Coadministration of Propofol and Midazolam Decreases Bispectral Index Value as a Result of Synergic Muscle Relaxant Action on the Motor System

To the Editor:—We read with great scientific interest the study of Vuyk et al. reporting three cases in which volunteers receiving combinations of propofol and midazolam remained responsive to verbal command although the Bispectral Index (BIS) values were at, or just above, 40. The area considered to be associated with adequate hypnosis for surgery (BIS, 40–60). Vuyk et al. note that the electroencephalographic activation induced by both propofol and midazolam has been difficult to interpret. They ascribe the particular low combination of propofol and midazolam, which at these concentrations is not part of the BIS-behavioral database on which the BIS calculation is based, as a possible cause. As a result, the electroencephalographic pattern induced by this combination may well be misinterpreted by the BIS® monitor (Aspect Medical Systems, Newton, MA) as an electroencephalographic pattern associated with a patient experiencing a surgical hypnotic sedation level instead of actually being responsive to verbal commands. This hypothesis is very interesting, but we believe that alone, it is not enough to give a reasonable explanation.

Neuromuscular activity impairs BIS monitoring. A biasing effect of the electromyogram on the BIS may explain discrepancies in previous studies assessing BIS in the presence of neuromuscular activity. Electromyographic activity has previously been reported to elevate the BIS, whereas it may be lower in patients receiving neuromuscular blockade.

Midazolam and propofol have direct relaxant properties. Midazolam exhibits a well-known myorelaxant effect as a result of a block of inactivated Na channels in skeletal muscle fiber. Moreover, interaction of midazolam, at very low concentrations, with the nicotinic acetylcholine receptor leads to a substantial reduction of the current amplitude, which suggests an additional closed channel block responsible, to some extent, for the muscle-relaxing effects of midazolam. Midazolam is capable of attenuating opioid rigidity. Propofol also provides some degree of muscle relaxation. Mean muscular activity recorded on an electromyography decreases from 100 mV to 10–25 mV as a result of propofol administration, with restoration to previous levels within 10 min. At clinical concentrations, propofol acts on peripheral parts of the motor system, depressing spinal motor neuron excitability. Motor evoked potentials are also affected by propofol. Because of their muscle relaxation properties, propofol and midazolam are used in tetanus management not only for sedation but also for muscle relaxation.

These data, taken together, widely indicate that in sedated patients coadministration of both propofol and midazolam may result in a synergic muscle relaxant action on the motor system and therefore in a decrease in BIS value. This hypothesis is consistent with a study reporting that the central part of the motor system is also impaired when propofol is coadministered in a midazolam-fentanyl based anesthesia.

The clinical relevance is that when BIS is assessed during or after the coadministration of midazolam and propofol, despite the absence of a neuromuscular blockade, it is necessary to evaluate the potential synergic muscle relaxant action on BIS before making conclusions about depth of sedation or anesthesia. Finally, this hypothesis further supports the wise statement by Vuyk et al. reporting that the BIS is a measure of drug effect, not an independent measure of brain function.

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Normal Bispectral Index Values in Healthy Volunteers

To the Editor—Vuyk et al., in a recent series of case reports, concluded that three volunteers were responsive with bispectral index (BIS) values of 40–50. The case reports (and corresponding video) raise some interesting questions regarding the methodology utilized as well as the applicability of this information to routine clinical practice.

First, it is our understanding that these patients were volunteers undergoing pharmacokinetic-dynamic study while monitored with BIS® (BIS® monitor, Aspect Medical Systems, Newton, MA). It has been shown previously that healthy asleep volunteers demonstrate BIS levels well into the 40s (and below), independent of pharmacologic intervention. It is not surprising, therefore, that BIS decreased as it did, nor is it surprising that it rose with prodding. The video clearly and repeatedly shows the rapid increase in BIS after either verbal or physical stimulation despite the inherent lag time of 15 to 30 s for raw data smoothing.

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Second, the value of 40 is reemphasized in the report, when in fact the graphs clearly show that values in the 40–50 range were only very briefly obtained. These episodes did correspond to a level of Deep Sedation, as defined by the American Society of Anesthesiologists, as evidenced by the fact that the subjects did not maintain adequate ventilation and were repeatedly told to take deep breaths. It would have been far more valuable for the researchers to report the corresponding data from pulse oximetry without the use of supplemental oxygen. This would have provided meaningful information as to the relationship between BIS and respiratory function.

Third, it would have been interesting to note whether these patients had recall of the prodding. Movement to command does not necessarily translate into conscious decision-making or recall of the event. An interesting follow-up study design would include specific voice and tactile commands with a subsequent assessment of recall. It should be emphasized that the researchers demonstrated responsiveness and not awareness. The clinical applicability is debatable and in our opinion does not warrant the suggested reevaluation of the BIS-XP algorithm.

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In Reply.—We thank Fodale et al. for their positive remarks concerning the scientific importance of our manuscript regarding the low bispectral index (BIS) values in awake volunteers receiving a combination of propofol and midazolam and are happy to respond to their comments.1 The bottom line of the letter from Fodale et al. is that hypnotic agents like propofol and midazolam have muscle relaxant properties and thus reduce electromyographic activity, thereby lowering BIS. The authors thus argue that the low BIS values in the awake volunteers may be partially the result of the muscle relaxant effects of propofol and midazolam.

Previously, BIS values, even when using the BIS-XP® (Aspect Medical Systems, Newton, MA), have been shown to be affected in various environments2 and to decrease significantly in sedated intensive care unit patients in response to the administration of a muscle relaxant.3 In this study by Vivien et al.3 atracurium 0.5 mg/kg reduced mean electromyographic activity in midazolam-sufentanil sedated patients from 37 dB to 28 dB, thereby diminishing mean BIS-XP values from 67 to 43 while the midazolam-sufentanil administration was maintained unchanged.

