Full Disclosure

Not Just of Conflict, but Also of Data

THE events of the past 2 yr since the initial controversial publication by Mangano et al.,1 regarding the effect of aprotinin on renal failure and mortality have been of great interest to the anesthesiology community. In this issue of ANESTHESIOLOGY, Dietrich et al.2 test the hypothesis that any potential nephrotoxic effect of aprotinin (Bayer Healthcare Inc., Toronto, Ontario, Canada) is dose dependent. This hypothesis is rooted in the original article by Mangano et al., where they reported an increase in risk of the composite renal outcome from 7% to 18% (P < 0.001) comparing low- and high-dose aprotinin. Dietrich et al. were unable to replicate this finding in either univariate or multivariate analysis (odds ratio, 0.98; 95% confidence interval, 0.90–1.07) in an adequately powered and statistically robust study, for identical renal outcome measures to those used by Mangano et al. Importantly, three reality checks of the results are reassuring: the overall incidence of the composite outcome in aprotinin-treated patients (8%) is similar to that reported by Mangano et al. (8%); the multivariable model reported by Dietrich et al. contains clinically sensible variables that are in overall concordance with those reported by Mangano et al.; and finally, analysis of each of the effects of aprotinin dose on each of the individual components of the composite renal outcome variable shows a lack of effect of aprotinin.

No matter which side of the debate one takes, there is little doubt that much of the discussion has been fed by lack of information. The report by Mangano et al. was questioned for its lack of detail and conflict with prior publications from the Multicenter Study of Perioperative Ischemia group.3 The furor was further fueled by a notable lapse in judgment by Bayer, when at the US Food and Drug Administration (FDA) public meeting on aprotinin on September 21, 2006, Bayer officials failed to disclose preliminary findings of a large observational cohort being examined by faculty of the Harvard School of Public Health (Boston, Massachusetts), at Bayer’s request, that supported the findings of Mangano et al.4 These preliminary findings were later repudiated.‡†‡

So, we are left with a conundrum. Why do two studies, performed by respected and statistically savvy researchers using similar surgical populations, show diametrically opposing results? Subtle but important differences in study design and definitions may contribute to this discrepancy. Alternatively, access to the raw data in both data sets could allow a more complete analysis and perhaps allow one to resolve the discrepancy. One merely has to look at the Web site of the National Center for Biotechnology Information§ to grasp the ready availability and power of such information. The penultimate example of the dissemination of information is seen at the National Institutes of Health Database of Genotype and Phenotype,|| where the complete genotyping of more than 32,000 individuals is available to accredited researchers. Secure methods for data deposition and distribution that “demonstrate a new commitment to shared scientific knowledge that should facilitate rapid advances” are logistically feasible and imperatively.4 Quite simply, it is time that journals encourage the public availability of source data as a prerequisite for publishing human drug studies.

It is also time that this obligation be extended to the drug approval process and the data provided by pharmaceutical companies to the FDA. The FDA does not require full disclosure of all information that comprises a New Drug Application. It is time that data from every patient reported to the FDA for a New Drug Application be made available to the research community. Arguments against such action that invoke proprietary information and patient confidentiality can be countered by review of which data should be released and by the benefit of such release to the public. In the heyday of support of faster drug approval seen in the early 1990s, Congress passed the Prescription Drug User Fee Act to...
Mito-controversies

