■ CORRESPONDENCE

Efficacy of Intravenous Iron Sucrose Administration for Correcting Preoperative Anemia in Patients Scheduled for Major Orthopedic Surgery

To the Editor:—Preoperative anemia is a common condition among surgical patients, and it is an independent risk factor for blood transfusion in major surgery with moderate to high blood loss. Consequently, the first step to be taken in the setting of elective surgery will be the preoperative identification and evaluation of anemia early enough to implement the appropriate treatment. In this regard, we read with interest the report by Theusinger *et al.*[1] about the use of intravenous iron sucrose for the treatment of iron deficiency anemia in orthopedic surgical patients. They found a mean maximum increase in hemoglobin (1.0 ± 0.6 g/dl) 2 weeks after the start of intravenous iron treatment, indicating that administration of intravenous iron 2–3 weeks before surgery may be optimal. We would like to comment regarding the patients' inclusion criteria, the dosage and administration schedule of iron sucrose, and the comparison of their data with those of the study by Cuenca *et al.*[2] in patients sustaining a pertrochanteric hip fracture.

First, although Theusinger *et al.*[1] clearly defined anemia according to World Health Organization criteria as hemoglobin level < 12 g/dl for women and hemoglobin < 13 g/dl for men, their definition of iron deficiency was complex and somehow arbitrary. According to other authors, iron deficiency anemia is defined by anemia with mean corpuscular volume < 80 fl, ferritin level < 15–30 μg/l, and transferrin saturation < 15%.[1] On the other hand, in the event of inflammation (C-reactive protein > 5 mg/l), iron deficiency may be defined as transferrin saturation < 20% and ferritin < 50–100 μg/l.[3] Therefore, the cutoff values used in this paper (ferritin < 100 mg/l or 100–300 μg/l with transferrin saturation < 20%) are compatible not only with iron deficiency anemia but also with anemia of chronic disease, with or without true iron deficiency.[3,4] Thus, it is conceivable that a mixed anemic patient population was included in this study. This may be important, because the endogenous erythropoietin response to low hemoglobin is more substantial in iron deficiency anemia than in anemia of chronic disease, and erythropoietin increases the mobilization and incorporation of iron into the erythron.[3] Inflammatory mediators involved in anemia of chronic disease also impair duodenal iron absorption and iron mobilization from body stores.[4]

Second, the authors stated that in the current study group iron stores were empty, but without additional information on the inflammatory status, mean baseline ferritin levels (78 ± 70 mg/l) do no support this statement for all patients. However, the authors chose a dose of intravenous iron (≤ 900 mg) that may be insufficient for certain patients, whereas for others it covered the theoretical total iron deficit. In addition, the authors did not take into account the iron loss induced by perioperative blood loss. Assuming that 1 mg/l of ferritin is roughly equivalent to 8 mg of stored iron, and that 165 mg of iron are needed to reconstitute 1 g/dl of hemoglobin in a 70-kg adult, these patients may not have enough stored iron (preoperative ferritin ≥ 100 mg/l) to reconstitute their perioperative hemoglobin loss (3–4 g/dl) and keep a normal iron store (ferritin > 30 mg/l).[5]

On the other hand, most of the injected iron sucrose will be cleared from the plasma into the reticuloendothelial system within 24 h (plasma half-life, 6 h) and the rate of transfer of iron from the reticuloendothelial system into circulating red cells may be highly variable: It is more rapid and more complete in patients with iron deficiency than in patients with cancer or inflammation due to several circulating factors (*e.g.*, hepcidin).[6] Nevertheless, a small fraction of the injected agent (4–5%) likely bypasses the intracellular steps and donates iron directly to transferrin in plasma.[7] Thus, the relatively small effect of iron sucrose on hemoglobin levels observed by Theusinger *et al.*[1] might have been enhanced administering the agent at lower doses but more frequently (*e.g.*, 100–200 mg, 2–3 times per week). Using this approach, García-Erce *et al.*[8] reported that the administration of iron sucrose (1,000 mg, range 600–1800) to 10 anemic orthopedic patients awaiting surgery increased their hemoglobin (+ 2.6 g/dl; P < 0.01), ferritin (+ 198 mg/l; P < 0.01), and transferrin saturation (+ 21%; P < 0.01) without significant side effects, and only one patient was transfused.

Third, Theusinger *et al.*[1] inadequately compared their data with the data of the control group and the treated group of Cuenca *et al.*[2], who studied the effects of 200–300 mg of iron sucrose on transfusion requirements in patients with a pertrochanteric hip fracture, starting just 3 days before surgery, and found a reduction both in the percentage of transfused patients and in the transfusion rate, as well as a reduction in postoperative infection rate. However, the reduction in transfusion requirements was only significant for patients with baseline hemoglobin > 12 g/dl. To improve these results, in a subsequent study of 83 patients with hip fracture, they administered a higher iron dose (3 × 200 mg/48 h, perioperatively), plus a single preoperative dose of erythropoietin (40,000 IU) if baseline hemoglobin was < 13 g/dl (75 of 83, 90%), and achieved a significant reduction of transfusion requirements with respect to a control group (71% *vs.* 24%; P < 0.01).[9] Given that the study by Theusinger *et al.*[1] was performed in elective orthopedic patients, their results should be better compared with those reported by Cuenca *et al.*[10] for 31 patients with preoperative hemoglobin < 13 g/dl scheduled for total knee replacement, who received oral iron during the 30–45 days preceding surgery and were managed with a restrictive transfusion protocol. When compared with a previous series of anemic patients (control group, n = 25), this treatment resulted in a significant reduction in transfusion requirements (61.5% *vs.* 19.3%, respectively). This transfusion rate, which is similar to that of Theusinger *et al.*, was reduced further in a subsequent series of patients with preoperative hemoglobin < 13 g/dl (12.3 ± 0.5 g/dl; n = 19) receiving perioperative iron sucrose (2 × 200 mg/48 h) plus a single dose of erythropoietin (1 × 40,000 IU), but 44% of patients were still anemic on postoperative day 30.[5]

In conclusion, the use of intravenous iron should be considered for patients with intolerance to or impaired absorption of oral iron, as well as when time to surgery is too short for oral therapy. However, the total iron dose should be calculated on an individual basis taking into account weight, baseline hemoglobin, iron stores, and predicted perioperative blood loss, to provide each patient with the adequate amount of iron. Finally, in the presence of inflammation, the efficacy of iron sucrose may be further enhanced by the repeated administration of low doses.