In the three volunteers participating in the pharmacokinetic-dynamic study of the case report, electromyographic activity decreased from baseline values of 52 ± 14 dB to as low as 32 ± 9 dB in the presence of the combination of propofol and midazolam. We may thus confirm the notion that the combination of propofol and midazolam reduces electromyographic activity. However, the electromyographic activity in the three volunteers still exceeded the electromyographic activity as reported in patients by Vivien et al.3 after these had received 0.5 mg/kg atracurium. Had the electromyographic activity been even more depressed, the BIS values in our volunteers might actually have been even lower. This even more endorses the conclusion of our case report that propofol and midazolam, by reducing electromyographic activity, may have affected the BIS levels in our volunteers. However, because electromyographic activity was still present at the highest midazolam and propofol concentrations and BIS thus may still have been overestimated, this only strengthens the case report in its conclusion that patients may be awake at low BIS levels. We thus stress again the need for a careful interpretation by the anesthesiologist of the BIS-XP values in the clinical setting as well as the need for further research of the influence of combinations of agents on the BIS.

We thank Soto et al. for their kind remarks regarding our study1 and for their suggestions for future investigations and are happy to respond to their concerns. The authors question whether the low BIS values may have been the result of an additional effect of natural sleep on BIS. The possibility of interference by natural sleep, of course, crossed our minds as well. However, two facts made us reject this option. First of all, the study in the three volunteers was performed at 10:00 am after a good night sleep. It seemed unlikely that several subjects would fall asleep spontaneously in these circumstances, particularly because during baseline measurements volunteers appeared widely awake. Recently, further data became available that patients may be aware in the presence of low BIS values.4 The incidence of awareness in this study decreased dramatically in the presence of BIS monitoring, but still, 18% of awareness cases remained undetected by the BIS®.

In conclusion, we agree with Fodale et al. that propofol and midazolam, by reducing electromyographic activity, may have affected the BIS levels in our volunteers. However, because electromyographic activity was still present at the highest midazolam and propofol concentrations and BIS thus may still have been overestimated, this only strengthens the case report in its conclusion that patients may be awake at low BIS levels. We thus stress again the need for a careful interpretation by the anesthesiologist of the BIS-XP values in the clinical setting as well as the need for further research of the influence of combinations of agents on the BIS.

Fig. 1. The hypnogram ((N)REM = (non)rapid eye movement phase, SWS = slow wave sleep phase), and BIS versus time in a volunteer during natural sleep. After 2.5 h the volunteer returned to consciousness, exhibiting a rapid return of BIS from 50 to >95.
sponded correctly to our questions. In contrast to the suggestion by the authors, all volunteers maintained adequate ventilation. They were repeatedly asked, for example, to take a deep breath just to show the viewers of the video that the participants of the study were capable of performing certain tasks when asked to. Similarly, volunteers correctly looked to their right or left when asked to or were able to correctly calculate simple equations in the presence of a BIS well below 60. We agree with the authors that it would have been valuable to note whether patients had any recall of the periods they correctly answered questions and performed tasks. However, the study was not designed for this evaluation, so no conclusion regarding this can be drawn.

In contrast to the authors, we feel strongly that, both in clinical practice and in research, often much more can be learned from those patients that do not respond as we expect and do not confirm our expectations than from those that do confirm our hypotheses. We therefore do not agree with the authors that no further research using the BIS-XP® is desirable. Hardly any data exist regarding drug interactions and BIS, whereas in clinical practice the BIS® is nearly always used in the presence of a combination of agents.

In conclusion, natural sleep cannot explain our findings described in the case report. Further research may elucidate the value of the BIS® in the presence of propofol-midazolam combinations.

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**To the Editor:**—We read the publication by Kihara et al.1 with great interest. On close examination of the text, we noted numerous similarities between their publication and a manuscript that we previously published.2 In fact, substantive parts of the Abstract, Methods, Results and Discussion were identical to those in our publication. We would like to offer Kihara et al. an opportunity to explain the nature of the apparent plagiarism of our manuscript.


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**In Reply:**—We would like to apologize to Drs. Lerman and Crawford for using five identical sentences from their manuscript. This was unintentional and arose because of a misunderstanding between the Japanese speaking author, Dr. Kihara, who wrote the first draft, and the English speaking author, Dr. Brimacombe, who prepared it for submission unaware of these identical sentences.

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**Why Should Primary Care Physicians Even Wait for Surgery in High Risk Patients?**

**To the Editor:**—The recent article by London et al., and the associated editorial were written in the context of perioperative medicine, perhaps obfuscating answers to their own questions.1,2 The use of perioperative β blockers has now “...recently been highlighted as a top tier patient safety practice by the Institute of Medicine.”1 Specifically: if the administration of perioperative β blockers “...should start as soon as the eligibility of high risk patients for surgery is confirmed. If possible, this should occur days to weeks before surgery,”2 why are “high risk” patients NOT ALREADY ON perioperative β blockers when they present?

Admittedly, it is “recommended to follow the American College of Cardiology/American Heart Association guidelines and to perform coronary bypass grafting or percutaneous transluminal coronary angioplasty if they are indicated independently of the need for noncardiac surgery.”1,2 If the lesson learned from coronary bypass grafting/percutaneous transluminal coronary angioplasty guidelines is to uncouple surgery from therapeutic need, isn’t this also appropriate for perioperative β blockers? High-risk patients are typically referred to us after intervals by primary care physicians or internists, or ultimately surgeons! Why should primary care physicians even wait for surgery in...

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high-risk patients? Are we guilty of enabling inferior care by assuming responsibility to initiate perioperative β blockers at the less opportune time of induction? Are these efforts misplaced or in need of redirection?

‘Institution of perioperative β blockers before induction . . . may not be required if hemodynamics are well controlled. This contrasts to emergence when ischemia is particularly common.’

Apparent, careful administration of anesthetic agents provide stress mitigation intraoperatively, possibly equal to perioperative β blockers found in research protocols. The best anesthetic is one given frequently, and a sudden paradigm shift to acutely adding perioperative β blockers to typical induction drug regimens may increase the incidence of undesirable periods of hypotension. Post-induction hypotension may alone be the reason against adding yet another sympathetic agent acutely at induction. Must something be removed or replaced to “make room” for perioperative β blockers?

