greenland S. Philadelphia, Lippincott-Raven, 1998, pp 147-61
11. Vandenbroucke JP: When are observational studies as credible as randomized trials? *Lancet* 2004; 363:1728-31

12. Grimes DA, Schulz KF: Compared to what? Finding controls for a case-control studies. *Lancet* 2005; 365:1429-33

13. Arbous MS, Grobbee DE, van Kleef JW, de Lange JJ, Spoormans HHAJM, Touw P, Werner FM, Meursing AEE: Mortality associated with anaesthesia: A qualitative analysis to identify risk factors. *Anaesthesia* 2001; 56:1141-53

14. Warner MA: Perioperative mortality: Intraoperative anesthetic management matters. *ANESTHESIOLOGY* 2005; 102:251-2

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## Of Mice and Men and Type II Errors

*To the Editor:*—In response to the hypothesis that prolonged exposure of neonates to anesthetic drugs causes long-term neurocognitive deficits in humans, as it seems to do in mice and rats,<sup>1</sup> Soriano *et al.*<sup>2</sup> published a graph of the IQs at ages 4 and 8 yr of children who had undergone surgical repair of congenital heart defects as neonates using a standardized anesthetic regimen including high-dose barbiturates and opiates. Those IQ results were interpreted as showing “no significant differences between the study groups and the population norms.”<sup>2</sup>

The graphical representations of the IQ data are not accurate, but the means and SDs can be obtained from table 5 of Ferranti *et al.*<sup>3</sup> At both 4 and 8 yr of age, the full-scale IQs of children exposed to sustained anesthesia as neonates were statistically significantly lower than population norms ( $P < 0.0001$  and  $P < 0.02$ , respectively). The 95% confidence interval at age 4 yr is 90.2–94.9, and the 95% confidence interval at age 8 yr is 94.7–99.5. The 95% confidence interval for age 8 yr includes the risk of an IQ decrement of one third of an SD. The 95% confidence interval at age 4 yr indicates that a one-third SD decrement is highly probable, and it includes the risk of a two-thirds SD decrement.

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*In Reply:*—Dr. Hartung is correct in pointing out that we erroneously stated that there were “no significant differences between the study groups and population norms.”<sup>1</sup> The purpose of our letter to the editor was not to disprove the hypothesis that “data obtained in rodents apply to humans” in the context of anesthetic neurotoxicity and the developing brain. This phenomenon should be examined in a formal prospective case-control study in humans with validated outcome measures. The point that we wanted to make in the graph was that, despite the severity of cardiac lesions and the operative conditions (*i.e.*, hypoxia,<sup>2</sup> prolonged anesthesia/sedation, and circulatory arrest/support), the mean neurocognitive outcomes at 4 and 8 yr were somewhat lower but within the normal range of the normative values ( $100 \pm 15$ ) of the general population.<sup>3,4</sup> Delayed repair of congenital heart disease is associated with progressive decrement of cognitive function and justifies early surgical intervention in neonates.<sup>5</sup> These data are not a direct test of the neurocognitive effects of prolonged anesthesia/sedation in human neonates but should provide some impetus for further investigations. To paraphrase Shakespeare in *Love's Labour's Lost*, “Beauty is bought by judgment of the eye, not utt'ered by base sale of chapmen's tongues.”<sup>6</sup> We acknowledge our utterance of incorrect statistical analysis of existing data and stand corrected. However, there are no existing human experimental data that clearly demonstrate the neurotoxic effect of anesthetics in pediatric patients.

Statistical significance notwithstanding, clinical significance is often in the eye of the beholder. In the eye of this beholder, these data do not argue against the hypothesis that the data obtained in rodents apply to humans.

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### References

1. Olney JW, Young C, Wozniak DF, Ikonomidou C, Jevtovic-Todorovic V: Anesthesia-induced development neuroapoptosis: Does it happen in humans? *ANESTHESIOLOGY* 2004; 101:273-5
2. Soriano SG, Anand KJ, Rovnaghi CR, Hickey PR: Of mice and men: Should we extrapolate rodent experimental data to the care of human neonates? *ANESTHESIOLOGY* 2005; 102:866-8
3. De Ferranti S, Gauvreau K, Hickey PR, Jonas RA, Wypij D, du Plessis A, Bellinger DC, Kuban K, Newburger JW, Laussen PC: Intraoperative hyperglycemia during infant cardiac surgery is not associated with adverse neurodevelopmental outcomes at 1, 4, and 8 years. *ANESTHESIOLOGY* 2004; 100:1345-52

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### References

1. Soriano SG, Anad KJ, Rovnaghi CR, Hickey PR: Of mice and men: Should we extrapolate rodent experimental data to the care of human neonates? *ANESTHESIOLOGY* 2005; 102:866-8
2. Bass JL, Corwin M, Gozal D, Moore C, Nishida H, Parker S, Schonwald A, Wilker RE, Stehle S, Kinane TB: The effect of chronic or intermittent hypoxia on cognition in childhood: A review of the evidence. *Pediatrics* 2004; 114:805-16
3. Bellinger DC, Wypij D, Kuban KC, Rappaport LA, Hickey PR, Wernovsky G, Jonas RA, Newburger JW: Developmental and neurological status of children at 4 years of age after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass. *Circulation* 1999; 100:526-32
4. Bellinger DC, Wypij D, du Duplessis AJ, Rappaport LA, Jonas RA, Wernovsky G, Newburger JW: Neurodevelopmental status at eight years in children with dextro-transposition of the great arteries: The Boston Circulatory Arrest Trial. *J Thorac Cardiovasc Surg* 2003; 126:1385-96
5. Newburger JW, Silbert AR, Buckley LP, Fyler DC: Cognitive function and age at repair of transposition of the great arteries in children. *N Engl J Med* 1984; 310:1495-9
6. Shakespeare W: *Love's Labour's Lost*. Act II, Scene i. 1598

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## Interscalene Block Superior to General Anesthesia