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In Reply:—We thank Dr. Cuenca *et al.* for their comments on our article about the efficacy of intravenous iron sucrose in the treatment of preoperative anemia in patients undergoing major orthopedic surgery,[1] and are glad to answer their comments.

We used the World Health Organization definition for anemia as inclusion criteria for our study and reviewed the literature concerning iron deficiency anemia. Interestingly, there is not one universally applicable definition for iron deficiency anemia. Recent papers by Thomas *et al.*[2–4] indicate that the traditional definition for iron deficiency anemia with mean corpuscular volume < 80 fl or a ferritin level < 15–30 μg/l or transferrin saturation < 15% does not take into account the effect of a possible inflammatory state. Therefore, we measured C-reactive protein as well as leukocyte count for every patient at the moment of inclusion. Leukocyte counts ranged from 4,300 to 9,500/μl (reference values being 4,000–10,000/μl in our laboratory) and C-reactive protein ranged from 0 to 12 mg/l (reference, < 7 mg/l). By measuring the soluble transferrin receptor and calculating the ferritin index (soluble transferrin receptor/log ferritin ratio), and using different cutoff values depending on the measured C-reactive protein, we were able to select iron deficiency anemia.

The theoretical total iron deficit for a target hemoglobin of 15 g/dl was calculated for every patient. Total iron deficit was 1,088 ± 239 mg, indicating that the administered dose of 900 mg was indeed slightly less than theoretically needed. Therefore, higher doses may be used in future studies. The perioperative blood loss was not considered in the calculation of the total iron dose, because only the preoperative hemoglobin increase was assessed.

We compared the transfusion outcome of our group of patients with the study of Cuenca *et al.*[5] and found astonishing similarities in both groups treated with intravenous iron. Comparing our results with a combined erythropoietin and intravenous iron treatment[6] or a treatment with oral iron[7] appears inadequate.[8]

The question on repeated low dose intravenous iron was assessed in patients on hemodialysis.[9] Schiesser *et al.*[9] showed that it is possible to maintain the iron status and the hemoglobin level with low dose intravenous iron. However, such a regimen did not allow improving the hemoglobin level. Nevertheless, in orthopedic surgery a direct comparison between repeated low dose *versus* high dose intravenous iron regimen may be the subject of a future study.

In conclusion, intravenous iron should be considered for the relative rapid correction of iron deficiency anemia. However, the real benefit of such a regimen in the context of (orthopedic) surgery needs to be proven in a future prospective, randomized, placebo-controlled trial.

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Xenon and Air Bubble Injection during Cardiopulmonary Bypass

To the Editor:—In an article by Jungwirth *et al.*[1] investigating influences of xenon application to rats undergoing cardiopulmonary bypass, it was reported that when rats received either xenon or nitrogen during ventilation on cardiopulmonary bypass, repeated air injections into the internal carotid artery were found only to negatively influence neurologic outcomes of animals exposed to cardiopulmonary bypass (CPB) procedures, regardless of the gas used for ventilation. Animals not undergoing CPB (sham groups) had significantly better neurologic outcomes. The kind of gas used for ventilation (xenon *vs.* nitrogen) did not influence the results; outcomes were influenced only by the total volume of injected air.[1]

Those findings contradict results published earlier by the same group.[2] Using the same model (injected air while on CPB), they found that the inhalation of xenon adversely affected the neurologic and histologic outcomes of the rats as compared with rats not being ventilated with xenon, but with nitrogen, during CPB.[2]

The results of the group published in 2006 were also at variance with experimental studies having found:

- Only negligible small bubble expansion caused by xenon in a CPB circuit,
- Preclinical findings of beneficial effects of xenon for rats reducing neurologic damages in a comparable CPB model,
- And no adverse effect of xenon delivered on CPB to humans.[3–7]

The different findings in both studies, as published by other groups, deserve some attention regarding the experimental procedures. It would also be beneficial to allow a few questions concerning some descriptions of experimental details to erase possible misunderstandings. Finally, the interpretations of the results could be discussed briefly. For a complete assessment, we have not only studied the publications from Jungwirth *et al.*, but also both doctoral theses on which the publications were based and which are published electronically by the academic library of the University of Munich.*†

Establishing and Validation of the Model

The timeline of presenting and publishing all related papers is rather confusing to the author of this letter. The study published in 2006 is based on a doctoral thesis submitted by Carlsen JM to the veterinary faculty of the University of Munich. Its primary subject is neurologic outcome after xenon treatment in rats after CPB. The thesis submitted by Berkman was carried out to establish and validate the animal model,*† and was submitted in Munich on the same day as the treatment study, but was made available to a broader audience not before 2007, 1 yr after the results were published.

Title of the Studies

"Xenon impairs neurocognitive and histologic outcome after cardiopulmonary bypass combined with cerebral air embolism in rats" contains two speculations that were not investigated: The bubbles' "distance of travel" and "time to rest" in the brain's vascular system are not known and were not investigated. Neither is it known whether persisting occlusions of the brain vessels were responsible for infarcts, found in histologic examinations. Any other factor known to negatively influence outcomes after CPB (*e.g.*, nonpulsatile flow, solid emboli, absence of cerebral autoregulation) at the least also could have been the cause of the troubles.

That the differences found between groups were caused by protective or destructive acting agents must take into account differences in adverse outcomes, which already were found in rats being treated with no significantly different agents. The causes of those varying outcomes in rats are extreme varieties of collateral brain perfusion. Another question concerns this detail: Cerebral infarct volumes were given as a mean $\pm$ SD of 82.7 ± 16.2 mm^3 in xenon animals and 33.2 ± 19.1 mm^3 in controls.[2] In the corresponding doctoral thesis, these values are given as 82.7 ± 51.3 mm^3 and 33.2 ± 60.4 mm^3, respectively.*† Replacing the given SD with SEM values does not solve that problem.

Selection Criteria of Animals, Entering Calculations

"After CPB, animals demonstrating *severe neurologic dysfunction* were killed."[2]*† "Animals not recovering from anesthesia after 3 h are subjected to brain death diagnostic and exsanguinated in deep isoflurane anesthesia. Animals exhibiting severe neurologic damage also are sacrificed during the first postoperative hours. In addition, euthanasia is carried out in animals showing clear signs of neurologic damage, *e.g.*, not being able to eat or drink."*† It is described in ANESTHESIOLOGY that "after CPB all neurologic, cognitive, and behavioral test procedures were performed by an investigator, blinded for the treatment." It is not mentioned that prior to those test procedures an unknown number of animals presenting "severe neurologic dysfunctions" such as "not having recovered from anesthesia until 3 hours after CPB" were killed by the (unblinded) main investigators. It therefore cannot be excluded that this selection process was influenced by bias that makes all results questionable.