Opoid administration historically (before modern beta blockers) emerged to mitigate stress responses at intubation and reduce minimum alveolar concentration requirements (hence the noticed “stability until emergence,” when respiratory depression becomes problematic, limiting further narcotic administration). However, there is no pain in an unconscious patient. Would restricting opioid use before the final 20 min of anesthesia (specifically treating only pain upon emergence, when painful stress responses develop), better maximize perioperative β blocker effects and utilization? What role do/should opioids play in modern anesthesia in the age of perioperative β blockers: postemergence pain therapy? What research is taking place in this direction?

Will potential dangers of widespread perioperative β blockers result from indiscriminate use in virtually all patients (i.e., if good for high risk = beneficial to all; avoid malpractice litigation)? Will increased utilization of central venous pressure/pulmonary artery catheters to monitor filling pressures result, as perioperative β blocker induced hypotension and bradycardia would now encumber interpretation of classic signs of surgical hypovolemia? Will acute perioperative β blocker introduction at induction improve overall care or simply shift morbidity (i.e., catheterization, hypotension)? Is “during surgery” a forthcoming of, and truly superfluous in, the title of the editorial? Are we really ready, willing, and if appropriate, able to take on this cause at induction now, based on the available choices, without randomized multicenter studies?

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Solid (Concrete) Evidence Needs Both Cement and Sand

To the Editor.—London et al. are to be congratulated on highlighting the physiologic foundations and current clinical controversies regarding the use of β-blockade in the perioperative period; however, we cannot agree that there is justification for the editorial statement by Kertai et al. that “β blockers should be prescribed to all patients with one or more risk factors correlated with higher risk of cardiac complications.”

Kertai et al. assume the case for this intervention is made and consider some possible reasons why this intervention has not been more widely implemented. Many of the comments in the editorial are valid but fail to address other important issues important in the integration of evidence into practice.

There are two influential randomized controlled trials showing that perioperative β blockade improves outcome in defined small samples of patients. These trials, carried out in single centers, provide evidence of the efficacy of perioperative β blockade. We need evidence not only of efficacy but also of effectiveness. The efficacy of an intervention is the degree to which the desired health outcomes are achieved in the best possible circumstances. The effectiveness of an intervention is the degree to which the desired health outcomes are achieved in clinical practice. There is a history in anesthesia practice that a powerful effect observed in a study with a small sample size carried out in a single center in which efficacy has been demonstrated does not necessarily translate into similar effects in a larger multicenter trial examining the effectiveness of an intervention.

We acknowledge that the trials of perioperative β blockade use a simple protocol to guide indications for and the administration of these drugs. These trials have not shown an adverse effect associated with the intervention. The nonoccurrence of an adverse event in a series of patients does not necessarily mean that it cannot happen. On the basis of the data contained within the two major trials of perioperative β blockade in the perioperative period, in which a total of 158 patients have received the active intervention, the upper 95% confidence interval for adverse effects may be as high as 2% (3 of 158). It is noticeable that four of the six studies Kertai et al. cite as showing no adverse effect are in fact two studies that have reported separate short-term and long-term outcomes in the same groups of patients.

Integrating evidence into clinical practice takes time; this is a challenge in all areas of medical practice. When we compare the number of studies, number of patients recruited, and variety of settings these patients have been recruited from for studies on the use of β blockade after myocardial infarction the difference is stark. In this scenario there is not just evidence of efficacy but also of effectiveness. The current guidelines for the use of β-blockers after myocardial infarction to reducing all cause mortality, cardiac mortality and nonfatal myocardial infarction are based on multicenter studies encompassing more than 16,000 patients and systematic reviews including 82 randomized controlled trials enrolling a total of more than 54,000 patients. The practitioner is more confident about the magnitude of effect that may be seen in his or her own practice and the standard of care in this area of medical practice is clearly defined.

It is odd that members of an active research group, such as Kertai et al., fail to identify the lack of effectiveness studies as a stumbling block to the introduction of perioperative β blockade into clinical practice. The challenge for us as anesthesiologists is to provide this level of evidence. London et al. in the concluding paragraph of their article highlight that there are now several such large-scale trials underway. At this time, although much has been done to establish the efficacy of perioperative β blockade, only when the effectiveness of perioperative β blockade has been demonstrated in large-scale trials will we be able to state clearly which patients benefit from perioperative β blockade, the size of the effect we might see in our own practice, and for whom it is a standard of care. At that time we will need to reflect on those additional steps that may promote the implementation of evidence into practice.

Michael Basler, M.B. Ch.B., F.R.C.A., Malcolm Daniel, M.B. Ch.B., F.R.C.P. (EDIN), F.R.C.A.: Glasgow Royal Infirmary, Glasgow, United Kingdom. mdb25s@udcf.gla.ac.uk
A Large Trial Is Vital to Prove Perioperative β-blockade Effectiveness and Safety before Widespread Use

To the Editor—London et al. state that the “evidence for the efficacy of perioperative β-adrenergic receptor blockade is strong” and Kertai et al. state that the perioperative β-blocker data provide solid evidence for their efficacy. Both groups advocate perioperative β-blockade for high-risk patients undergoing noncardiac surgery. However, they are recommending perioperative β-blockade for millions of patients, annually, worldwide on the basis of randomized controlled trials that include only 886 patients, with only 15 cardiac deaths and 18 nonfatal myocardial infarctions. We believe that these results, although promising, do not justify such enthusiasm. More definitive evidence from large-scale randomized controlled trials is required before strong recommendations can be made. Such a trial, the PeriOperative Ischemic Evaluation (POISE) trial, is currently recruiting patients in six countries to evaluate the effectiveness of perioperative β-blockade in 10,000 moderate-risk and high-risk patients undergoing noncardiac surgery.

Despite their conclusions, London et al. acknowledge several limitations in the perioperative β-blocker randomized controlled trial data. Among the 886 patients randomized most of the events (i.e., 11 deaths and nine nonfatal myocardial infarctions) occurred in the trial of Polderman et al., which is limited by lack of generalizability and blinding and which was stopped early because of an unexpectedly high risk reductions (100% for nonfatal myocardial infarction and 80% for cardiovascular death). In Kertai et al.’s editorial (in fig. 1), a reduction of death and myocardial infarction from 18 of 38 (47%) in the control patients to 11 of 40 (25%) in treated patients is quoted. If Polderman et al.’s data were true, one would expect fewer than three events, not 11, among these patients receiving perioperative β-blocker therapy. This suggests that the data in Polderman et al.’s trial are too good to be true. Indeed, these results are inconsistent with everything we know about β-blockade from randomized trials of tens of thousands of patients with myocardial infarction and heart failure that demonstrate relative risk reductions of 25–30% rather than 80–100%.