*To the Editor:*—I read with interest the article by Hadzic *et al.*<sup>1</sup> about the use of interscalene block compared with general anesthesia for outpatient rotator cuff surgery. Although I agree that there are advantages to using nerve block anesthesia for outpatient shoulder surgery, I believe the comparator group receiving general anesthesia in the current Clinical Investigation<sup>1</sup> was a recipe for failure. I am not surprised by the 16% hospital admission rate for refractory pain observed in those patients receiving general anesthesia. I would hope with our current understanding of the pathophysiology of acute pain that we as anesthesiologists will offer our patients more effective perioperative analgesic techniques. I was surprised that the current clinical investigation failed to use nonopioid analgesics, including nonsteroidal anti-inflammatory drugs, in a multimodal approach to perioperative pain management as outlined by the recent American Society of Anesthesiologists Practice Guidelines for acute pain management in the perioperative setting state.<sup>2</sup> A more aggressive preventive multimodal pharmacologic approach<sup>3</sup> including the use of nonsteroidal anti-inflammatory drugs, acetaminophen, intraarticular local anesthetics, opioids, and  $\alpha_2$  agonists and postoperative cold therapy may have resulted in a less dramatic benefit compared with interscalene block. Failure to do

so may result in inadequate analgesia for our patients, as demonstrated in the current study by Hadzic *et al.*<sup>1</sup>

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### References

1. Hadzic A, Williams BA, Karaca PE, Hobeika P, Unis G, Dermksian J, Yufa M, Thys DM, Santos AC: For outpatient rotator cuff surgery, nerve block anesthesia provides superior same-day recovery over general anesthesia. *ANESTHESIOLOGY* 2005; 102:1001-7
2. Ashburn MA, Caplan RA, Carr DB, Connis RT, Ginsberg B, Green CR, Lema MJ, Nickinovich DG, Rice LJ: Practice guidelines for acute pain management in the perioperative setting: An updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *ANESTHESIOLOGY* 2004; 100:1573-81
3. Reuben SS, Gutta SB, Maciolek H, Sklar J: Effect of initiating a multimodal analgesic regimen upon patient outcomes after anterior cruciate ligament reconstruction for same-day surgery: A 1200-patient case series. *Acute Pain* 2004; 6:87-93

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## Benefits of Regional Anesthesia over General Anesthesia for Outpatient Rotator Cuff Surgery

*To the Editor:*—I read with interest and am in full agreement with the findings of Hadzic *et al.*<sup>1</sup> regarding the benefits of regional over general anesthesia for outpatient rotator cuff surgery. Patients undergoing shoulder surgery during interscalene block (ISB) anesthesia and intraoperative sedation were able to bypass phase I postanesthesia care unit in greater numbers than patients receiving general anesthesia (GA). In addition, regional anesthesia resulted in fewer unplanned hospital admissions, a faster time to discharge, fewer adverse events (including nausea, vomiting, sore throat), and greater patient satisfaction. None of the patients in the ISB group required treatment for pain before discharge home, whereas 80% of patients in the GA group required pain management despite wound infiltration and intraarticular instillation of local anesthetic by the surgeon.

However, the authors seem to have overlooked a study published by us out of Columbia University Medical Center (formerly Columbia-Presbyterian Medical Center) in which we reviewed 103 consecutive patients who underwent shoulder arthroscopic surgery during either GA or ISB anesthesia with sedation between August 1988 and March 1990.<sup>2</sup> Before the primary author's arrival at Columbia-Presbyterian Medical Center in July 1989, most shoulder surgery was performed during GA. The use of ISB anesthesia was subsequently encouraged, and the benefits were so obvious that within a short time, the suggestion that GA be used for shoulder surgery was met with a great degree of resistance from the surgeons. As with the study of Hadzic *et al.*, we found that the benefits of ISB over GA for shoulder surgery included a shorter hospital stay, fewer unplanned admissions, fewer adverse events, and greater patient satisfaction.<sup>2</sup>

The comments by Hadzic *et al.*<sup>1</sup> regarding the study by Weber and Jain<sup>3</sup> are certainly valid and are supported by similar comments in our study regarding perceived disadvantages of regional anesthesia. With respect to the time factor, regional anesthesia is performed at Columbia University Medical Center in a "block room" before the patient's entry into the operating room. After completion of the operative

procedure, the patient is wide awake, pain free, without GA-associated side effects, and ready to be discharged to the postanesthesia care unit immediately after placement of the surgical dressing, *i.e.*, time is *saved* when the practice of regional anesthesia is optimized. Weber and Jain<sup>3</sup> reported a 13% incidence of failed ISB, and 92% of patients required additional opioid analgesics after ISB. This high percentage of patients requiring postoperative opioid analgesics raises the question as to how successful the ISBs were, because it is most unusual for a patient to require any form of analgesia in the postoperative period after an ISB for shoulder surgery until the effect of the local anesthetic has worn off. Adequate training and experience certainly play a major role in the success as well as the complication rate associated with regional anesthesia.

At Columbia University Medical Center, we would have a great deal of difficulty attempting to perform a study similar to that performed by Hadzic *et al.*<sup>1</sup> because approval by the surgeons to perform shoulder surgery during GA as part of a study would be all but impossible. Hence, the study by Hadzic *et al.*<sup>1</sup> is an extremely welcome reminder of the benefits of regional over general anesthesia for shoulder surgery.

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### References

1. Hadzic A, Williams BA, Karaca PE, Hobeika P, Unis G, Dermksian J, Yufa M, Thys DM, Santos AC: For outpatient rotator cuff surgery, nerve block anesthesia provides superior same-day recovery over general anesthesia. *ANESTHESIOLOGY* 2005; 102:1001-7
2. Brown A, Weiss R, Greenberg C, Flatow E, Bigliani L: Interscalene block for shoulder arthroscopy: Comparison with general anesthesia. *Arthroscopy* 1993; 9:295-300
3. Weber SC, Jain R: Scalene regional anesthesia for shoulder surgery in a community setting: An assessment of risk. *J Bone Joint Surg Am* 2002; 84-A: 775-9

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## Interscalene Block Superior to General Anesthesia: A Discussion of the Conclusions Regarding These Two Anesthesia Techniques