Blood Pressures

In the most recent paper,[1] the mean arterial pressures of sham animals were between 105 ± 18 mmHg after 45 min of CPB and 126 ± 20 mmHg after 90 min of CPB. CPB-treated animals had mean arterial pressures of 81 ± 16 mmHg after 45 min of CPB to a maximum of 86 ± 20 mmHg after 90 min of CPB. At the same time, neurologic impairments were found to be more severe in CPB-treated animals, with no differences between groups.

In the authors' earlier paper,[2] the lowest blood pressures occurred during the first 45 min of CPB in the xenon groups, 71 ± 15 mmHg *versus* 88 ± 22 in the CPB nitrogen animals, and the values were 76 ± 11 mmHg in the xenon group *versus* 75 ± 14 mmHg in the nitrogen group at 90 min, the end of CPB. Sham animals during the same phase had mean arterial pressures between 127 ± 13 and 129 ± 17 mmHg during the same phases. Differences were found in neurologic outcomes comparing xenon to nitrogen animals submitted to CPB treatment. Duration of hypotensive phases was not given in any group. The authors only state that, "Hypotension is caused by the nature of CPB." Can it therefore be asked whether the titles of both papers are slightly misleading in assuming that "cerebral air emboli" have caused any negative outcomes in rats? Cerebral air embolism is an event that was not investigated in the animals. Instead, "air bubbles" were injected into carotid arteries, and the authors speculated that these occluded cerebral vessels.

Differences in outcomes were found only between groups with different mean arterial blood pressures during CPB. Other investigators have described other external factors that can influence blood pressure: Low temperatures or elevated hydrostatic pressures (mean arterial pressure, intracranial pressure) can decrease bubble size, high flow velocities can destroy bubbles and lead to "foaming" effects, and low blood velocities can lead bubbles to form large entities.[8–10] In addition, low arterial blood pressures impair collateral perfusion of ischemic areas. Maintaining adequate blood pressure is one method to prevent neurologic damage during CPB and especially in cerebral embolism.[11,12] Hypotension, as remarked by the authors in both publications, may be caused by the "nature" of CPB. Should the "nature" of the anesthesiologist accept that fact without adequate reactions or therapeutic interventions, knowing that other investigators have published that the control of adequate levels of arterial blood pressures is mandatory during CPB with known gaseous embolic load?[12]

In summary, I would like to learn how severely the authors assessed the influences of differences in arterial blood pressures on the results and the interpretation of their studies. In addition, it would be interesting to know why animals displaying the most severe results were excluded from the study population, whether or not a blinded or nonblinded investigator carried out those exclusions, and how many animals in each group were excluded using that procedure.

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In Reply:—We are more than happy to resolve some of the misconceptions that may have been the primary motivation for Dr. Marx to write this letter. First of all, the two experimental studies under discussion were designed with the sole rationale to investigate the safety aspect of xenon when administered during cardiopulmonary bypass (CPB) in the presence of cerebral air emboli (CAE).[1,2] To achieve this goal, we first established an appropriate disease model that incorporates CAE into an existing rodent model of CPB.[2,3] Aiming to identify a suitable CAE volume that would allow for both a high degree of survival and a quantifiable cerebral injury, we selected a dose-escalating approach to investigate the effect of various volumes of CAE during CPB on survival and gross neurologic injury.[2] This study will be further referred to as the "dose-finding study." Based on this work, we designed a second experiment (or "treatment study") that analyzed the effect of xenon on the primary outcome cognitive performance following CPB combined with CAE.[1]

We agree that the order of publication may have contributed to some of the confusion. However, knowing that the human study later published by Lockwood *et al.*[4] was ongoing, this sequence was chosen to ensure timely information about relevant safety concerns for the use of xenon during CPB in the presence of CAE. The subsequent delay in publication of the dose-finding study was primarily due to a lengthy review process.

We appreciate the opportunity to further discuss any differences in terms of study design and primary endpoints of our two studies, because this will allow us to demonstrate that the findings are far from controversial. The primary endpoint of the dose-finding study was survival with an aspired survival rate of about 50%. Therefore, all animals euthanized due to severe neurologic damage were included in the study and were not replaced. There was no difference in survival in animals exposed to xenon *versus* those exposed to nitrogen, but exposure to CPB was associated with lower survival rate compared with sham-operation.[2] Based on this dose-finding study, a CAE volume of 0.3 μl associated with a mortality rate of only 1% was used in the treatment study. As expected, none of the animals in the treatment study showed severe neurologic injury requiring euthanasia, but two animals were excluded from further data analysis and consequently replaced because of the development of cervical hematoma and inspiratory stridor, a condition due to postoperative bleeding rather than neurologic injury. In agreement with the dose-finding study, there was no difference between the xenon- and the nitrogen-treated animals in terms of survival rate in the treatment study.[1]

In the two studies discussed, neurologic outcome was evaluated as both gross neurologic function, reflecting the integrity of the motor cortex, and cognitive performance, mirroring hippocampal injury. Of note, these two outcomes represent two very different executive functions assessed with two distinct batteries of tests: Gross neurologic outcome was assessed with assays of prehensile traction and beam performance and cognitive function with the modified hole board test.

Gross neurologic function in the dose-finding study was worse in animals exposed to CPB compared with sham-operated animals but was not different between xenon and nitrogen groups (original fig. 2[2]) with identical findings in the treatment study (original fig. 1[1]).

Cognitive function also was assessed in both studies. The modified hole board test was performed by two veterinarians, each acknowledged in the associated manuscripts. As mentioned by Dr. Marx, each veterinarian wrote a doctoral thesis in German. However, these theses will not be further discussed for several reasons: (a) They do not represent peer-reviewed publications; (b) they are written in German and are therefore not available to a broader audience; and (c) the results as represented in these theses are identical to those in the published manuscripts. Dr. Marx's confusion about potential differences between the manuscripts and their respective theses is mainly due to the fact that he mistakenly assigned the theses to the publications, meaning the thesis associated with the dose-finding study was assigned to the treatment study and *vice versa*. However, the dose-finding study was designed to treat cognitive function as secondary outcome to explore the feasibility of cognitive assessment in the context of the combined model of CAE and CPB. As discussed in the manuscript, significant limitations need to be considered when interpreting the results: (a) Owing to the study design, only 26 out of 60 animals were available for cognitive testing; (b) surviving animals were subjected to different CAE volumes; and (c) the multiple logistic regression analysis was based on cognitive outcomes on postoperative day seven and not on the entire observation period.[2] Taken together, it does not come as a surprise that no differences in cognitive outcome were seen among treatment groups (original fig. 3[2]). In fact, the dose-finding study did not even demonstrate a difference in cognitive function between the CPB and the sham-operated groups. In contrast, the treatment study was designed to treat cognitive outcome as the primary endpoint. In that study, 10 surviving animals per group (exposed to CPB and CAE with constant volumes) had their cognitive function assessed over 14 days with the modified hole board test.