Similarly, a constellation of problems limits the reliability of Mangano et al.’s results. For example, only events that occurred after the patients stopped taking the study drug were counted in their analyses. In fact, if all the deaths are included, then the results are no longer statistically significant. As London et al. report, the limitations of Mangano et al.’s data resulted in a class IIa recommendation for this type of cohort in the American College of Cardiologists/American Heart Association guidelines.

London et al. state that “it can be argued that given strong efficacy in secondary prevention after myocardial infarction, additional perioperative studies are unnecessary.” However, as they themselves point out, these data may not be applicable to patients who merely have risk factors for coronary artery disease. These patients make up the majority of patients for whom perioperative β-blockade is advocated. The numbers needed to treat may be substantially higher in this group, which may mean that patients are exposed to the risks of perioperative β-blockade without much chance of benefit.

Despite the reassurance of Kertai et al., the safety of perioperative β-blockade is not well established among the 866 patients that have been randomized. Safety data are lacking on the impact of age, acute β-blockade, blood loss, and other pharmacologic interventions both acute and chronic. In addition, as acknowledged by London et al. and Kertai et al., there is no consensus about the logistics of perioperative β-blockade (i.e., how much, how long, by what route?). Along with the lack of definitive evidence, these factors have limited the current enthusiasm of clinicians for perioperative β-blockade.

The evidence for perioperative β-blockade in patients undergoing noncardiac surgery is encouraging but limited. The current evidence does not justify strong recommendations for the routine use of perioperative β-blockers. We, as anesthesiologists, need to heed the lessons learned in internal medicine over several decades: large trials are essential to confirm promising (but potentially incorrect) results from small trials.

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In Reply.—We greatly appreciate the insightful comments submitted to ANESTHESIOLOGY regarding our recent clinical concepts and commentary and the accompanying editorial remarks of Kertai et al.1–5 All of them raise cogent and valid concerns on this complex and controversial topic.

Dr. Kempen has raised the issue of timing of beta blockade and its interactions with the clinicians existing ‘best’ anesthetic practices and intraoperative opioid administration. We agree with much of his assessment, but we do maintain that the ability of the clinician to control hemodynamic stress and myocardial ischemia on emergence from anesthesia, even with liberal use of opioids, has always been recognized as being quite limited. This is one area in which liberal use of beta blockade is nearly universally accepted as a major advance in anesthetic management. Beta blockers likely (but not definitely) have additional or superior benefits on modulating at least several aspects of ‘plaque stabilization,’6 although opioids may play a more active role in myocardial preconditioning. With regard to the interaction and ‘substitution’ of these therapies with existing practices, the early work of Zaugg et al.7 using bispectral index guided administration of intravenous atenolol identified intriguing hypotheses that form the basis of a large scale study currently funded by the National Institutes of Aging on functional recovery after surgery in the elderly using beta blockade as an integral component of the entire anesthetic.*

Drs. Basler and Daniel are concerned regarding the recommendation of Kertai et al.2 to prescribe beta blockers to patients with one or more risk factors correlated with higher risk of cardiac complications. We certainly do not advocate an uncritical use of perioperative beta blockade and feel that use of a criteria of one risk factor alone is problematic given the potential for perioperative hypotension in the acutely beta-blocked naive patient or those on other antihypertensive medications (a complication that we all have anecdotally observed but appears to be rarely associated with any substantial adverse outcome).

A prime concern raised by Drs. Basler, Daniel, Leslie, and Devereaux is the lack of adequately powered randomized controlled trials demonstrating the effectiveness of perioperative beta blockade precludes firm treatment recommendations, particularly in patients with coronary artery disease risk factors only. We particularly thank Dr. Leslie and Devereaux for their specific mention of the Perioperative Ischemic Evaluation (POISE) trial with a target goal of 10,000 patients. We had alluded to several trials in planning or progress in our review but space constraints precluded presenting specifics. The first author of this response is familiar with the POISE study, given his attempts in advancing a proposal for a similarly powered large-scale randomized controlled trial in the Department of Veterans Affairs in 2002 (DVA Cooperative Study #534 Proposal, ‘Perioperative β-adrenergic receptor blockade in patients undergoing major noncardiac surgery.’) Martin London, M.D., Kamal Itani, M.D., Co-Principal Proponents, Department of Veterans Affairs, Washington, DC), which was independently powered to 10,000 patients. Direct communication with the executive committee of POISE was instituted at that time to preclude duplication of efforts. Because the specifics of the POISE protocol remain confidential, we cannot directly critique it here. However, as noted by Leslie and Devereaux, POISE is evaluating effectiveness in “moderate-risk and high-risk patients.” Our efforts in the Department of Veterans Affairs were aimed at ‘low and moderate risk’ patients, particularly those undergoing nonvascular surgery (given the large numbers of eligible patients and substantial logistical issues involved in widespread implementation of potentially lengthy periods of beta blockade). We believe that these are the patients that the majority of clinicians are most interested in.