*To the Editor:*—We read with interest the article by Hadzic *et al.*<sup>1</sup> regarding the use of scalene regional anesthesia in rotator cuff surgery. Any prospective, randomized study on this topic is to be applauded, although Kinnard *et al.*<sup>2</sup> also performed a prospective randomized study in 1994. We had a number of questions about the study of Hadzic *et al.* Rotator cuff repair can be performed with a variety of techniques, and the type of technique—arthroscopic, mini-open, or open—must be described in the method section, because randomization does not guarantee that equal numbers would be presented in each group. All arthroscopic rotator cuff repair in particular does not require any extraordinary efforts to manage perioperative pain and might have changed the results of this study. Clearly the physicians, nursing staff, and patients could not possibly have been blinded to the presence of a paralyzed, anesthetic extremity, and the study for this reason is not blinded. The term “light sleep” might be better defined, because some might define these patients as having both scalene and general anesthesia. The 16% rate of admission for general anesthesia for rotator cuff surgery is quite atypical and worrisome; in an outpatient center, any persistent rate of admission of more than 10% of patients would cause the facility to be discredited by the Joint Commission on Accreditation of Healthcare Organizations. The study clearly states that after discharge, there was no difference between the two techniques of any kind except for the patient choice to do the same technique again, a difficult decision for a patient who has had experience with only one of the two techniques.

Our greatest concern was over cost analysis and the discussion of complications. One of the most difficult sections of our article was the discussion of cost of general *versus* regional anesthesia.<sup>3</sup> In our institution, scalene regional anesthesia resulted in an increased cost of \$1,507. The modest savings reported in this study generated by bypassing the phase 1 postanesthesia care unit would not offset this. In most outpatient centers, the phase 1 and phase 2 postanesthesia care unit patients would be commingled, with no savings generated at all. Serious complications remain the primary concern with scalene blocks. Although experience does decrease the rate of complications, it does not obviate them. One of the two neurologic injuries reported

in our study occurred at a leading clinic with significant experience in regional anesthesia,<sup>3</sup> and the serious complication reported by Tetzlaff *et al.*<sup>4</sup> occurred at Cleveland Clinic after a report of several hundred successful blocks. The authors freely admit that their study was underpowered to make a conclusion about a variety of outcomes of the study. Statistical analysis shows that their study would have required 103 patients in the block group to detect a 3.6% difference in their complication rate with a 95% confidence level. Because this is the difference in complication rates reported between their study and ours, their study is underpowered to make the conclusion that their complication rate is significantly different from ours as well.

The primary problem remains the rare but measurable rate of serious complications present in all large studies. Any single significant complication would offset the modest improvement in perioperative pain control. As recent lively discussions on this topic at the 2004 American Shoulder and Elbow Surgeons' meeting (New York, New York, September 29, 2004 through October 02, 2004) can attest, this subject is far from closed.

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### References

1. Hadzic A, Williams BA, Karaca PE, Hobeika P, Unis G, Dermksian J, Yufa M, Thys DM, Santos AC: For outpatient rotator cuff surgery, nerve block anesthesia provides superior same-day recovery over general anesthesia. *ANESTHESIOLOGY* 2005; 102:1001-7
2. Kinnard P, Truchon R, St-Pierre A, Montreuil J: Interscalene block for pain relief after shoulder surgery: A prospective randomized study. *Clin Orthop* 1994; 304:22-4
3. Weber SC, Jain R: Scalene regional anesthesia for shoulder surgery in a community setting: A critical assessment of risk. *J Bone Joint Surg.* 2002; 84A: 775-9
4. Tetzlaff JE, Dilger J, Yap E, Brems J: Idiopathic brachial plexitis after total shoulder replacement with interscalene brachial plexus block. *Anesth Analg* 1997; 85:644-6

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*In Reply:*—We thank Dr. Reuben for his comment and agree with him in that a more aggressive preventative approach to multimodal pain management may have affected the outcome of our study. Our study however, was designed before the Practice Guidelines for Acute Pain Management in the Perioperative Setting were published by the American Society of Anesthesiologists Task Force on Acute Pain Management.<sup>1</sup> Regardless, without a trial comparing interscalene block (ISB) *versus* general anesthesia and incorporating such a multimodal approach in patients having outpatient rotator cuff surgery, any discussion regarding the outcome can be only speculative.

We thank Dr. Brown for his comments and agree with his remarks. We would also like to apologize for failing to cite the report by Dr. Brown *et al.*<sup>2</sup>; this publication simply did not come up in our literature search.

We thank Drs. Weber, Parise, and Jain for taking an interest in our study.<sup>3</sup> For the sake of completeness, we would like to clarify the terminology used—Drs. Weber, Parise, and Jain repeatedly use the

term *scalene anesthesia*; the proper term is *interscalene block*.<sup>4</sup> More importantly however, their comments are in sharp contradiction to the available literature including their own data.<sup>5</sup> Drs. Weber, Parise, and Jain say that rotator cuff repair does not require “any extraordinary efforts to manage perioperative pain” and that the 16% admission rate for pain management in our study is unacceptable. In their own report, however, 170 (78%) of 218 patients had rotator cuff repair, of which 92% were admitted and required parenteral narcotics.<sup>5</sup>

Both in their publication and in this letter, Drs. Weber, Parise, and Jain repeatedly emphasize the risk of neurologic complications related to ISB and support their concerns by citing a report by Tetzlaff *et al.*<sup>6</sup> However, as the title of the publication by Tetzlaff *et al.* indicates, they did not describe a neurologic complication of ISB, but an unusual case of idiopathic brachial plexitis.