Statistical analyses were not restricted to one single day, but rather applied to the entire observation period as routinely done when analyzing learning tasks. Therefore, the treatment study appears to be sufficiently powered to evaluate cognitive outcome as primary endpoint while demonstrating a worse outcome for animals treated with xenon.

We agree with Dr. Marx that the results of our treatment study differ from at least one clinical and one experimental study demonstrating no adverse effects of xenon delivery during CPB.[1,4,5] However, this does not surprise us, because our study is the first to experimentally address the impact of xenon on neurocognitive and histologic outcome following CAE during CPB. Several other differences apply: Ma et al.[5] did not integrate CAE into the rodent model of CPB, restricted the application of xenon to time on CPB, and used a different test to assess neurocognitive outcome. Although the recent small human study by Lockwood et al.[4] concluded that xenon could safely be delivered to coronary artery bypass grafting patients while on CPB, that study did not include a detailed postoperative neurologic and neurocognitive assessment. Our results are not in disagreement with the results of the cited in vitro studies, because they confirm the potential of xenon to expand air bubbles, albeit to a smaller extent compared with nitrous oxide.[6,7]

We agree with Dr. Marx that blood pressure is an important factor potentially affecting bubble size and collateral perfusion of the brain, and therefore take issue with his statement that animals exposed to CPB were documented to have lower blood pressures while on CPB. As illustrated in table 1 of the treatment study, there is no difference in mean arterial blood pressure (MAP) between the two CPB groups, regardless of xenon.[1] Clinically, hypotension during CPB does not appear to impact cognitive or neurologic function after cardiac surgery,[8,9] and autoregulation remains intact within a wide normal range of MAP (50 to 100 mmHg) as long as pH and arterial carbon dioxide are kept constant.[10,11] In another clinical study investigating the effect of MAP on outcome, MAPs of 80–100 mmHg were assigned to the "high" MAP group whereas patients with MAPs of 50–60 mmHg during CPB were assigned to the "low" MAP group.[12] Therefore, Dr. Marx confuses the issue when considering MAP values of 70–80 mmHg during CPB in our study as "hypotensive." In conclusion, blood pressure may present an important contributing factor to an adverse cerebral outcome following cardiac surgery, but is unlikely to be the reason for an adverse cognitive outcome in the CPB group treated with xenon, as MAPs were comparable to rats subjected to CPB and ventilated with nitrogen.[1]

Although the kinetics and content of CAE were not studied directly, we believe that indirect information about xenon's effect on cerebral air emboli was generated in our treatment study[1]; therefore, we speculate— but do not conclude—that potential neuroprotective effects of xenon may have been masked by the effects of xenon on CAE. Critical physiologic parameters such as MAP and arterial PCO_2 were controlled and any selection bias was avoided by selecting a suitable CAE volume based on the dose-finding study allowing for long-term survival and functional testing.[2]

We strongly believe that interpretation of data obtained from any model must always take into consideration the limitation of the model itself. Even the most sophisticated animal models likely will fail to simulate the clinical situation completely. Models such as ours only offer insights into certain aspects of clinical problems, and therefore one needs to use caution when making an interpretation or comparison.

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P6 Acupuncture Point Stimulation for Prevention of Postoperative Nausea and Vomiting

To the Editor:—We read with great interest the article by Arnberger et al.[1] in which the authors successfully demonstrated a significant reduction in the incidence of nausea and vomiting, compared with a control group. It was interesting that a conventional nerve stimulator, which is readily available, was used for this purpose. The overall incidence of postoperative nausea and vomiting (PONV) was 61% in the control group. However, even with intervention, the frequency of PONV in the intervention group remained unacceptably high (45%). Although the use of transcutaneous acupressure stimulation for prevention of PONV has been reported previously,[2,3] it has not been shown that P6 stimulation would provide a reduction in PONV when given in combination with other prophylactic therapies. It was reported previously that the combination of acupressure and ondansetron had a 73% response rate, versus 40% for acupressure alone, when used for treatment of PONV.[4]

Given the low cost of ondansetron, it has become standard practice at our institution to administer ondansetron prophylactically, often in combination with other standard therapies such as dexamethasone, to patients at risk for PONV who are undergoing general anesthesia. It would be of interest to repeat the study to determine whether P6 stimulation, when combined with prophylactic therapy such as ondansetron, would in fact further decrease rates of PONV. This would have greater applicability to the current standard of practice, in which most patients undergoing general anesthesia receive prophylaxis for prevention of PONV.

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P6 Stimulation Is Different from Monitoring Neuromuscular Blockade

To the Editor:—Dr. Arnberger *et al.*[1] are to be commended for their study showing the efficacy of P6 stimulation in reducing the incidence of nausea and vomiting in female patients undergoing laparoscopic surgery. They stimulated the P6 acupuncture site by altering the technique that most anesthesiologists use to monitor neuromuscular blockade. Instead of placing the electrodes over the ulnar nerve, as is commonly done, they placed them over the median nerve. The median nerve innervates almost all of the muscles in the thenar eminence, including muscles responsible for abduction, flexion, and opposition of the thumb. Stimulating this variety of muscles of the thumb and its effect on interpretation and significance of accelerography data has not been extensively studied.

All patients were reversed identically with 0.4 mg of glycopyrrolate and 2.5 mg of neostigmine until 100% of twitch height was reached, but were extubated based on clinical signs of full recovery. Recovery detected clinically occurs earlier than electromyographic or accelerographic evidence of "full recovery." If the patients were extubated on the basis of clinical data, many awake patients would have to be stimulated with 50 ma of current for varying degrees of time until their twitch height returned to 100%. If the patients were kept intubated until a return to baseline of twitch height was seen, then the patients would have been anesthetized for varying lengths of time after their surgery and clinical recovery of neuromuscular blockade was observed. No mention is made of what happened to patients who never returned to baseline, had problems with the accelerography measurement, or had significant protocol violations such as conversion to an open procedure or missing data points.