Mitochondrial Permeability Transition Pore and Myocardial Reperfusion Injury

POSTCONDITIONING, repetitive ischemia applied before reperfusion, protects against ischemia-reperfusion injury.1 Of the therapies proposed for protecting ischemic myocardium, postconditioning offers a significant clinical advantage; it obviates predicting when someone will have an ischemic attack. As such, mechanisms involved in postconditioning are of significant interest. In this issue of ANESTHESIOLOGY, Jang et al.2 demonstrate that ischemic postconditioning in the heart involves activation of δ-opioid receptors. Morphine, a mixed opioid agonist, produced postconditioning that was abolished by a δ-opioid receptor antagonist or pharmacologic opening (via atractylloside) of the mitochondrial permeability transition pore (mPTP). The authors showed that morphine exposure in isolated cardiac myocytes produced nitric oxide and attenuated hydrogen peroxide oxidant stress–induced loss of the mitochondrial membrane potential (ΔΨm). The attenuation of ΔΨm produced by morphine was sensitive to δ-opioid antagonism, a non-selective nitric oxide synthase inhibitor and an inhibitor of protein kinase G. The authors concluded that (1) postconditioning protects the heart by targeting the mPTP via activation of δ-opioid receptors and (2) the ability of δ opioids to activate the nitric oxide–cyclic guanosine monophosphate–protein kinase G pathway may account for the effect of postconditioning on the mPTP. The authors are to be complimented for their original work regarding a role for δ-opioid signaling on the mPTP.

Mitochondria, a source of cellular adenosine triphosphate, are increasingly being implicated in cell survival and death signaling. mPTP opening leads to an increase in mitochondrial membrane permeability to small molecules and plays an integral role in regulating cytoprotection. The mPTP, a putative high conductance channel on the inner mitochondrial membrane, is thought to be the final end effector in cardiac myocyte protection and therefore an important therapeutic target for cardiac protective strategies.3,4 The molecular composition of the mPTP is controversial. The pore putatively is composed of the adenine...
nucleotide translocase on the inner mitochondrial membrane, voltage-dependent anion channel on the outer membrane, and cyclophilin D in the mitochondrial matrix. These components exist as individual entities that assemble into a complex in response to stress to form the mPTP. A benzodiazepine receptor, hexokinase, and creatine kinase also have been proposed as regulators of the pore. The role of adenine nucleotide translocase and voltage-dependent anion channel in forming the pore recently has been questioned. The adenine nucleotide translocase may act as a regulator of the mPTP pore, but not as a pore-forming unit of the complex. In addition, voltage-dependent anion channel knockout mice (voltage-dependent anion channels 1, 2, 3, 1/3, and 1/2/3) show stress-induced mPTP opening indistinguishable from wild-type mitochondria, questioning whether the voltage-dependent anion channel is an essential component of the pore. Cyclophilin D seems to be the only essential component of the mPTP described thus far. The authors treat the mPTP as one entity, not a multiprotein complex. It is unclear whether cardiac protective agents work to inhibit the opening of a preformed mPTP complex, inhibit a particular subunit of the complex, or inhibit the assembly or organization of the complex. Recent work showed that increased phosphorylation of glycogen synthase kinase-3β in a model of protection reduces the affinity of the adenine nucleotide translocase for cyclophilin D, suggesting that assembly of the complex is targeted by protective signals to limit mPTP opening. A limitation of the current study deals with the indirect means by which mPTP opening was assessed. Tetramethylrhodamine ethyl ester, a dye used to measure ΔΨ_m, was used to infer mPTP opening. Although the literature largely agrees that mPTP opening can be inferred by loss of ΔΨ_m, they are not one in the same. A loss in ΔΨ_m can be caused by factors other than mPTP opening (e.g., increased adenosine triphosphate demand). To circumvent this limitation, calcine acetoxymethylster-loaded cells in the presence of Co_2+ can be used. Calcine is loaded into cells and taken up by mitochondria. Residual calcine is quenched by Co_2+. If a stress is induced to open the mPTP, calcine is released and fluorescence is lost; this is reversed by addition of cyclosporine A. Dual loading of cells with tetramethylrhodamine ethyl ester and calcine can measure both ΔΨ_m and mPTP opening simultaneously. In the whole heart, mPTP opening can be assessed by a method devised by Halestrap et al. in which radioactive 2-deoxyglucose (3H-DOG) is loaded into cells and accumulates as a phosphate. Functioning mitochondria exclude the 3H-DOG, and opening of the mPTP allows accumulation of 3H-DOG in mitochondria, which can be assessed by isolating mitochondria in the presence of EGTA to trap mitochondrial 3H-DOG during isolation.