We are also not surprised that these authors had difficulty with correlating the cost analysis that we presented in the Discussion section to the description of patient charges in their own article.<sup>5</sup> The

cited references in our article<sup>7,8</sup> used economic models based on complex, transformed regression, whereas the cost analysis by Weber *et al.* directed no attention to the distinction between costs and charges,<sup>9</sup> let alone the necessary econometric statistical maneuvers thereafter.<sup>10-13</sup>

Our study was not a repetition of that by Kinnard *et al.*<sup>14</sup> In our study, patients received general anesthesia *or* ISB. In the study by Kinnard *et al.*, all patients received general anesthesia with or without ISB at the end of surgery. The findings by Kinnard *et al.* are also in sharp contrast to those of Drs. Weber and Jain.<sup>5</sup> Kinnard *et al.* concluded that the use of ISB was without complications, significantly improved the postoperative comfort, and reduced the need for hospitalization after shoulder surgery. These findings prompted Kinnard *et al.* to institute routine use of ISB for all outpatient shoulder procedures at their institution and suggest the same to the readership, whereas Drs. Weber and Jain reemphasize the dangers and limitations of ISB.<sup>5</sup>

The results of their study cannot be directly compared with those of our study because of the substantial differences in methodology. Most importantly, (1) our study was a randomized, controlled trial, whereas theirs was a combination of retrospective chart review, two case reports, and a hypothetical cost analysis; and (2) ISB in our study was successfully used in all patients, with ISB as the sole anesthetic. In contrast, in the study by Drs. Weber and Jain, 13% of blocks failed outright, and 82% of patients required general anesthesia.<sup>5</sup>

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## References

1. Ashburn MA, Caplan RA, Carr DB, Connis RT, Ginsberg B, Green CR, Lema MJ, Nickinovich DG, Rice LJ: Practice guidelines for acute pain management in

the perioperative setting: An updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *ANESTHESIOLOGY* 2004; 100:1573-81

2. Brown A, Weiss R, Greenberg C, Flatow E, Bigliani L: Interscalene block for shoulder arthroscopy: Comparison with general anesthesia. *Arthroscopy* 1993; 9:295-300

3. Hadzic A, Williams BA, Kraca PE, Hobeika P, Unis G, Dermksian J, Yufa M, Thys DM, Santos AC: For outpatient rotator cuff surgery, nerve block anesthesia provides superior same-day recovery over general anesthesia. *ANESTHESIOLOGY* 2005; 102: 1001-7

4. Greene NM: Key words in anesthesiology, Key Words in Anesthesiology, 3rd edition. Edited by Greene NM. New York, Elsevier, 1988

5. Weber SC, Jain S: Scalene regional anesthesia for shoulder surgery in a community setting: An assessment of risk. *J Bone Joint Surg Am* 2002; 84:775-9

6. Tetzlaff JE, Dilger J, Yap E, Brems J: Idiopathic brachial plexitis after total shoulder replacement with interscalene brachial plexus block. *Anesth Analg* 1997; 85:644-6

7. Woolhandler S, Himmelstein DU: Costs of care and administration at for-profit and other hospitals in the United States. *N Engl J Med* 1997; 336:769-74

8. Williams BA, Kentor ML, Vogt MT, Vogt WB, Coley KC, Williams JP, Roberts MS, Chelly JE, Harner CD, Fu FH: The economics of nerve block pain management after anterior cruciate ligament reconstruction: Significant hospital cost savings *via* associated postanesthesia care unit bypass and same-day discharge. *ANESTHESIOLOGY* 2004; 100:697-706

9. Finkler SA: The distinction between cost and charges. *Ann Intern Med* 1982; 96:102-9

10. Ai C, Norton EC: Standard errors for the retransformation problem with heteroscedasticity. *J Health Econ* 2000; 19:697-718

11. Manning WG: The logged dependent variable, heteroscedasticity, and the retransformation problem. *J Health Econ* 1998; 17:283-95

12. Mullahy J: Much ado about two: Reconsidering retransformation and the two-part model in health econometrics. *J Health Econ* 1998; 17:247-81

13. Duan N: Smearing estimate: A nonparametric retransformation method. *J Am Statist Assoc* 1983; 78:605-10

14. Kinnard P, Truchon R, St-Pierre A, Montruil J: Interscalene block for pain relief after shoulder surgery. *Clin Orthop* 1994; 304:22-4

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## Is a New Classification of Postoperative Myocardial Infarction Justified?

*To the Editor:*—I read with interest the prospective audit of routinely measuring cardiac troponin I (cTnI) levels postoperatively in infrarenal aortic surgery by Le Manach *et al.*<sup>1</sup> The authors have proposed a classification of two separate groups of postoperative myocardial infarction (PMI) based on their findings. However, I think that aspects of both the methodology of the study and the presentation of results are open to criticism and that the validity of their distinction between early and delayed PMI is questionable.

It is not clear why the value for cTnI that the authors consider to be abnormal changed in the study and in their participating institution from 0.5 ng/ml from September 1995 to November 1999 to 0.2 ng/ml from November 1999 onward. It seems that the same machine was used for testing cTnI throughout the study period. This parameter is the basis of the definitions of both myocardial damage and delayed PMI and also the proposed difference between the early and delayed PMI groups and is clearly a key issue. Regardless of whether the institution changed its normal values for cTnI, it would seem that the most appropriate methodology would be to analyze the whole population by the same rules. It would be of interest whether the endpoints would differ from that reported if all patients were reanalyzed together at 0.2 ng/ml and at 0.5 ng/ml.

The abstract states that the cTnI profiles between the delayed PMI group before the cTnI threshold for PMI was reached and the myocardial damage group were identical. In the main part of the Results, it is only written that the profiles are comparable. Even so, the only evidence presented for this is a graph of two "representative" patients. To

describe the two profiles mentioned as identical would require descriptive statistics of cTnI values to be presented against time for each of the different groups, with a mathematical analysis of their difference. I also note that there was not even a "representative" example described of the other two groups.

The timing of the 24-h cutoff for the difference between early and delayed PMI was predetermined and arbitrary. The authors state that in the early PMI group, PMI was not preceded by subinfarction myocardial damage, but did any of the early PMI group patients have abnormal cTnI for 18 rather than 24 h? If so, how do we know that this was not significant myocardial damage? It would seem to be a more robust choice of timing if at first the pattern within the population was examined and then the most appropriate cutoff was chosen.

The authors note that only the early PMI group had an increased incidence of previous myocardial infarction and hint that this supports their hypothesis of different etiology in the two PMI groups. I note that 57 comparisons are made in table 2. Because the *P* values are only described as less than 0.05 and not specified, it is hard to know how significant their four *P* values of less than 0.05 in table 2 really are when you would expect almost three to occur just by statistical probability. Defining two groups on their differing temporal characteristics, proving statistical difference in a clearly related temporal parameter in the absence of any other differences in nonrelated parameters, and then inferring that the two groups are fundamentally different is a weak argument.