The authors recognized that a single-twitch method of monitoring neuromuscular blockade is not often used. This is because double-burst stimulation and train-of-four stimulation are more sensitive when qualitative methods of assessing residual neuromuscular blockade are employed. It is for these reasons that I must take issue with one of the concluding statements of the authors, that ". . . electrical stimulation of the P6 acupuncture point with monitoring neuromuscular blockade is simple and easy to perform, *without any danger to the patient* (emphasis added)." Changing standard neuromuscular monitoring techniques to reduce nausea and vomiting is laudable, as long as it does not diminish the clinician's ability to detect inadequate reversal. It is well established that incomplete reversal can be a cause of patient morbidity and mortality. Until well done studies are performed to show that this variation of monitoring is as effective in detecting inadequate reversal of neuromuscular blockade, labeling it as completely safe is premature.

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The Role of Smoking History in the Development of Postoperative Nausea and Vomiting

To the Editor:—We congratulate Dr. Arnberger *et al.*[1] on their recent work using nerve stimulation at the P6 acupuncture site to reduce the incidence of postoperative nausea and vomiting (PONV). This is obviously an important clinical work that could influence the management and multimodal approach to PONV. However, we are concerned about the validity of the conclusions secondary to the disproportionately higher number of smokers in the treatment group. The reasons for this concern are as follows.

According to the recently published guidelines from the Society for Ambulatory Anesthesia, the risk factors for PONV fall into four criteria. These include patient risk factors, anesthesia risk factors, surgical risk factors, and type of surgery.[2] The three most important patient risk factors are female gender, prior history of PONV or motion sickness, and nonsmoking status. In Arnberger *et al.*,[1] they controlled very well for the gender (all patients female, as mentioned in the editorial) and the history of motion sickness risk

factors ($P = 0.37$). Of particular concern is the higher percentage of smokers in the treatment P6 group. Any descriptive statistics with a P value less than 0.15 should be accounted for as a potential confounder, especially if the variable is known to influence the dependent variable. It has been demonstrated in multiple randomized controlled studies that smoking decreases the incidence of PONV and having a higher percentage in the treatment group has a strong possibility of affecting the conclusion. A stratified random sample procedure would have been a much better option to achieve equal numbers of smokers in each group. Given that this was not the case, to account for this potential confounder, a logistic regression analysis should have been used to ensure that the higher percentage of smokers didn't affect the clinical outcome in this study.

Several studies have shown that smoking is an important risk factor in the development of PONV. A Canadian study retrospectively reviewed the charts for 16,000 patients postoperatively for over 2 yr in four teaching hospitals using a multiple logistic regression analysis to show that nonsmokers were 1.79 times more likely to develop PONV.[3] Stadler *et al.*[4] had a sample size three times higher than Arnberger *et al.*,[1] and showed that nonsmoking status was highly significant for both nausea and vomiting ($P = 0.0070$ and 0.0074). In a Korean model derived from more than 5,000 patients, a multiple regression analysis showed that smoking status reduced PONV with an odds ratio of 2.0.[5]

The exact mechanism of smoking reducing the incidence of PONV is not fully explained; however, there are several potential explanations. Chronic exposure to one of the chemicals in tobacco may desensitize the patient to anesthetic gas or may a have direct antiemetic effect.[6] Another explanation is that the cytochrome p450 may be up-regulated in chronic smokers, which may increase metabolism of anesthetic agents and result in less PONV.[7]

In conclusion, we believe that the results of this study may be hampered by the uneven distribution of smokers in the treatment group. Our intent is to encourage further studies in the area and/or further statistical analysis performed to truly elucidate if this amazing effect is caused by this seemingly simple maneuver.

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In Reply:—We thank Drs. Neustein, Groudine, and Awad for their interest in our work on the effect of transcutaneous electrical stimulation of the P6 acupuncture point while neuromuscular blockade monitoring,[1] and would like to respond to their major comments about neuromuscular reversal and the use of stimulation modes as well as the potential confounder of nonsmoking as a trigger for postoperative nausea and vomiting (PONV).

Dr. Neustein notices a relatively high incidence of PONV in our study. We did a study in women using volatile anesthetics, which are well known PONV triggers.[2] We strongly agree that the reduction in nausea by the P6 stimulation plays an important role in a prophylactic multimodal antiemetic approach as proposed by Scuderi *et al.*[3,4]

All patients were reversed and extubated based on clinical signs of full recovery as is daily clinical practice at the hospital. No problems were found in any of the studied patients after extubation. The intention of the study was to reduce PONV by continuous monitoring of neuromuscular blockade over the P6 acupuncture point using single-twitch response during surgery. We thank Dr. Groudine for the comment that accelerography stimulated over the median nerve has not been extensively studied, and for noting that double-burst and train-of-four stimulation are more reliable in detecting residual blockade. For patient safety reasons, we also recommend changing from the single-twitch mode to one of the modes mentioned above, which is easy to do without harming the patient during recovery from neuromuscular blockade.

Conversion to open procedure occurred in five patients of the control group and in seven patients of the P6-stimulation group ($P = 0.77$, chi-square). We had only two problems with the accelerograph, and both were in the control group (ulnar nerve stimulation). The battery had to be replaced in both cases to continue the electrical stimulation.

Because we were concerned about trigger factors for PONV, we recorded risk factors that were evenly distributed between both groups; only smoking showed a higher difference of 11%. Dr. Awad is right that stratification would have omitted that, but stratifying for all of the major risk factors (PONV history, motion sickness, and smoking) would have complicated a rather simple study design. We assumed that our relatively large sample size would distribute all confounders equally in both groups. To assure that smoking was not a potential confounder affecting the outcome, we performed a multiple logistic regression analysis (including PONV history, motion sickness, postoperative opioid therapy, and smoking),[5] which revealed only the different stimulation side as a significant factor 0.028). Because no significant difference was found for the demographic and PONV-related data, we did not include that analysis in the original manuscript.

In summary, we would like to see further studies in this area using a multimodal prophylactic approach including acupuncture to reduce PONV. At the emergence from anesthesia, meticulous attention should be applied to avoid residuals of neuromuscular blockade using our approach. Smoking was evenly distributed between the ulnar nerve stimulation group and the P6-acupuncture stimulation group.

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(Accepted for publication March 26, 2008.)