The authors also used atractyloside, a pharmacologic mPTP opener, to block ischemic and opioid postconditioning, leading to the conclusion that opioids impact mPTP opening to affect postconditioning. Because mPTP opening is proposed to be an end effector of protection, interventions that open the mPTP pharmacologically would be expected to abrogate cardiac protection induced by any form of preconditioning or postconditioning (i.e., ischemic or pharmacologic). Atractyloside would not implicate a role for protective agents in the modulation of mPTP. Therefore, use of atractyloside does not address the role of mPTP in protection, but shows that mPTP opening is responsible for tissue injury. In addition, it has been reported that atractyloside not only opens mPTP but also inhibits adenosine diphosphate transport by inhibition of adenine nucleotide translocase, therefore limiting oxidative phosphorylation. As such, it would be difficult to differentiate the effects of atractyloside on mPTP opening versus loss of energy production as causative factors in attenuated protection. Therefore, to assess whether protective agents use mPTP as a downstream mechanism, future studies should directly test whether these agents impact mPTP opening in response to stress.

The role of nitric oxide and/or reactive oxygen species in postconditioning events is intriguing, especially with respect to their impact on the mPTP. We and others have shown a role for reactive oxygen species in triggering postconditioning induced by ischemia, isoflurane, and the δ-opioid agonist SNC-121. There is evidence that reactive oxygen species may impact downstream mediators of protection (e.g., mitochondrial adenosine triphosphate-sensitive potassium channels), however, the nature of the reactive species generated and the role in inducing protection is under debate. During severe ischemia–reperfusion injury, overproduction of reactive oxygen species and mitochondrial Ca^2+ overload produce mPTP opening, ΔΨ_m depolarization, inhibition of adenosine triphosphate production, mitochondrial swelling, additional reactive oxygen species production, and further Ca^2+ accumulation, all of which initiate mitochondrial dysfunction. However, reactive oxygen species at low concentrations can initiate signaling cascades that preserve mitochondrial integrity and myocardium during ischemia and reperfusion. The finding by Jang et al. that morphine generates nitric oxide and that changes in ΔΨ_m are sensitive to nitric oxide synthase inhibition may provide a potential mechanism of action for opioids in ischemic postconditioning and implicates nitric oxide as the triggering reactive species. Low levels of endogenous nitric oxide and low concentrations of nitric oxide donors (<1 μM) protect mitochondria via suppression of mPTP opening, whereas high concentrations of nitric oxide (>5 μM) can produce mPTP opening and cytochrome c release. The fact that nitric oxide could be detected by fluorescence microscopy (a relatively insensitive technique) begs the question: Was this a small or large concentration of nitric oxide, and what does it mean to downstream protection? The dilemma seems to be that if a reactive species is easily detectable, the level likely is high and potentially injurious, whereas if it is low, it may be a beneficial trigger to cytoprotective signaling but evade detection.
The current study by Jang et al.² has focused welcomed attention on a possible role for δ-opioids in the modulation of the mPTP. Future studies will need to focus on the effects of modulators of preconditioning and postconditioning directly on the mPTP at the cellular and molecular levels. Resolution of these mito-controversies will add important information to our understanding of anesthetics as cytoprotective drugs and potential therapeutics for ischemia-reperfusion injury.

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Continuous Spinal Analgesia for Labor and Delivery

A Born-again Technique?


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Editorial Views

The primary focus of the study was to investigate the incidence of neurologic sequelae. However, as the authors appropriately note, the study was powered to establish that the incidence of persistent or permanent deficit is less than 1% at the 95% confidence level. Although clearly insufficient to establish adequate safety, it was deemed sufficient to support premarket approval, with a slow introduction of the device, coupled with extensive postmarket surveillance.