The opinion that the time when the cTnI is abnormal but not



diagnostic of PMI should be considered a "golden period," and the hypothesis that intensive interventions may influence outcome is attractive. The description of the natural history of cTnI changes would be more useful if we knew whether the ischemia was silent or associated with evidence that would have resulted in appropriate therapy anyway. I would like to know whether the myocardial damage group or the patients with abnormal cTnI before PMI had chest pain, dyspnea, heart failure, arrhythmias, or other electrocardiographic changes suggestive of ischemia.

In conclusion, the authors have not shown a bimodal distribution that would justify the classification of PMI as early and delayed, nor have they conclusively shown a fundamental difference between rapid-onset and delayed-onset PMI groups on the evidence as presented.

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*In Reply:*—We thank Dr. Bould for his interest in our article.<sup>1</sup> Our definition of myocardial infarction was based on the normal values in our specific laboratory.<sup>2</sup> The threshold for abnormal cardiac troponin I (cTnI) was modified by the laboratory of our hospital, which, after an improved accuracy of the dosage technique of cTnI, considered as abnormal a value above the serum 99th percentile of the normal population.<sup>3</sup> Because the normal value in our laboratory changed, so did the definition of myocardial necrosis. This is in complete agreement with the definition of myocardial infarction in the literature, which clearly considers cTnI plasma level as the accepted standard to evidence postoperative myocardial infarction.

Dr. Bould suggests a complementary analysis to better describe differences between myocardial damage and delayed myocardial infarction. We believe that no complicated descriptive statistics are needed, because cTnI values of the two groups are very similar, as evidenced in figure 1. A 24-h delay was arbitrarily retained to separate the early myocardial infarction and delayed myocardial infarction groups. From a clinical standpoint, we consider that myocardial damage lasting more than 24 h preceding myocardial infarction provides a unique opportunity to introduce a treatment to improve myocardial oxygen balance. In addition, a 24-h interval has some statistical relevance, considering that a normal distribution cannot be excluded using a Shapiro-Wilk W test for the distribution of the delay to peak cTnI (and 1.5-ng/ml threshold) in the delayed myocardial infarction and postoperative myocardial infarction groups, whereas an abnormal distribution was found in the overall myocardial infarction population. Nevertheless, we assume that normality tests have low statistical power (probability of detecting nonnormal data) in small samples, and so those normality tests are not strong arguments to statistically separate two populations. Dr. Bould emphasizes that the statistical differences observed in table 2 might be due to change. We want to underline that these data are presented as more descriptive than explicative, and that no causal assumption could be made in this study.

Our conclusions are based on a significant difference in the incidence of previous myocardial infarction between early myocardial infarction and myocardial damage groups with a *P* value lower than 0.002.

A "representative" example of a control group in which by definition cTnI plasma level equals zero, cannot be shown in a figure in which cTnI plasma levels are represented on the vertical axis. In addition, this graph was included in the manuscript to illustrate a "golden period,"

Moreover, I think the suggestion that early PMI is "hitherto unrecognized in the postoperative setting" is unfounded.

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## Reference

1. Le Manach Y, Perel A, Coriat P, Godet G, Bertrand M, Riou B: Early and delayed myocardial infarction after abdominal aortic surgery. *ANESTHESIOLOGY* 2005; 102:885-91

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explaining why the inclusion of a "representative" patient of the early group would have been confusing for the reader.

As firmly established in the literature, abnormal postoperative cTnI levels are rarely associated with clinical symptoms. Moreover, pain, dyspnea, and hypotension have many extracardiac causes after major vascular surgery and are unacceptable surrogates for myocardial infarction.

In conclusion, there is a very clear temporal distinction between the groups as to both time to first abnormal cTnI value and time to peak cTnI value, whereas the time from the end of surgery to first abnormal value was the same. Consequently, we believe that our conclusions are justified. Numerous previously published articles describe considerably prolonged myocardial damage before postoperative myocardial infarction. This has led to the development of the prevalent theory of cumulative myocardial injury as the main process that leads to postoperative myocardial infarction. Our early myocardial infarction group clearly does not fit into that category. Hence, we dared to offer the hypothesis that there may be two types of postoperative myocardial infarction. Dr. Bould's arguments have not convinced us that our hypothesis is wrong.

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## References

1. Le Manach Y, Perel A, Coriat P, Godet G, Bertrand M, Riou B: Early and delayed myocardial infarction after abdominal aortic surgery. *ANESTHESIOLOGY* 2005; 102:885-91
2. Luepker RV, Apple FS, Christenson RH, Crow RS, Fortmann SP, Goff D, Goldberg RJ, Hand MM, Jaffe AS, Julian DG, Levy D, Manolio T, Mendis S, Mensah G, Pajak A, Prineas RJ, Reddy KS, Roger VL, Rosamond WD, Shahar E, Sharrett AR, Sorlie P, Tunstall-Pedoe H: Case definitions for acute coronary heart disease in epidemiology and clinical research studies: A statement from the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. *Circulation* 2003; 108:2543-9
3. Apple FS, Murakami MM: Serum 99th percentile reference cutoffs for seven cardiac troponin assays. *Clin Chem* 2004; 50:1477-9

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## Is Xenon Really Neuroprotective after Cardiac Arrest?

*To the Editor:*—Xenon has recently been shown to act as a neuroprotective agent in several *in vitro* and *in vivo* models of acute neuronal injury, probably inhibiting the *N*-methyl-D-aspartate receptor.<sup>1,2</sup> In the May issue of ANESTHESIOLOGY, Schmidt *et al.*<sup>3</sup> provided pioneering data on the effects of xenon on porcine brains assessed by hemodynamic, electrophysiologic, and metabolic measurements in a large animal model of cardiac arrest and subsequent cardiopulmonary resuscitation. Using a microdialysis technique, they documented that levels of glycerol, an integral part of the cell membrane, are significantly lower after 90 min of reperfusion in pigs that received xenon anesthesia before cardiac arrest was induced when compared with a control group that was anesthetized with a total intravenous regimen. No other parameter, including glutamate, lactate, lactate/pyruvate ratio, brain tissue partial pressure of oxygen, and intracranial pressure, showed significant differences between the groups.