ANESTHESIOLOGY, Its Mission, and 2007's "Best" Articles

To the Editor:—I read with interest the synopsis[1] of important research contributions published in ANESTHESIOLOGY during 2007 as chosen by the Editor-in-Chief and members of the Editorial Board. Two troubling issues raised by this article[1] deserve comment. First, as a former Associate Editorial Board Member (1999–2005), I was surprised to read that the mission statement of the journal as described in the article does not contain the word "anesthesiology" or any of its derivatives, instead advocating the advancement of the "science and practice of perioperative, critical care, and pain medicine."[1] While this stated mission may be a noble one, it is important to acknowledge that ANESTHESIOLOGY is the official journal of the American Society of Anesthesiologists, not the American Society of Perioperative, Critical Care, and Pain Medicine. The article's authors are faculty members in Departments of Anesthesiology or Anesthesia, and those who are physicians are certified by the American Board or European Academy of Anesthesiology. Omitting "anesthesiology" or "anesthesia" from the mission statement of ANESTHESIOLOGY seems to be a denial of our specialty's identity.

Second, I'm uncertain of the value of highlighting a few selected articles. All of the investigators who present their research findings in ANESTHESIOLOGY deserve our gratitude for their efforts.[1] The anesthesiologists who read ANESTHESIOLOGY are intelligent professionals who should be able to independently evaluate which contributions in each issue may be of significance. I would appreciate hearing from the Editors the reasons that they felt such an article was necessary.

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1. Eisenach JC, Borgeat A, Bosnjak ZJ, Brennan TJ, Kersten JR, Kochs EF, Weiner-Kronish JP. 2007 in review: A dozen steps forward in anesthesiology. ANESTHESIOLOGY 2008;108:149–55

(Accepted for publication April 10, 2008.)

Michael M. Todd, M.D., served as Handling Editor for this exchange.

In Reply:—I thank Dr. Pagel for his continuing service to the Journal in raising these issues, and for providing me another opportunity to describe the mission of the Journal. Why does the word "anesthesiology" not appear in the mission statement for this journal? To the current Editorial Board of the Journal and myself, anesthesiology is the practice of medicine—perioperative, pain, and critical care medicine. I am not ashamed of the name of our specialty, but chose to subdivide it into its three central aspects in the mission statement and in the new organization of the table of contents of the Journal.

As regards the Year in Review article,[1] I agree with Dr. Pagel that determining which articles best meet our mission statement is a subjective process, just like the peer review that aims to identify the most important observations with the greatest likelihood to advance our understanding and the care of our patients. Only approximately 30% of submitted manuscripts meet these criteria and are published in the Journal. We attempt to serve our readership by utilizing the best and brightest in our specialty, including Dr. Pagel, to make this selection, and to further highlight and translate the importance of these findings through editorials, placement on the home page of the Journal, and an active press release program. I recognize that our readers are busy and may miss some articles, and a major goal of the 2007 Year in Review article was to highlight articles that the Editorial Board and I felt were of particular importance, often of immediate clinical relevance.

As an aside, I might add that the Year in Review article originally was not indexed in Medline, which has a policy excluding articles that attempt to increase a journal's impact factor by reviewing and citing the journal's own articles. When we pointed out to Medline officials that we had deliberately altered our own journal's style to purposefully not cite the articles in this review, they recognized that this article was of interest and utility to our readership and agreed to index it.

James C. Eisenach, M.D., Wake Forest University School of Medicine, Winston-Salem, North Carolina. editor-in-chief@anesthesiology.org

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(Accepted for publication April 10, 2008.)

Maneuver to Relieve Kinking of the Endotracheal Tube in a Prone Patient

To the Editor:—We would like to report a case of intraoperative kinking of the endotracheal tube (ETT)[1] in a prone patient and a unique maneuver to restore its patency.

A 52-yr-old female was undergoing craniotomy for tumor resection in the prone position. A 7.5-mm polyvinyl ETT was placed without difficulty and secured at 21 cm at the teeth. The esophageal temperature was 36.6°C when peak airway pressures began to rise. Examination revealed an ETT that would not allow passage of a small flexible suction catheter beyond 19 cm, the point at which the pilot balloon line inserts. Extubation over a tube changer and then reintubating was considered, but rejected, because it was believed that even a smaller diameter tube changer would not fit through the kinked ETT. Given that the patient was prone and in pins with an open cranium, we felt it would have been difficult to return the patient to a supine position to troubleshoot the ETT obstruction.

A Berman intubating airway (Vital Signs, Totowa, NJ), often used as an aid to fiber-optic intubations, was spread longitudinally, lubricated, passed over the ETT, then slowly pushed into the mouth until the kinked area of the ETT was approximately in the middle of the Berman airway, thereby immediately relieving the kink. The case proceeded without further difficulty.

One need not remove the ETT connector, but should be careful not to pinch or tear the pilot balloon line. As can be seen in the figures, the Berman airway has a "hinged" side (fig. 1) and an open side. A partially inserted ETT is shown in figure 2. Because of dependent edema in airway tissues, lips, and tongue that often occurs after prolonged time in the prone position, one may deflate the ETT cuff and extubate through the Berman airway, leaving it in place to aid ventilation. The Berman airway comes in multiple sizes to accommodate larger or smaller ETTs.

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Fig. 1. Berman airway showing hinged side.

Fig. 2. Endotracheal tube partially inserted into Berman airway.

(Accepted for publication February 27, 2008.)

Low Plasma Fibrinogen Levels with the Clauss Method during Anticoagulation with Bivalirudin

To the Editor:—Bivalirudin is a bivalent direct thrombin inhibitor (DTI) with a plasma half-life of approximately 25 min. It is increasingly used as a heparin alternative in percutaneous coronary intervention procedures,[1] and in cardiac surgical patients with heparin-induced thrombocytopenia.[2,3] The anticoagulant effect of bivalirudin usually is monitored with activated clotting time, but the utility of viscoelastic monitors, including Thrombelastograph® or thromboelastometry (*e.g.*, ROTEM®; Pentapharm, Munich, Germany), has been recently demonstrated by us and the other group.[4,5] We herein describe a case in which bivalirudin monitoring with ROTEM® was found useful. A 68-yr-old, 110-kg female was diagnosed with acute myocardial infarction. The cardiac catheterization showed ostial occlusion of left anterior descending artery, 90% stenosis of right coronary artery, and 40% stenosis of circumflex artery. Past medical history was notable for hypertension, hypercholesterolemia, type II diabetes, chronic anemia, and mild cirrhosis. Given her previous history of heparin-induced thrombocytopenia and persistent antibody titer on admission, she was treated with argatroban infusion at 0.5 μg · kg · min until 4 h before the scheduled off-pump coronary bypass graft surgery. Baseline laboratory results showed hematocrit 33.3%, platelet $111 \times 10^3/mm^3$, fibrinogen 432 mg/dl, partial thromboplastin time 73.8 s, and celite-activated clotting time 188 s. For anticoagulation, bivalirudin was given at 0.75 mg/kg, followed by infusion at 0.75 mg · kg · h, according to her ideal body weight (70 kg). This regimen maintained activated clotting time above 400 s, and delayed tissue factor induced thrombus formation on ROTEM® (fig. 1A). Bivalirudin infusion was stopped at the beginning of proximal anastomoses, and laboratory values were hematocrit 21%, platelet $103 \times 10^3/mm^3$, and activated clotting time 278 s at the end of three-vessel bypass procedure. Two units of packed red blood cells were administered, and infusion of tranexamic acid 2 mg · kg · h was started. Notably, the plasma fibrinogen level using the modified Clauss method (BCS®, Dade Behring, Deerfield, IL) was reported at that time as less than 60 mg/dl, but the ROTEM®-based fibrinogen assay (maximal clot formation of FibTEM® [Pentapharm, Munich, Germany]) indicated functional fibrinogen level[6] throughout the bivalirudin infusion (fig. 1A). The postoperative chest tube drainage was 180 ml over 12 h.