Although there were no permanent neurologic deficits, minor or transient changes did occur, the significance of which is unclear. Two patients (one in each group) developed an abnormal gait believed to be secondary to postoperative pain. Fifteen patients receiving spinal anesthesia were noted to have mild changes in 11 of these cases, changes were restricted to deep tendon reflexes, one of which was attributed to preeclampsia. Only one patient had findings significant enough to warrant neurologic consultation, and these were considered consistent with nerve compression from the fetal head. Reports of postpartum weakness or loss of sensation occurred equivalently in 4% and 6% of the spinal and epidural groups, further underscoring the difficulties interpreting detailed sequential neurologic assessments in the obstetric population, given the unstable physiology compounded by the often underestimated potential for neurologic sequelae from the birthing process.

Patients receiving CSA had a higher incidence of PDPH (9% vs. 4%), although this did not achieve statistical significance. However, this lack of significance likely reflects the study’s limited power, and the higher than expected rate of PDPH associated with the epidural procedure. It thus remains to be seen whether this is the true incidence and, if so, whether modifications in design or technique (e.g., leaving the catheter in place for a longer period) might reduce this to a more acceptable rate. One of the important target populations for CSA, morbidly obese parturients, is thought to have a lower incidence of PDPH, so at least in this application, PDPH may be less problematic. Similarly, PDPH poses less of a barrier to the use of these devices in the general surgical population.

As catheter diameter decreases, so does tensile strength. The force required for withdrawal decreases as well, but unfortunately, not to the extent that tensile strength diminishes. Consequently, catheter breakage has been an important consideration since the introduction of these devices into clinical practice. Care in their removal is mandatory, but there are also material modifications that can potentially reduce risk.

In terms of efficacy, CSA performed well against the epidural technique, resulting in more immediate pain control and greater satisfaction at 24 h. These findings are more impressive when one considers that the epidural technique might have had an unfair advantage. Years had passed since the clinical use of microcatheters, which had been limited to start, while the experience during this study was diluted among 17 investigators at seven institutions, and the device itself required modification after initiation of the study. The tightly controlled protocol mandated a single drug for spinal infusion, in contrast to the epidural’s combination therapy. In addition, there was limited previous experience with CSA for labor on which to base the treatment algorithm, contrasting sharply with the epidural technique that has been fine-tuned over decades. Conversely, while CSA had faster onset and produced greater early satisfaction, equivalent results are likely achievable with the combined spinal–epidural technique.

There are several potential advantages of CSA that are not evident in this study. Dosage is minimized, eliminating concern for systemic toxicity or fetal exposure, even with a misplaced catheter. In contrast, the epidural dosing carries significant risk of systemic toxicity with intravascular injection, while intrathecal misplacement can result in complete spinal block and neural injury from anesthetic neurotoxicity. In contrast to identification of the epidural space, spinal placement is facilitated by the well-defined endpoint, permitting use in patients with altered or abnormal neuraxial anatomy, and CSA has an additional potential advantage in patients with a current or previously failed, one-sided or patchy epidural block. CSA has also been used successfully in a number of patients with significant comorbidities who might not have tolerated the hemodynamic changes associated with the less controllable lumbar epidural anesthesia. Because of the more rapid onset with spinal administration, transition to surgical anesthesia can be achieved more readily, potentially circumventing the need for general anesthesia. One of the difficult problems in obstetric anesthesia is what to do after a failed attempt to convert from labor epidural analgesia to surgical anesthesia. In this setting, spinal anesthesia is somewhat unpredictable and carries an increased risk of high or total block. The availability of CSA can be a welcome option in this not-uncommon situation. Finally, of course, CSA is the clear answer for the anxious Oral Boards candidate when faced with the semimythical case of the morbidly obese, severely preeclamptic, asthmatic parturient with the class 4 airway presenting for urgent cesarean delivery.
With respect to CSA, size does matter, particularly with regard to regulatory restrictions, because practitioners currently remain at liberty to use large-bore catheters for this purpose. Indeed, many resort to this technique after inadvertent dural puncture during attempted epidural placement. More fundamentally, there are important differences in subarachnoid distribution between injections made through large- and small-bore catheters, although these result from differences in flow rate, which will be blurred with drugs administered by slow infusion.