In the Western hemisphere, approximately 800,000 people annually experience sudden cardiac death.<sup>4,5</sup> Although survival rates are increasing, complete neurologic recovery is often far from certain, and by the time of hospital discharge, every second patient is neurologically severely disabled or comatose.<sup>6</sup> Accordingly, there is urgent need to find strategies that ameliorate neuronal injury.

In this respect, the study by Schmidt *et al.*<sup>3</sup> is of high clinical relevance. However, we believe that some major limitations in the study design and the interpretation of the results are not adequately discussed.

First, a major drawback of this study that detracts from its clinical significance is that the authors elected to use an extremely short duration of cardiac arrest that results in only minor brain damage, if at all.<sup>7</sup> It is therefore not surprising that the authors failed to establish differences in extracellular glutamate values. In contrast, the evidence for glycerol as a surrogate for neuronal damage is weak because glycerol is a naturally occurring three-carbon alcohol that is ubiquitously present in considerable amounts in the human body and an integral part of the energy metabolism.<sup>8</sup> Glycerol readily moves across the blood-brain barrier, and therefore, increases in dialysis fluid are not exclusively indicative of nerve cell damage but might reflect overall metabolic changes or changes due to exogenous sources.<sup>9,10</sup> Second, animals received xenon before cardiac arrest was induced. In the overwhelming majority of cases, however, cardiac arrest occurs suddenly and unexpectedly. A possible indication for xenon pretreatment might be procedures that require short periods of circulatory standstill, such as insertion of implantable cardioverters/defibrillators, which is known to be associated with neurocognitive sequelae.<sup>11</sup> Third, the authors should consider the possibility that the anesthetic regimen might have biased the results because they used an opioid for pain relief, which reportedly exerts neuroprotective properties.<sup>12</sup> Finally,

definitive parameters of neurologic injury, *i.e.*, measurements of serum markers of nervous tissue damage and neurohistopathologic examinations of vulnerable brain regions, would have been of major benefit to the study. In conclusion, the authors did not demonstrate that xenon is really neuroprotective in the setting of global ischemia and reperfusion, and accordingly, we believe that the title of the article, "Xenon Attenuates Cerebral Damage after Ischemia in Pigs," overstates the data presented. Notwithstanding these important limitations, we acknowledge and appreciate that the authors have applied xenon for the first time in this clinically highly relevant model, and we hope that the article will stimulate further research in this area.

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### References

1. Wilhelm S, Ma D, Maze M, Franks NP: Effects of xenon on *in vitro* and *in vivo* models of neuronal injury. ANESTHESIOLOGY 2002; 96:1485-91
2. de Sousa SL, Dickinson R, Lieb WR, Franks NP: Contrasting synaptic actions of the inhalational general anesthetics isoflurane and xenon. ANESTHESIOLOGY 2000; 92:1055-66
3. Schmidt M, Marx T, Gloggl E, Reinelt H, Schirmer U: Xenon attenuates cerebral damage after ischemia in pigs. ANESTHESIOLOGY 2005; 102:929-36
4. de Vreede-Swagemakers JJ, Gorgels AP, Dubois-Arbouw WI, van Ree JW, Daemen MJ, Houben LG, Wellens HJ: Out-of-hospital cardiac arrest in the 1990's: A population-based study in the Maastricht area on incidence, characteristics and survival. J Am Coll Cardiol 1997; 30:1500-5
5. Zheng ZJ, Croft JB, Giles WH: Sudden cardiac death in the United States, 1989 to 1998. Circulation 2001; 104:2158-63
6. Wenzel V, Krismer AC, Arntz HR, Sitter H, Stadlbauer KH, Lindner KH, European Resuscitation Council Vasopressor during Cardiopulmonary Resuscitation Study Group: A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. N Engl J Med 2004; 350:105-13
7. Radovsky A, Safar P, Sterz F, Leonov Y, Reich H, Kuboyama K: Regional prevalence and distribution of ischemic neurons in dog brains 96 hours after cardiac arrest of 0 to 20 minutes. Stroke 1995; 26:2127-33
8. Robergs RA, Griffin SE: Glycerol: Biochemistry, pharmacokinetics and clinical and practical applications. Sports Med 1998; 26:145-67
9. Berger C, Sakowitz OW, Kiening KL, Schwab S: Neurochemical monitoring of glycerol therapy in patients with ischemic brain edema. Stroke 2005; 36:e4-6
10. Gliemroth J, Klaus S, Bahlmann L, Klohn A, Duysen K, Reith A, Arnold H: Interstitial glycerol increase in microdialysis after glycerol enema. J Clin Neurosci 2004; 11:53-6
11. Murkin JM, Baird DL, Martzke JS, Yee R: Cognitive dysfunction after ventricular fibrillation during implantable cardioverter/defibrillator procedures is related to duration of the reperfusion interval. Anesth Analg 1997; 84:1186-92
12. Lim YJ, Zheng S, Zuo Z: Morphine preconditions Purkinje cells against cell death under *in vitro* simulated ischemia-reperfusion conditions. ANESTHESIOLOGY 2004; 100:562-8

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*In Reply:*—The study presented in "Xenon Attenuates Cerebral Damage after Ischemia in Pigs"<sup>1</sup> was designed and performed in our Department of Cardiac Anesthesia (Ulm, Germany). After cardiac bypass surgery, neurologic complications are well known to be a major problem leading to prolonged intensive care unit stay and additional costs.<sup>2</sup> With this investigation, we aimed to simulate a situation of *expected* transient cessation of cerebral perfusion with a definitive offset and onset. In this clinically relevant situation, the depletion of central

nervous system's energy stores occurs within 2-4 min of anoxia, leading to cellular damage and possible consecutive irreversible cell death. As described, this *expected* situation might be relevant, *e.g.*, in temporary clipping in cerebral aneurysm, aortic arch surgery, or carotid surgery.

In preliminary studies, we observed that the percentage of animals with return of spontaneous circulation after cardiac fibrillation times exceeding the period as applied in our study significantly decreased.

Therefore, the given times were found to be the maximum periods of ventricular fibrillation in pigs with a realistic option of successful cardiac resuscitation.