To evaluate the effect of direct thrombin inhibitors (DTIs) on the fibrinogen measurements using the modified Clauss method, argatroban, bivalirudin, lepirudin, and heparin at various concentrations were added *in vitro* to the pooled human plasma, (CRYOcheck lot No. A1044; PrecisionBioLogic, Dartmouth, Nova Scotia). The concentrations of DTIs and heparin used in our study span from therapeutic to supratherapeutic levels according to the reported plasma (molar) concentrations; argatroban 1–5 μg/ml (2–10 μM), bivalirudin 2–20 μg/ml (1–10 μM), lepirudin 1–5 μg/ml (0.15–0.75 μM), and heparin 0.4–4 U/ml.[7–9] The measured fibrinogen level in the presence of three DTIs and heparin was progressively lowered in the BCS® system relative to the baseline measurement (311 ± 7.6 mg/dl), and it also was affected to a lesser extent in the STA-R Evolution® system (Diagnostica-Stago, Parsippany, NJ) (table 1). The fibrinogen measurements using the maximal clot formation parameter of ROTEM® were unchanged when the spiked plasma samples were recalcified and activated with tissue factor, although DTIs delayed the clotting process (fig. 1B). Because bovine thrombin is used as a reagent for these assays based on the modified Clauss method,[10] test results are susceptible to antithrombin
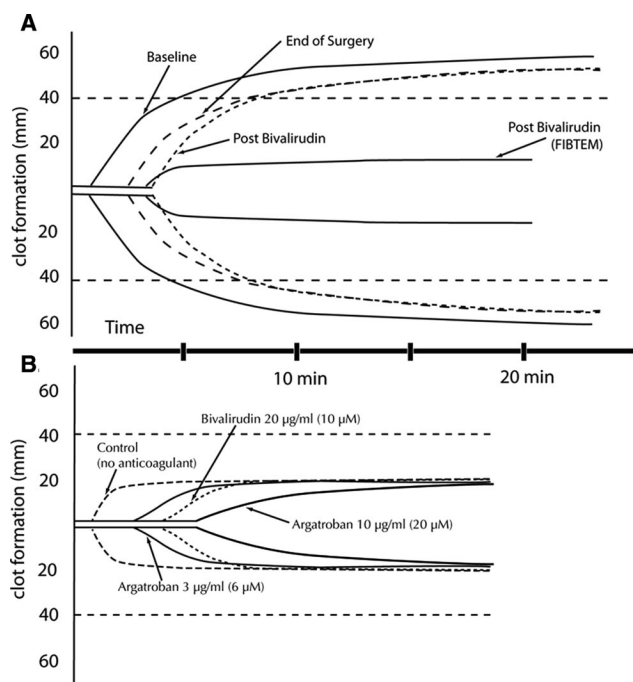
Fig. 1. *A* Thromboelastometry (ROTEM®; Pentapharm, Munich, Germany) tracings during bivalirudin anticoagulation. Native whole blood samples (300 μl) were triggered with 20 μl of the commercial tissue factor reagent EXTEM (Pentapham). FibTEM® assays were performed similarly with the addition of cytochalasin D to exclude platelet interactions with polymerized fibrin. It is notable that blood clotting (*i.e.*, fibrin polymerization) occurs even after the bolus bivalirudin injection after a delay. *B* Thromboelastometry (ROTEM®) tracings in pooled plasma spiked with argatroban or bivalirudin. Plasma samples (300 μl) were triggered with 20 μl of EXTEM reagent and $CaCl_2$. The onset of fibrin polymerization was more delayed with argatroban at 10 μg/ml than bivalirudin at 20 μg/ml due to lesser molar concentration of the latter (20 μM *vs.* 10 μM). The maximal clot formation reaches the same level over time.

effects of DTIs and heparin. This effect was more evident at therapeutic concentrations of bivalirudin tested when using the BCS® system compared with STA-R® (table 1). The difference may be attributed to the clot detection mechanisms, or different amounts of exogenous thrombin added for clotting. The BCS® system derives fibrinogen levels using photo-optical turbidity changes, whereas STA-R® magnetically senses an increased viscosity due to clotting using the pendulum motion of a steel ball. The rate of change in turbidity (*i.e.*, fibrin polymerization) is clearly affected by DTIs, particularly argatroban (table 1). The STA-R® and ROTEM® maximal clot formation seem to be less susceptible to DTIs, due to their viscosity detection mechanisms, but α-angle of ROTEM®, which reflects the rate of fibrin polymerization, is reduced by DTIs (fig. 1B).[4,5,11] Our present data demonstrate that fibrinogen measurements are affected in the order of argatroban > bivalirudin > lepirudin for the BCS® method. Because the molecular weight of argatroban (527 Da) is much smaller than that of bivalirudin and lepirudin (2,180 Da and 6,980 Da, respectively), exogenously added thrombin for the fibrinogen assay is more inhibited in the molar

Table 1. Plasma Fibrinogen Levels according to the Clauss Method

μg/ml	Argatroban BCS®	Argatroban Stago	Bivalirudin BCS®	Bivalirudin Stago	Lepirudin BCS®	Lepirudin Stago	U/ml	Heparin BCS®	Heparin Stago
0	304	311	317	307	303	322	0	311	309
1	197	307	238	299	252	300	2	314	302
3	< 60	251	141	283	230	296	4	285	300
5	< 60	172	< 60	264	157	299	8	165	297
10	< 60	< 60	< 60	232	< 60	264	—	—	—