Because of the substantial challenges and obstacles in conducting a study of this nature, the current data are likely the best that will be collected anytime soon, which is unfortunate given the numerous questions that remain. Among the most critical, identification of the optimal combination of analgesic/anesthetic agents and the optimal method of delivery has yet to be determined. It is well established that slow infusion potentiates restricted distribution, and a reduction in required dosage, improved analgesia, and reduced risk of anesthetic neurotoxicity might be achievable if an anesthetic is administered by repetitive bolus injection. However, the extent to which this can be realized with these high-resistance catheters also remains a question.

In their 1944 report of CSA for labor and delivery, Hinebaugh and Lang concluded: “While no serious complications occurred in this series, further trial is necessary to evaluate its future place in obstetrical anesthesia.” These words are perhaps as relevant now as they were 60 years ago.

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preexisting neurologic deficits, and recognizing the limitations of ultrasound-guided technology in preventing neurologic injury.

Perioperative nerve injury is a complex phenomenon that can be caused by a multitude of clinical factors. Patient, surgical, and anesthetic risk factors have all been identified as potential contributors to postoperative neurologic dysfunction. The case presented by Koff et al. likely represents a clinical scenario in which several patient, surgical, and anesthetic variables contributed to an adverse neurologic event. It is unlikely that a single identifiable agent was the definitive cause of injury. In fact, a review of the American Society of Anesthesiologists Closed Claims database suggests that despite intensive medicolegal investigation, the cause of postoperative neurologic injuries is rarely identified.4

Patient Risk Factors

Patient risk factors most commonly associated with perioperative nerve injury include male sex, increasing age, extremes of body habitus, and preexisting diabetes mellitus.5 However, it has been suggested that patients with preexisting neurologic deficits may be at increased risk as well. The patient presented in the case report by Koff et al. was an elderly man with preexisting MS. The presence of chronic, underlying nerve compromise secondary to mechanical, ischemic, toxic, metabolic, or in this case demyelinating conditions may theoretically place these patients at increased risk of further neurologic injury.6,7 As described by Koff et al., the “double-crush” phenomenon suggests that patients with preexisting neural compromise may be more susceptible to injury at another site when exposed to a secondary injury.7 Secondary injuries may include a variety of concomitant patient, surgical, or anesthetic risk factors.

Many clinicians are unaware that subclinical neural compromise may be present within the peripheral nervous system of patients with MS.8,9 In fact, subclinical sensorimotor deficits have been identified in 45% to 74% of MS patients, with up to 43% having abnormalities in one peripheral nerve distribution. This often ignored or poorly recognized phenomenon has been appropriately highlighted by Koff et al. The authors emphasize the need for clinicians to consider these and other factors when evaluating MS patients for peripheral nerve blockade. Unfortunately, neural compromise may be present within the peripheral nervous system in the absence of clinical signs or symptoms and does not seem to be correlated with patient age, disease onset, or progression of the disease course. This lack of clinical correlation presents a unique challenge to anesthesia providers when evaluating MS patients for peripheral regional techniques.

Surgical Risk Factors

Surgical risk factors associated with perioperative nerve injury include direct intraoperative trauma or stretch, vascular compromise, perioperative infection or inflammation, hematoma formation, tourniquet ischemia, or improperly applied immobilizers or casts. Surgical variables may be the primary etiology of postoperative neurologic deficits in up to 88% of cases.10 One of the most important surgical risk factors may be the surgical procedure itself. Koff et al. briefly alluded to the fact that the surgical procedure may have been a contributing factor in the development of the patient’s severe brachial plexopathy. Total shoulder arthroplasty may be associated with postoperative neurologic deficits in up to 4.3% of cases—regardless of anesthetic technique—with the majority of injuries being localized to the upper trunks of the brachial plexus.11