The effect of ischemia/hypoxia was investigated using cerebral microdialysis in identical setups during anesthesia with inhalation of xenon *versus* total intravenous anesthesia. Regarding the results of intracerebral microdialysis, we have discussed that the lack of peak increase of glutamate concentrations could also be due to harvesting time of microdialysis fluid volume. Regarding the question of glycerol concentrations and possible extracerebral sources, we measured identical changes of concentrations until 90 min after cardiac arrest for both groups. This finding is not surprising at all, because the primary lesion due to anoxia, the described resuscitation regimens, and the measured cardiopulmonary resuscitation times did not differ significantly between the groups. In case of relevant extracerebral production of glycerol, differences in glycerol concentrations should be seen directly after return of spontaneous circulation, which was not the case. Therefore, it is not likely that changes in glycerol kinetics or extracerebral sources would explain the differences in glycerol concentrations between the groups after 90 min of reperfusion. Even if there would be a relevant exogenous concentration of glycerol, the effect, if at all, would be same in both groups. In our opinion, the difference in glycerol concentrations after 90 min during the time of reperfusion is more likely to be interpreted as a neuroprotective effect of xenon.

Like Fries *et al.*, we considered the influence of comedication to contribute to a possible neuroprotective effect, which in that case would not have been the effect of xenon. However, the contribution of a different depth of anesthesia leading to a different level of metabolism in the central nervous system during hypoxia/ischemia was considered to have an important influence on our findings, too. Therefore, we adjusted the level of background anesthesia according to comparable electroencephalographic levels, and, as described in our article, *reduced* amounts of comedication were administered in the xenon group. The difference in glycerol kinetics after establishment of return of spontaneous circulation with *lower* postcardiopulmonary resuscitation concentrations in the xenon group is therefore not likely to be explained by *lower* amounts of comedication.

We agree with Fries *et al.* and regard it to be an advantage if additional diagnostic tools are used to contribute to the explanation of central nervous system damage assessment. Being a noninvasive tool and therefore possibly an option for human studies as well, magnetic resonance imaging scans were added to this experimental setting. We performed magnetic resonance imaging scans 4 h after return of spontaneous circulation and calculated the apparent diffusion coefficients, being used as a method to assess the water content of the central nervous system as a parameter for tissue damage.<sup>3</sup> Interpretation of technical and anatomical aspects regarding the achieved data was difficult because, to our knowledge, there have been no comparable data published about German Landrace pigs until the present. Preliminary technical data from this study were published recently.<sup>4</sup>

Regarding neuroprotective effects of xenon after global ischemia, we found a significant benefit for the xenon-treated group *versus* the total intravenous anesthesia group in apparent diffusion coefficients results. The combination of magnetic resonance imaging findings and cerebral microdialysis results are regarded to be valuable to demonstrate the neuroprotective effect of xenon more clearly.

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## References

- Schmidt M, Marx T, Glöggel E, Reinelt H, Schirmer U: Xenon attenuates cerebral damage after ischemia in pigs. *ANESTHESIOLOGY* 2005; 102:929-36
- Roach GW, Kanchuger M, Mangano CM, Newman M, Nussmeier N, Wolman R, Aggarwal A, Marshall K, Graham SH, Ley C: Adverse cerebral outcomes after coronary bypass surgery. Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation Investigators. *N Engl J Med* 1996; 335:1857-63
- van Dorsten FA, Olah L, Schwind W, Grune M, Uhlenkukken U, Pillekamp F, Hossmann KA, Hoehn M: Dynamic changes of ADC, perfusion, and NMR relaxation parameters in transient focal ischemia of rat brain. *Magn Reson Med* 2002; 47:97-104
- Marx T, Schmidt M, Schirmer U, Reinelt H: Cerebral damage assessment using apparent diffusion coefficients and intracerebral microdialysis. *Biomed Eng* 2005; 50:239-40

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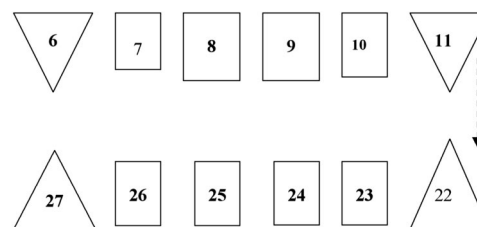
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## A Simple Preanesthesia Dental Examination

*To the Editor:*—Damage to the teeth can occur during general anesthesia<sup>1</sup> and is a common cause of claims against anesthesiologists.<sup>2,3</sup> A detailed knowledge of the preanesthesia dental status provides a reliable way to distinguish valid from fraudulent (and often expensive) claims of injury. Here we present a simple system for performing and documenting a dental examination.

In North America, the standard convention for numbering teeth starts with No. 1 as the right upper wisdom tooth, proceeds around the maxillary arch to No. 16, drops to the wisdom tooth immediately below (No. 17), and thence proceeds around the mandibular arch to the lower right wisdom tooth (No. 32). The numbers are assigned to specific teeth, so a missing tooth is counted even though it is not there.

The anterior teeth are of most interest to an anesthesiologist because these are most likely to be damaged during intubation, or if a partially anesthetized patient should bite down hard on a rigid airway.<sup>3</sup> A simplified charting system for these teeth is shown in figure 1. The right upper canine (No. 6) is easy to identify. It and the left upper canine (No. 11) bracket two central incisors, Nos. 8 and 9 (the “Bunny” teeth) and two smaller lateral incisors on each side (Nos. 7 and 10). The trick to the numbering system is realizing the correspondence between upper and lower teeth. The left lower canine is No. 22 (remember: “11 times 2 equals 22”), and normal teeth are symmetric around to the right lower canine (No. 27).



**Fig. 1.** Easy tooth-numbering guide based on the concept that “11 times 2 equals 22.”

Our typical documentation of a preexisting dental condition contains comments such as “missing No. 6, and chipped No. 23.” The presence of caps, crowns, bridges, and loose teeth should also be noted with the relevant tooth number. A drawing of a specific tooth is

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an additional way to indicate the degree of damage. On occasion, only a few teeth will be present, and the absence of reference teeth may make it difficult to determine which number or numbers apply. A simple description of the remaining teeth and their locations will suffice in this situation.

