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.\(^1\) and the accompanying editorial written by Warner.\(^2\) 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 time of day or the exigent nature of the procedure?

“Anesthesia Management and Perioperative Mortality”

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(Accepted for publication June 20, 2005.)
To the Editor:—I applaud Arbous et al.1 for attempting a large multi-center 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 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. Warner2 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.

Kenneth A. Schmidt, M.D., Valley Hospital, Ridgewood, New Jersey. kschmidt99@aol.com

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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.1 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.2 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.3 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.4

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 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.

Guélay Bilen-Rosas, M.D., Menelaos Karanikolas, M.D., Alex Evers, M.D., Michael Avidan, M.B.B.Ch. Washington University Medical School, St. Louis, Missouri. bilenrog@msnotes.wustl.edu

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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.1 and my editorial2 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.

Mark A. Warner, M.D., Mayo Clinic, Rochester, Minnesota. warner.mark@mayo.edu

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

<table>
<thead>
<tr>
<th>Group</th>
<th>ASA I or II</th>
<th>ASA III–V</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead (cases)</td>
<td>68</td>
<td>739</td>
<td>807</td>
</tr>
<tr>
<td>Alive (controls)</td>
<td>692</td>
<td>191</td>
<td>883</td>
</tr>
<tr>
<td>Total</td>
<td>760</td>
<td>930</td>
<td>1,690</td>
</tr>
</tbody>
</table>

ASA = American Society of Anesthesiologists.

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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.’ 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). For a rare outcome such as death after anesthesia, a case–control study is a particularly efficient research design. 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 anesthetic 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.7–12

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 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.1,12 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.11

M. Sesmu Arbous, M.D., Ph.D., Anneke E. E. Meursing, M.D., Ph.D., Jack W. van Kleef, M.D., Diederick E. Grobbee, M.D., Ph.D. *Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, and Dutch Association for Anesthesiology, Utrecht, The Netherlands. d.e.grobbee@jc.uu.nl

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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, Soriano et al. 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.’

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. 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.

Anesthesiology 2006; 104:206

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.” 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, 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 ± 15) of the general population. Delayed repair of congenital heart disease is associated with progressive cognitive decline and justifies early surgical intervention in neonates. 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 uttered by base sale of chapmen’s tongues.” 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.

Anesthesiology 2006; 104:206

Of Mice and Men and Type II Errors

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.

John Hartung, Ph.D., State University of New York, Brooklyn, New York. john.hartung@downstate.edu

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Accepted for publication August 30, 2005.

Sulpicio G. Soriano, M.D.,* Paul R. Hickey, M.D. *Children’s Hospital Boston, Boston, Massachusetts. sulpicio.soriano@childrens.harvard.edu

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Accepted for publication August 30, 2005.
Interscalene Block Superior to General Anesthesia

To the Editor—I read with interest the article by Hadzic et al.1 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 Investigation1 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.2 A more aggressive preventive multimodal pharmacologic approach including the use of nonsteroidal antiinflammatory drugs, acetaminophen, intraarticular local anesthetics, opioids, and alpha2 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.1

Scott S. Reuben, M.D., Baystate Medical Center and the Tufts University School of Medicine, Springfield, Massachusetts. scott.reuben@bhs.org

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(Accepted for publication August 30, 2005.)

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.1 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 that 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. Hence, the study by Hadzic et al.1 is an extremely welcome reminder of the benefits of regional over general anesthesia for shoulder surgery.

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.1 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.1 is an extremely welcome reminder of the benefits of regional over general anesthesia for shoulder surgery.

Anthony R. Brown, M.B., Ch.B., F.F.A.S.A., Columbia University, New York, New York. arb6@columbia.edu

References

(Accepted for publication August 30, 2005.)
To the Editor—We read with interest the article by Hadzic et al.1 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.2 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 anesthesia. The 16% rate of admission for general anesthesia for rotator cuff surgery is quite atypical and worrisome; in an outpatient center, any anesthesia provides superior same-day recovery over general anesthesia. ANESTHESIOLOGY 2005; 102:1001-7

In our institution, scalene regional anesthesia resulted in an increased cost of $1,507. The modest savings reported in this study generated by by-...
To the Editor— I read with interest the prospective audit of routinely measuring cardiac troponin I (cTnI) levels postoperatively in infranidal aortic surgery by Le Manach et al.1 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 cited references in our article7,8 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,9 let alone the necessary econometric statistical maneuvers thereafter.10–13 Our study was not a repetition of that by Kinnard et al.14 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.5 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.5

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.5

Admir Hadzic, M.D., Ph.D.,* Brian A. Williams, M.D., M.B.A., Doug Unis, M.D., Paul Hobeika, M.D. *St. Luke’s-Roosevelt Hospital Center, College of Physicians and Surgeons of Columbia University, New York, New York. ah149@columbia.edu

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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 infranidal aortic surgery by Le Manach et al.1 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.

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The opinion that the time when the cTnI is abnormal but not
In Reply:—We thank Dr. Bould for his interest in our article.1 Our definition of myocardial infarction was based on the normal values in our specific laboratory.2 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.3 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,’ explaining why the inclusion of a ‘representative’ patient of the early group would have been confusing for the reader.

Moreover, I think the suggestion that early PMI is ‘hitherto unrecognised in the postoperative setting’ is unfounded.

Reference


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(CORRESPONDENCE)

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(Accepted for publication October 12, 2005.)
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.1,2 In the May issue of ANESTHESIOLOGY, Schmidt et al.3 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.3,4 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.6 Accordingly, there is urgent need to find strategies that ameliorate neuronal injury.

In this respect, the study by Schmidt et al.3 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.7 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.8 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.9,10 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 often an integral part of the energy metabolism.9,10 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.12 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.

Michael Fries, M.D., Joachim Weis, M.D., Ph.D., Rolf Rossaint, M.D., Ph.D.* University Hospital RWTH Aachen, Aachen, Germany.
mfries@ukaachen.de

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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 identitical 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. 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.

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.

Michael Schmidt, M.D., P.D.,* Helmut Reinelt, M.D., P.D., Thomas Marx, M.D., P.D. *University of Ulm, Ulm, Germany. michael.schmidt@medizin.uni-ulm.de

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To the Editor—Damage to the teeth can occur during general anesthesia and is a common cause of claims against anesthesiologists. 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. 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 ‘Bugs 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).

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

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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.

Charles W. Buffington, M.D.,* Manuel C. Vallejo, D.M.D., M.D.
*University of Pittsburgh, Pittsburgh, Pennsylvania.
buffingtoncw@anes.upmc.edu

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.1 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 echocardiography. 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 tittered administration of cryoprecipitate and platelets. Approximately 30 min after the commencement of this transfusion, there was sudden cardiogenic shock that required emergent CPB after reheparinization. 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.2–5 Aprotinin has been associated with thrombosis after valve surgery for endocarditis despite adequate heparinization but in the setting of congenital fibrinogenemia.6 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.

John G. Augoustides, M.D.,* Todd Kilbaugh, M.D., Hilary Harris, B.A., John H. Glick, M.D., Michael Acker, M.D., Joseph S. Savino, M.D. *Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania. yiandoc@hotmail.com

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