The Clauss method of fibrinogen determinations (in mg/dl) was performed in duplicate according to the manufacturer's instructions using the BCS® (Dade Behring, Deerfield, IL) and STA-R Evolution® (Diagnostica-Stago, Parsippany, NJ) systems. Reported fibrinogen levels below detection limits are indicated as "< 60."

excess of argatroban. Similarly, Warkentin *et al.*[12] previously demonstrated that DTIs affect prothrombin time in a molar concentration dependent manner, thus therapeutic concentrations of argatroban prolong prothrombin time more than bivalirudin and lepirudin. Heparin also affects fibrinogen measurements, but less extensively than lepirudin (table 1). Presently, there is no antidote for anticoagulation with DTIs. Low fibrinogen levels during DTI therapy may worsen bleeding because all DTIs compete with fibrinogen for thrombin. The maintenance of fibrinogen levels is critical in achieving hemostasis after cardiac surgery.[13,14]

In summary, we demonstrate the turbidmetric fibrinogen assay is particularly affected by DTIs, and falsely low fibrinogen levels are reported during bivalirudin anticoagulation. The modified thromboelastometry using abciximab or cytochalasin D can be used to assess functional fibrin polymerization, and it may be useful for evaluating hemostatic function and recovery from bivalirudin therapy.[5,6,15]

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(Accepted for publication March 20, 2008.)

Labor and Cesarean Delivery Patterns

To the Editor:—The unpredictability and variations in obstetric patient load make staffing anesthesiologists on the labor floor very difficult. If we were more aware of the actual workload patterns, then we could improve obstetric anesthetic service. Some studies[1–3] suggest that patients' circadian rhythms influence delivery times; others[4–7] suggest that institutional factors exert a greater influence.

To help us determine delivery patterns, we recently reviewed data we collected during a 3-month period from our labor and delivery unit at Lucile Packard Children's Hospital, Stanford, California. Our institution, a tertiary referral center with dedicated day and night obstetric anesthesia coverage, performs more than 5,000 deliveries per year. Of these deliveries, 25–30% are cesarean, and the labor epidural rate is > 80%. Up to four cesarean deliveries are scheduled daily (Monday to Friday), but only one is scheduled per day on the weekends. We admit patients to the labor and delivery suite at 7 AM for induction of labor.

Figure 1 compares the scheduled number of cesarean deliveries with the actual number of cesarean deliveries (scheduled plus nonscheduled) that occur during a week. Although the majority of scheduled cesarean deliveries were performed on Tuesday, Wednesday, and Thursday, the actual cesarean deliveries peaked on Thursday and Friday. Figure 2 shows a similar peak (Thursday and Friday) in the weekly pattern of total (vaginal and cesarean) number of deliveries. The mean ± SD number of total deliveries per day during the week was 14.2 ± 4.5 compared with the 12.7 ± 4.2 during the weekend ($P = 0.13$). The mean ± SD of actual
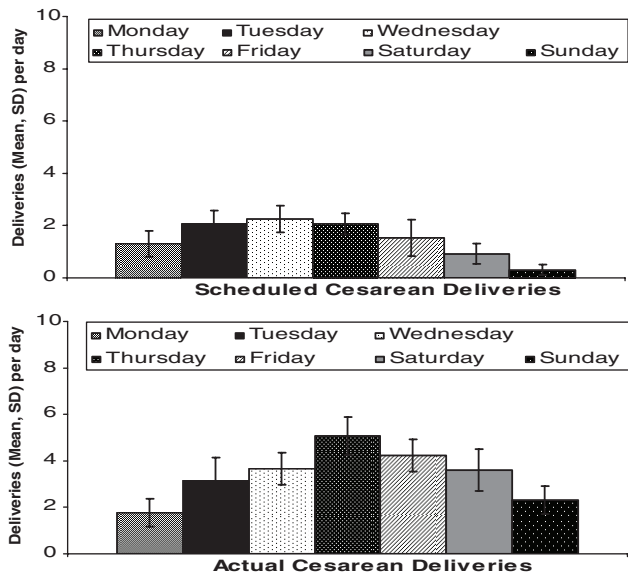
Fig. 1. Scheduled *(top)* and actual (scheduled plus nonscheduled) *(bottom)* cesarean deliveries. Values are means ± SD.

cesarean deliveries per day during the week was 3.6 ± 1.9 compared with 3.0 ± 1.6 during the weekend ($P = 0.15$).

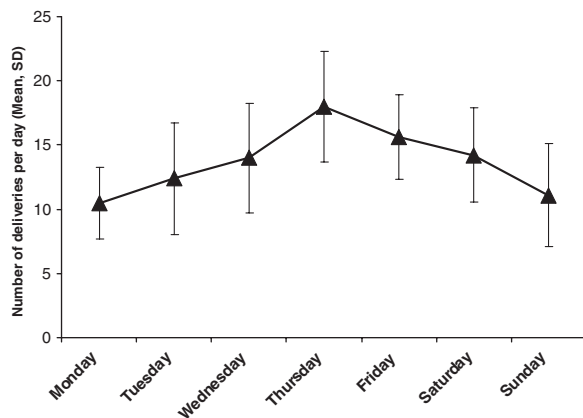A number of studies have found that institutional factors are more influential than natural factors on the delivery workload.[4–7] Despite the fact that scheduled cesarean deliveries at our institution account for 53% of our total cesarean deliveries, the scheduled ones did not appear to impact the overall cesarean workload pattern. Our results show that despite a bias toward more scheduled cesarean deliveries earlier in the week, the peak workload occurs in the latter part of the week. We are not sure why this workload bias exists. Clinicians may increase cesarean deliveries on Thursday and Friday in anticipation of the weekend. Induction policies may influence overall cesarean delivery times more than do scheduled deliveries. We did not find that cesarean and total deliveries were significantly reduced over the weekend. Reduced weekend and night coverage may give clinicians the impression of an increased workload.

We recommend that institutions review their obstetric workload to help plan their anesthetic coverage and staffing requirements. Obstetricians' practices and organizations vary greatly among institutions. Our findings suggest that increasing the number of scheduled cesarean deliveries earlier in the week may compensate for the increased deliveries in the latter part of the work week, evening out the workload throughout the week. Our obstetricians and nursing management are aware of these workload biases and plan to use this data to organize future staffing and scheduling changes. However, constraints related to physicians, nurses, patients, and families may make altering weekly patterns in cesarean delivery workload very difficult. In addition, the benefits derived from institutional and/or patient factors that have cause these observed biases may outweigh the increased costs related to this nonuniform, less-efficient workload pattern.

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Fig. 2. Number of total deliveries (vaginal and cesarean) per day. Values are means ± SD.