In that effort, we were obliged to follow the model of the ‘large simple trial’ (by the experienced “trialists” in Department of Veterans Affairs Cooperative Studies) that is so eloquently explained by Dr. Devereaux and Yusuf, both of whom are involved with the design and conduct of the POISE study) in a highly recommended review.5 As noted in that review, not infrequently the results of small randomized controlled trials (as Mangano et al.8 and Poldermans et al.9 fall into the category of) are invalidated by larger “meta-trials” and or meta-analysis of small randomized controlled trials. After concerted efforts, the Department of Veterans Affairs effort was unsuccessful at the final evaluation step given the uncertainty (and thus lack of enthusiasm) of the Department of Veterans Affairs Cooperative Studies Evaluation Committee (comprised predominantly of internists and cardiologists) with regards to several key methodologic issues including the accurate assessment of short and long-term cardiac morbidity and mortality in the general surgical population critical to the sample size calculations (even using the Department of Veterans Affairs sophisticated federally mandated National Surgical Quality Improvement Project),8 developing a ‘simple’ perioperative treatment protocol particularly with background use of chronic beta blocker use estimated at 35–40% (and increasing annually) and the unavoidable interaction of a study patient with multiple perioperative care providers, “cross-over” issues given very high prevailing use of beta blockers for early perioperative treatment of hypertension and tachycardia, “intent to treat” issues related to cancellation or delay of surgery, and adequately defining a ‘nontreatment’ arm given that a placebo trial in the United States at this time would be considered unethical given existing “small scale” data, quasi-guidelines, and newer revisions to the Declaration of Helsinki.9

The experience with this process, and the observation that not all internists or cardiologists encountered in a variety of realms (both research and clinical) consider this as important an issue as we do, leads us to believe that no single study (POISE included) is likely to provide widely accepted “guidance” and that careful analysis and comparison of outcomes of local practice patterns (preferably collaborative efforts by all clinicians providing perioperative care), as well as ongoing consideration of potential new therapies, will remain important factors to consider. The latter is particularly highlighted by the intriguing, but speculative, protective “associations” of statins, based on the uncontrolled, observational case control analysis of Poldermans et al.,10 a very recent long-term observational analysis of Kertai et al.,11 and the unpublished data from figure 1 of the editorial by Kertai et al.12 Well, intriguing prospective, observational data on the independent impact of impaired baseline endothelial dysfunction measured in the brachial artery on outcome in vascular patients by Gokce et al.13 have been recently reported. Of note, the latter factor appears to not be influenced by beta blockade.13 It would appear that “classic trialists’
are somewhat at odds with the “progressive evidence-based medicine” specialists who have made sophisticated treatment recommendations based solely on analysis of existing prospective and retrospective observational data (and in the case of Boersma et al.14 and Kertai et al.15 by inclusion of their local “larger universe” of patients from which the randomized controlled trials were derived).16,17 Publication of a meta-analysis by Stevens et al. shortly after our review went to press has provided a unique perspective.18 Analysis of 11 beta blocker studies conducted prior to 1990 compared treatment with placebo or standard care suggests that beta blockers reduce intraoperative and postoperative ischemic episodes, reduce perioperative myocardial infarction (but only when trials with the highest frequency of previous myocardial infarction are included), and reduce perioperative death (but only when the data of Poldermans et al. with its high outcome rate are included).

As noted by Kertai et al.2 and in our recently published national survey of perioperative practitioners in the Department of Veterans Affairs,19 this topic remains one that is closely watched and has a high rate of informal use by interested practitioners but likely a low use overall and lower still on a formal clinical pathway. The good news is that a multipronged attack strategy appears to be in an active state of development and should provide reasonably comprehensive results in the very near future.

In Reply—We appreciate the interest of Drs. Kempen, Basler and Daniel, Leslie, and Devereaux in our Editorial View published in the January issue of Anesthesiology.

β-blockers have shown to reduce morbidity and mortality in non-surgical patients with coronary artery disease, including myocardial ischemia and reduced left ventricular function.1,2 Thirty percent of patients undergoing noncardiac surgery each year in the United States are at risk for or are known to have coronary artery disease.3 In two randomized controlled trials β-blockers have been shown to reduce perioperative mortality.4,5 Oddly enough, β-blocker prescription in the perioperative setting is considered as a different indication.

Dr. Kempen is concerned about the issue of why primary care physicians should not be routinely prescribing β-blockers to high-risk patients. He is also concerned that anesthesiologists be considered to be “enabling” inferior care by assuming responsibility to initiate perioperative β-blocker therapy. A less opportune time of intervention, we would be delighted if primary care physicians would prescribe β-blockers, but as reported by Nass et al., only 30% of patients with a history of coronary artery disease or those at risk referred to high-risk surgery are prescribed β-blockers. From our own experience (written communication, Don Poldermans, M.D. Ph.D., Professor, Department of Anesthesiology, Erasmus MC, Rotterdam, the Netherlands; April, 2004), only 25% of patients referred to high-risk surgery are chronic β-blocker users. The ability to initiate β-blocker use for a defined period before surgery represents the ideal situation, but often patients will present shortly before surgery without receiving β-blocker therapy. Realizing this important concern, Fleisher et al. conducted a cost-effectiveness analysis of different perioperative β-blocker strategies in high-risk patients. Their findings reveal that perioperative β-blocker use is both cost effective and efficacious from a short-term provider perspective.

Furthermore, the results showed that if a β-blocker has not been started before the day of surgery, then the use of a short-acting intravenous or longer-acting oral medication would be cost-effective in high-risk surgery. Given these findings we feel that anesthesiologists could be enablers of appropriate care by initiating perioperative β-blocker use.

Drs. Basler and Daniel touch on issues related to efficacy and effectiveness of perioperative β-blocker use. In this context, they feel that the Editorial View failed to identify the lack of effectiveness studies as a stumbling block to the introduction of perioperative β-blocker use.

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into clinical practice. They are also urging for larger-scale trials to be able to state clearly which patients will benefit for perioperative β-blocker use. We acknowledge that large-scale clinical trials should provide the ultimate solution to the issue of perioperative β-blocker use in patients of different risk categories, but we disagree that lack of effectiveness studies prevent integrating evidence into clinical practice. In that respect we would like to refer to the studies of Boersma et al.7 and Fleisher et al.8 showing effectiveness and cost-effectiveness of perioperative β-blocker use in patients with known coronary artery disease or those at risk undergoing high-risk surgery. In our opinion refraining of perioperative β-blocker use in high-risk patients just because there are no larger-scale studies would potentially subject these patients to the same level of risk of perioperative cardiac complications as before the introduction of perioperative β-blocker use.