A clear record of preexisting dental problems provides a firm basis for assessing claims of dental injury during anesthesia.

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## References

1. Warner ME, Benenfeld SM, Warner MA, Schroeder DR, Maxson PM: Peri-anesthetic dental injuries: Frequency, outcomes, and risk factors. *ANESTHESIOLOGY* 1999; 90:1302-5
2. Chadwick RG, Lindsay SM: Dental injuries during general anaesthesia. *Br Dent J* 1996; 180:255-8
3. Givol N, Gershtansky Y, Haramish-Shani T, Taicher S, Perel A, Segal E: Perianesthetic dental injuries: Analysis of incident reports. *J Clin Anesth* 2004; 16:173-6

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## Fatal Thrombosis after Mitral Valve Replacement for Endocarditis: Aprotinin and Disseminated Intravascular Coagulation

*To the Editor:*—We recently reported fatal aortic thrombosis in an adult undergoing repair of a thoracoabdominal aneurysm using cardiopulmonary bypass (CPB) and deep hypothermic circulatory arrest in the setting of aprotinin and adequate heparinization.<sup>1</sup> We report a second case of fatal thrombosis after mitral valve replacement for endocarditis in the setting of aprotinin and disseminated intravascular coagulation.

A 69-yr-old woman presented with fatigue and right-sided weakness. She had a history of breast carcinoma treated with mastectomy and high-dose chemotherapy. She was taking tamoxifen. Her physical examination was positive for purpura, right hemiplegia, and an apical holosystolic murmur with radiation to the axilla. She had no peripheral stigmata of endocarditis. Brain imaging showed multiple embolic cerebral infarcts. A transthoracic echocardiogram revealed multiple, large mitral vegetations and severe mitral regurgitation. Her laboratory studies revealed thrombocytopenia, hypofibrinogenemia, and disseminated intravascular coagulation. Blood cultures were sent, and empiric antibiotic therapy was commenced. After consultation with a hematologist, the patient was given cryoprecipitate. The patient was subsequently referred for mitral valve surgery.

The patient underwent general endotracheal anesthesia. Anesthetic monitoring consisted of standard monitors (as per the American Society of Anesthesiologists), a radial arterial line, an oximetric pulmonary arterial catheter, and transesophageal echocardiograph. The patient was given aprotinin (Bayer Corporation, Pittsburgh, PA) as follows: 2 million kallikrein inhibitory units intravenously as a load, followed by an infusion of 0.5 million kallikrein inhibitory units per hour. The CPB crystalloid prime was also loaded with aprotinin (2 million kallikrein inhibitory units). The aprotinin was commenced just after induction of general anesthesia. Heparinization was with bolus bovine heparin to maintain the kaolin activated clotting time greater than 400 s. The patient underwent uncomplicated bioprosthetic mitral valve replacement on hypothermic CPB.

Separation from CPB was uneventful. After protamine administration, there was still significant microvascular bleeding. This was treated with titrated administration of cryoprecipitate and platelets. Approximately 30 min after the commencement of this transfusion, there was sudden cardiogenic shock that required emergent CPB after re-heparinization. During this time, transesophageal echocardiography demonstrated thrombus in the left atrium and descending aorta. Left atriotomy revealed significant thrombus on the mitral prosthetic valve as well. Separation from CPB thereafter was impossible because of refractory biventricular failure. Further resuscitative efforts were stopped.

To our knowledge, this is the first reported case of fatal thrombosis

after mitral valve surgery for endocarditis in the setting of aprotinin and disseminated intravascular coagulation. Aprotinin reduces transfusion burden in valve surgery for endocarditis and is possibly beneficial in disseminated intravascular coagulation.<sup>2-5</sup> Aprotinin has been associated with thrombosis after valve surgery for endocarditis despite adequate heparinization but in the setting of congenital afibrinogenemia.<sup>6</sup> This recently reported case occurred in a young adult with multiple perioperative thrombotic events. There was cardiogenic collapse after separation from CPB due to coronary thrombosis. The patient survived after a prolonged hospital stay. The accompanying expert commentaries comprehensively discuss the role of aprotinin in this scenario, including disseminated intravascular coagulation and endocarditis. The reader is referred to these commentaries for further details.

Clearly, in our case, there was a complex interaction of procoagulant and anticoagulant influences that ultimately resulted in a net fatal thrombotic result. It is not possible on the basis of one case to delineate the exact role of aprotinin in this complex pathophysiology. This case demonstrates, however, that fatal thrombosis is possible in association with aprotinin in the setting of cardiac surgery for endocarditis and acquired hypofibrinogenemia. Further research is required to understand and prevent this uncommon but important perioperative complication.

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## References

1. Augoustides JGT, Lin J, Gambone AJ, Cheung AT: Fatal thrombosis in an adult after thoracoabdominal aneurysm repair and deep hypothermic circulatory arrest. *ANESTHESIOLOGY* 2005; 103:215-6
2. Bidstrup BP, Royston D, Taylor KM, Sapsford RN: Effect of aprotinin on need for blood transfusion in patients with septic endocarditis having open-heart surgery. *Lancet* 1988; 1:366-7
3. Royston D: A case for aprotinin in patients having deep hypothermic circulatory arrest. *J Card Surg* 1997; 12:214-20
4. Moriau M, Rodhain J, Noel H, Beys-Col CD, Masure R: Comparative effects of proteinase inhibitors, plasminogen activators, heparin and acetylsalicylic acid on the experimental disseminated intravascular coagulation induced by thrombin. *Thromb Diath Haemorrh* 1974; 32:171-88
5. Jochum M, Witte J, Schiessler H, Selbmann HK, Ruckdeschl G, Fritz H: Clotting and other plasma factors in experimental endotoxemia: Inhibition of degradation by exogenous proteinase inhibitors. *Eur Surg Res* 1981; 13:152-68
6. Chun R, Poon MC, Haigh J, Seal D, Donahue B, Royston D: Case 1-2005: Cardiac surgery in congenital afibrinogenemia with thrombo-occlusive disease. *J Cardiothorac Vasc Anesth* 2005; 19:109-17

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