Anesthetic Risk Factors

Regional anesthetic factors that may contribute directly or indirectly to perioperative nerve injury include needle- or catheter-induced mechanical trauma, ischemic nerve injury secondary to vasoconstrictors or neural edema, and chemical injury from direct local anesthetic neurotoxicity.12 Several authors have investigated the role of mechanical trauma, including the role of needle gauge, type, and bevel configuration on peripheral nerve injury. The disruption of perineural tissue around nerve fascicles compromises the blood–nerve barrier and results in the herniation of endoneurial contents (i.e., myelinated nerve fibers) into the perineural space. However, needle-to-nerve contact by itself—in the absence of local anesthetic injection—rarely produces clinical or functional abnormalities. Rather, it is the combined effect of needle penetration and injection of local anesthetic into the neural fascicle that causes axonal degeneration and subsequent neurologic injury.12

Limitations of Ultrasound-guided Regional Anesthesia

Finally, the ability of ultrasound-guided regional anesthesia to become the “holy grail” of regional anesthesia—providing neural blockade with rapid onset, long duration, and improved success, without complications—has recently been discussed.13 Although many advocates of ultrasound theorize that direct visualization of neural targets and needle advancement may decrease the frequency (and severity) of neurologic injury, preliminary results do not support the hypothesis that ultrasound guidance decreases the risk of neurologic complications.13 This should not be surprising if we consider
the risk factors associated with neurologic injury and the ability (or lack thereof) of ultrasound in preventing these risk factors from making a clinical impact. For example, clearly the use of ultrasound guidance will have no impact on patient risk factors associated with nerve injury. The patient described by Koff et al. will have the associated risk factors of male sex, increasing age, and a preexisting neurologic deficit regardless of anesthetic technique. Similarly, the use of ultrasound guidance will have no effect on surgical factors. Patients undergoing total shoulder arthroplasty will still be at risk of intraoperative trauma or stretch to the brachial plexus, hematoma formation, and perioperative inflammation. However, it is not unreasonable to presume that ultrasound may have a positive impact on anesthetic risk factors—albeit small. Of the anesthetic risk factors involved in perioperative nerve injury (mechanical trauma, neural ischemia, and local anesthetic toxicity), ultrasound guidance may be able to modify one, or at most two contributing factors, namely, mechanical trauma and local anesthetic neurotoxicity.

The ability of ultrasound guidance to avoid needle-to-nerve contact and mechanical trauma is an appealing assumption. However, is this assumption a true reflection of clinical practice? For example, the ability to visualize both the needle tip and relevant neural targets at all times is extremely difficult. In fact, data from Koff et al.’s own institution suggests that failure to maintain needle visualization during advancement may occur in up to 43% of novices (<10 ultrasound-guided blocks) and 10% of experienced providers (>60 ultrasound-guided blocks) performing ultrasound-guided techniques. This is not a criticism, but rather a reflection of the difficulty associated with maintaining needle alignment within the narrow plane (1 mm) of the ultrasound beam. Finally, preliminary evidence is beginning to suggest that ultrasound-guided technology may allow regional techniques to be performed with lower volumes of local anesthetic while maintaining similar degrees of block efficacy. This benefit may theoretically influence risk factors of neural injury associated with direct local anesthetic neurotoxicity. However, definitive data are currently lacking on these assumptions as well.

In summary, the case report by Koff et al. highlights several important points. First, clinicians must identify all potential risk factors associated with perioperative nerve injury prior to performing regional techniques. This includes recognizing that patients with preexisting neurologic deficits may be particularly susceptible to secondary injuries. Second, consider whether the perceived benefits of regional anesthesia justify the potential for added risk (mechanical trauma, neural ischemia, local anesthetic toxicity). If so, consider modifying your anesthetic technique to minimize the impact of additional risk factors. Modifications may include reducing local anesthetic concentrations, eliminating epinephrine additives, or proceeding with general anesthesia. Finally, recognize the limitations of ultrasound-guided technology in reducing the risks associated with neurologic complications. Failure to appreciate the limitations of ultrasound may breed complacency and create an illusion of safety—factors that may increase the risk of nerve injury and adverse patient outcomes.

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