Finally, Drs. Leslie and Devereaux would like to see more definitive evidence from large-scale randomized clinical trials before embarking on strong recommendations. They fear that current evidence is limited and does not justify routine use of perioperative β-blocker use. To overcome these concerns they propose to wait until their own trial would provide more solid evidence about the effectiveness of perioperative β-blocker use. We agree that information with regard to the protective effect of perioperative β-blocker use in patients with moderate risk for cardiac complications is limited. However, we feel that there is scientific evidence that perioperative β-blocker use in high-risk patients proved to be effective for the reduction of perioperative cardiac complications.5,9 Given these findings the practice guidelines of the American College of Cardiology/American Heart Association and the American College of Physicians recommend perioperative β-blocker therapy with one or more risk factors correlated with higher risk of cardiac complications.

In summary, perioperative β-blocker use should be considered inherent to the patient at risk and not the type of surgical procedure to be performed. Evidence from the available studies can already be used to plan an effective approach for perioperative β-blocker use in high-risk patients while ongoing clinical trials will provide further evidence for recommendations using β-blockers in patients at low-to-intermediate risk for perioperative cardiac complications.

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Effects of Long-term Nerve Blockade in the Spared Nerve Injury Model

To the Editor.—Nerve injury discharge and spontaneous discharge arising from the injury site may be responsible for the development of persistent postoperative pain. Suter et al.1 suggested that this is an unlikely scenario. Using the rat spared nerve injury model they demonstrated that sciatic nerve block lasting at least 6 days does not prevent the development of allodynia or hyperalgesia after block resolution. We studied the effect of long-lasting nerve block in the model of hyperalgesia that can be viewed as a spared nerve injury model.2 Our experimental results seem to agree with the main conclusion reached by Suter et al. with an important exception.

Our methodology was close to that of Suter et al. but had the following major differences. The first is related to the method of spared nerve injury. We transected the saphenous nerve and measured hyperalgesia in the sciatic nerve territory, whereas Suter et al. sectioned the tibial and common peroneal nerves and studied the consequences of the injury in the sural and saphenous nerve territories. The second difference is related to the agent used to achieve nerve block and the duration of the block. We induced long-lasting nerve block with N-butyll butyl tetracaine, an agent that combines local anesthetic and neurolytic properties and provides complete nerve block for more than 2 weeks.3 Suter et al. produced blockade with bupivacaine microspheres for at least 6 days.

Our experiments demonstrated that long-lasting blockade of the saphenous nerve did not prevent late (1 to 3 weeks) hyperalgesia in the sciatic nerve territory caused by the saphenous nerve transection. In this regard, our results agree with those of Suter et al. However, we found that in approximately 1 to 2 weeks the saphenous nerve blockade alone caused hyperalgesia in the sciatic skin territory. The effect of blockade on early hyperalgesia was obvious. Long-lasting block completely prevented it for the first 24 h and significantly reduced the degree of hyperalgesia for almost a week. In the Suter et al. study, blockade of the sciatic nerve reduced the early changes in mechanical threshold in the saphenous skin territory; however, it was statistically significant only on day 7 after surgery. Thus, Suter et al. had an indication of at least some preventive effect of the block on early hyperalgesia. In conclusion, we agree with the authors that peripheral long-term nerve blockade probably has no detectable effect on late hyperalgesia, but that does not include early hyperalgesia.

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CORRESPONDENCE

Effects of Long-term Nerve Blockade in the Spared Nerve Injury Model

To the Editor.—Nerve injury discharge and spontaneous discharge arising from the injury site may be responsible for the development of persistent postoperative pain. Suter et al.1 suggested that this is an unlikely scenario. Using the rat spared nerve injury model they demonstrated that sciatic nerve block lasting at least 6 days does not prevent the development of allodynia or hyperalgesia after block resolution. We studied the effect of long-lasting nerve block in the model of hyperalgesia that can be viewed as a spared nerve injury model.2 Our experimental results seem to agree with the main conclusion reached by Suter et al. with an important exception.

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Self-extraction of Intrathecal Pump Opioid

To the Editor:—Neuraxial opioids have been used successfully to treat chronic malignant and nonmalignant pain since Wang et al.1 demonstrated pain relief with intrathecal morphine in 1979.2 Intrathecal drug delivery systems are internalized devices capable of administering analgesic medications such as opioids, clonidine, and local anesthetics in precisely controlled doses. Noncoring port access device needles are used to gain access to the pump for refills and aspirations.

Candidates for an intrathecal drug delivery system have chronic intractable pain and, despite other methods of pain control, have not experienced sufficient pain relief or have developed intolerable side effects from systemic analgesics. Before implanting a permanent system it is important to document a reduction in pain intensity, improvement in function, and significant reduction in oral or systemic analgesics.3 We report the case of a patient who withdrew opioid from his intrathecal pump and injected it intravenously.

A 39-yr-old male was referred to Carolina Pain Consultants in March, 1999 with a diagnosis of lumbar postlaminectomy syndrome4 causing chronic low back and bilateral leg pain. Previously, he had undergone five spine surgeries, including a Steffee fusion. In addition, he had a spinal cord stimulator implanted before his referral. Despite improved symptomatology with the spinal cord stimulator, the patient had a persistently high opioid requirement. The patient had also suffered intractable pain and, despite other methods of pain control, have not experienced opioid withdrawal.6

He was sent to the emergency room for psychiatric evaluation and admission to a substance abuse program. We present this case to illustrate an important point. Accurate measurement of the residual volume in the pump reservoir at the time of refill and comparison to the expected residual volume is critical. Any deviation from the expected residual volume must be investigated. Our pain clinic has approximately 75 patients with intrathecal pumps. Our experience with hundreds of pump refills is that the actual residual volume aspirated from the pump consistently differs from the expected residual volume by less than 1 ml.

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References

To the Editor.—The sciatic nerve is one of the first nerves reported to be scanned with ultrasound. However, its sonographic visibility can be challenging in many patients, especially those with advanced age or obesity. In the popliteal fossa, differentiation of the sciatic nerve from adjacent muscle and adipose tissue, as well as the detection of separation into its tibial and common peroneal components, demands substantial skill and experience. Although generally considered static structures, peripheral nerves can move within the body. Nerves normally adapt to changes in bed length resulting from limb movement by path straightening and fascicle stretching. Although nerve motion associated with upper extremity movement has been described with ultrasound, there are no such reports for the lower extremity. Here we utilize dynamic scanning (ultrasound imaging during extremity movement) to identify the tibial and common peroneal components of the sciatic nerve in the popliteal fossa. Rotational and rocking motions of the sciatic nerve and its more distal components in the popliteal fossa greatly enhance the sonographic differentiation of these nerves from their surroundings.

With institutional review board approval, we reviewed ultrasound clips of the popliteal fossa. We imaged the sciatic nerve using a compact (26-mm footprint) linear transducer (15L8s at 14 MHz) and an Acuson Sequoia C256 ultrasound machine (Siemens Medical Solutions, Mountain View, CA). In short axis (transverse) scanning, we observed a reproducible external rotation of the sciatic nerve during active or passive dorsiflexion of the foot with the knee in full extension (35 ± 21 degrees, mean ± SD, n = 10 legs; fig. 1). During dorsiflexion of the foot, the tibial component of the sciatic nerve moved towards the posterior surface of the leg (fig. 1A). During plantarflexion, the common peroneal component of the sciatic nerve moved towards the posterior surface (fig. 1B). We noted these observations in 10 individuals, imaged with and without foot movement (table 1). Foot movement improved visibility of the sciatic nerve (P < 0.01, Wilcoxon signed-rank test). We call the component movements the “seesaw” sign because of the alternating tilt motion.

Movement of the tibial and common peroneal components of the sciatic nerve occurs independently of adjacent structures and proximal to the origins of muscles that control foot movement. Nerve movement relates to the position of these nerves relative to the axis of joint movement. The tibial nerve lies dorsal to the axis of the talocrural joint and is therefore stretched during dorsiflexion. The end branches of the peroneal nerves lie ventral to the axis of the talocrural joint and are therefore stretched during plantarflexion. Additional hip flexion during foot flexion intensifies the seesaw sign but does not alone result in sciatic nerve movement. In long axis (longitudinal) imaging, the tibial component of the sciatic nerve clearly stretches towards the foot during dorsiflexion in movement that corresponds to nerve sliding and elongation.

The easiest patient position to elicit the seesaw sign is prone, with feet hanging over the end of the operating table. Inversion and eversion of the foot provoke similar, but less pronounced, nerve motions as those obtained with dorsiflexion and plantarflexion. Neither isometric foot flexion nor foot flexion in the presence of a flexed knee provoke the seesaw sign. Color Doppler imaging does not improve sonographic visualization of the seesaw sign because the velocity of nerve movement is near the lower limit of detection for this technique.4

The surface movements of the tibial and common peroneal nerves

| Table 1. Foot Movement Improves Sciatic Nerve Visibility in the Popliteal Fossa |
|-----------------|------------------|------------------|
| Visibility      | No Foot Movement | Foot Movement    |
| Excellent       | 2                | 8                |
| Fair            | 5                | 2                |
| Poor            | 2                | 0                |
| None            | 1                | 0                |

Foot Movement = alternating dorsiflexion and plantarflexion of the foot; No Foot Movement = foot maintained in the neutral position; Visibility = subjective visibility scores of the sciatic nerve in the popliteal fossa. Ultrasound scans were obtained in the prone position as described in the text. Table entries indicate the number of observations in each category. Paired observations were compared with the Wilcoxon signed-rank test (P < 0.01).
or occur in an antagonistic way, thereby causing the seesaw sign. In the thigh, the two components of the sciatic nerve are analogous to two adjoining ropes: one being strained while the other relaxes. Imaging the proximal popliteal fossa shows these nerves move in concert with more rotational direction, presumably indicating the presence of a common epineural sheath. The tibial nerve component moves more extensively than the common peroneal nerve component, causing a stronger rotation of the sciatic nerve during dorsiflexion.

In the upper extremity, straightening of the median nerve path from wrist extension induced strain results in movement to the anterior surface of the forearm. No transmission of stretching forces to the upper arm occurs until the median nerve is under significant tension in the forearm. Consistent with this observation, the seesaw sign is seen only with the knee in full extension.

Nerve stimulation is a common approach to sciatic nerve block in the popliteal fossa. These blocks have a variable execution time and success rate. Anatomic variation in the level at which the sciatic nerve divides into its two components is a possible cause of incomplete blockade with this blind technique, leading to efforts to improve sciatic nerve blockade using ultrasound imaging.

Independent nerve movement may be valuable in identifying neural structures with ultrasound. Using dynamic scanning, we find that both the tibial and common peroneal components of the sciatic nerve can clearly be identified in real time. Although the seesaw sign may be of limited value in patients with reduced mobility of the foot at the ankle joint, it can be applied to other patients requiring foot and ankle surgery. Sciatic nerve movement is thus a useful tool to improve the feasibility and success of sciatic nerve blockade.

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One-Millimeter Thickness Makes a Great Difference

To the Editor—Routine inspection and examination of anesthesia equipment before use may fail to detect certain manufacturing defects. We describe a case of an endotracheal pilot balloon that failed to inflate as a result of a defective 12-ml Luer Lock Tip syringe.

A 55-yr-old man was scheduled for a right inguinal hernia repair under general anesthesia. After induction and intubation using a pre-checked 7.0-mm internal diameter, high volume, low pressure cuff, endotracheal tube (Rusch Inc., Duluth, GA), attempts to inflate the endotracheal cuff through the pilot balloon using a 12-ml Luer Lock Tip syringe (MONOJECT, Sherwood Davis & Geck, St. Louis, MO) were unsuccessful. Air could not be injected from the syringe into the pilot balloon even under extreme force. With a probable diagnosis of the pilot valve being stuck in the closed position and the presence of a large air leak around the uninflated cuff, the endotracheal tube was replaced with an identical endotracheal tube that was successfully inflated using a different 12-ml syringe. The remaining course of anesthesia was uneventful. Inspection of the initial endotracheal tube and the original 12-ml Luer Lock Tip syringe revealed a defective tip on the syringe as the cause of this incident (fig. 1).

The pilot balloon valve is a spring-loaded bidirectional valve that is by default in the closed position. When the tip of the Luer Lock Tip syringe presses the shaft of the springloaded valve inward, it depresses the internal ring, thus opening the valve and allowing inflation and deflation of the cuff (fig. 2, top). Any defect in the syringe tip prevent-

Fig. 1. Photograph of two 12-mlliliter Luer Lock Tip syringes. “Arrow A” shows the functional tip, “Arrow B” shows the defective tip.
the ability to depress the shaft and hence the internal ring, the valve is kept in the closed position preventing the passage of air. (fig. 2, bottom).

Because a different syringe was used to test the endotracheal tube, the malfunction was not observed during the preoperative period. It was not until after intubation when the defective syringe was used that the cuff failed to inflate. The defect in the syringe was not immediately identified, as a 1-mm discrepancy in luminal wall thickness of the syringe tip was not readily apparent. Using the same syringe perioperatively could have prevented this incident, thus preventing unnecessary extubation and reintubation of the trachea.

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Temporary Pacemaker Who Wouldn’t Quit

To the Editor:—Temporary pacemakers are frequently of perioperative value. Unexpected interruption of the pacing can have dire consequences.¹ We recently encountered the contrary malfunction. One of our pacemakers developed a fault that caused the device to unexpectedly become turned on.

In preparation for anesthesia for a patient requiring coronary revascularization, a fresh 9-volt battery was placed in a dual chamber temporary pacemaker (5388; Medtronic, Minneapolis, MN). The pacemaker appeared to be undamaged and indicated a successful self-test upon installation of the battery. The pacemaker was turned off and set aside but was soon found to be turned on to deliver 10-mA atrioventricular pulses at a rate of 80/min in the demand mode. Those settings are programmed to occur if the “on” button is firmly depressed. We assumed that the button had been inadvertently hit. The “off” button was pushed twice (as required), and, accordingly, the display panel indicated that the device was turned off. A few minutes later, the device was found to be turned on again. No corporeal perpetrator was apparent and a restless soul was feared to be at work.² Thankfully, a mechanical defect accounted for the vexation.

An internal part of the device had come loose so that accelerated motion of the pacemaker tended to turn the pacer on. The most economical motion occurred when the facedown pacer was grasped in the pronated right hand and the hand was then supinated. Until this feature was appreciated, the malfunction appeared to have a random component. After the persistent pacer had been set aside for a weekend, the deteriorating device turned itself on after any gentle motion.

The Medtronic 5388 pacemaker has two “on” buttons. One initiates demand pacing, and the other, labeled “emergency,” initiates asynchronous pacing. Our malfunction involved the demand-pacing button. A similar malfunction involving the emergency button, leading to asynchronous pacing, could have proven clinically disastrous.

The Medtronic 5388 pacemaker has been previously cited for its ability to lock itself off during awkward attempts to turn it on quickly.³ That is, if another button is pushed too soon after the “on” button is depressed, the machine self-test fails. Unknown to some operators, the battery must then be reinserted to permit reactivation of the frozen pacer. Our problematic pacer emphasizes another caveat. Although turned off, a cardiac pacemaker attached to a patient requires vigilant attention.

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References


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Transdiaphragmatic Hernia and Hypoxemia during Colonoscopy

To the Editor:—Arterial oxygen desaturation during colonoscopy with sedation is a well-documented complication occurring in 41–50% of patients.1 Potential causes for the decrease in oxygen saturation include respiratory depression, older age, increased intraabdominal pressure resulting from air insufflation into the colon, external manipulation of the abdomen, and suppression of airway reflexes resulting in aspiration of gastric contents.1,2

A 64-yr-old, 82-kg, 5’ 1” woman with a history of hypertension, asymptomatic heart murmur, arthritis, diverticulosis, and breast cancer was scheduled for a colonoscopy and polypectomy. Past surgery and recent colonoscopy were tolerated without incident. Propofol sedation was given with the patient in the left lateral decubitus position. Air insufflation of the colon was done as part of routine practice. Forty-five minutes into the procedure, the patient began coughing and the pulse oxygen saturation decreased to 85%. A small amount of clear secretions was suctioned from the oropharynx and the patient was given 100% oxygen by mask. The pulse oxygen saturation increased to 93–95% but decreased breath sounds and wheezing were noted in all lung fields. The patient was given albuterol and 100% oxygen by face mask and transported to the postanesthesia care unit. A portable chest radiograph obtained in the postanesthesia care unit showed extensive herniation of the entire stomach and portions of the colon into the chest cavity (fig 1). The cardiac silhouette was obscured by a large transdiaphragmatic hernia. A follow-up chest radiograph showed an infiltrate consistent with aspiration pneumonia and a slight decrease in the size of the colonic loops within the chest cavity. On further review of the case, an earlier chest radiograph was uncovered showing herniation of the stomach and colon but to a lesser extent. The patient was asymptomatic, had an uneventful colonoscopy, and did not reveal this information in preoperative assessment. The patient was discharged home on the third hospital day after receiving antibiotic treatment for a clinical diagnosis of postcolonoscopy aspiration pneumonia, although compression atelectasis could have also accounted for similar symptoms.

Transdiaphragmatic hernias are most often the result of blunt (5%) or penetrating (10%) trauma and less so as varying sizes of hiatal hernias.3,4 There are case reports of transdiaphragmatic hernia first discovered during colonoscopy.5,6 In one case, the patient developed acute respiratory distress with resulting fatal tension pneumothorax.5 In another case, the patient had extensive bowel herniation into the chest cavity with incarceration that required emergency surgical intervention.5 Approximately 25% of all people over the age of 50 have a hiatal hernia. Transdiaphragmatic hernia, in contrast, is more pronounced and often involves herniation of stomach and bowel into the chest. The patient gave no history that indicated that a chest radiograph was necessary for the planned procedure. In retrospect, the size of this patient’s transdiaphragmatic hernia would have precluded monitored anesthesia care and required general anesthesia with tracheal intubation.

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Fig. 1. Portable chest radiograph obtained in the postanesthesia care unit showing extensive herniation of the entire stomach and portions of the colon into the chest cavity (arrow).

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