

## Contrast Imaging while Breast-feeding

*To the Editor:*—We read with interest the case report by Albertin *et al.*<sup>1</sup> regarding a spontaneous arachnoid postpartum leak and headache. In the case report, the authors state that the magnetic resonance imaging scanning was done without contrast because the patient was breast-feeding. However, current recommendations suggest that the use of radiographic contrast media is compatible with breast-feeding.<sup>2</sup> Although the proper diagnosis was made in the case by Albertin *et al.*, it is important for physicians to be aware of current recommendations regarding the safety of various medications during lactation to allow for optimal treatment options or, in this case, optimal imaging.

**William Camann, M.D.,\* Alison Stuebe, M.D.** \*Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts. [wcamann@partners.org](mailto:wcamann@partners.org)

### References

1. Albertin A, Marchetti C, Mamo D, Poli D, Dedola E: Intracranial hypotension: A case of spontaneous arachnoid rupture in a parturient. *ANESTHESIOLOGY* 2006; 104:609–10
2. Webb JA, Thomsen HS, Morkos SK, members of Contrast Media Safety Committee of European Society of Urogenital Radiology: The use of iodinated and gadolinium contrast media during pregnancy and lactation. *Eur Radiol* 2005; 15:1234–40

(Accepted for publication August 17, 2006.)

*In Reply:*—In our case report, we state that the magnetic resonance imaging scanning was performed without contrast because the patient was breast-feeding.<sup>1</sup> As Camann and Stuebe wrote, current recommendations suggest that the use of radiographic contrast media is compatible with breast-feeding.<sup>2</sup>

However, the informative sheet of all three contrast brands in use at our hospital state that breast-feeding is a relative contraindication to contrast medium use. One contrast medium producer recommends a 24-h suspension of breast-feeding for lactating women in case of contrast medium administration. Kubik-Huch *et al.*<sup>3</sup> have demonstrated that small amounts of radiographic contrast medium are excreted into human breast milk during lactation, but the amount transferred to a nursing infant orally is so small that the authors state that the recommendation of a 24-h suspension of breast-feeding for lactating women should be reconsidered.

The clinical relevance of contrast medium excretion into human breast milk is not known. But because magnetic resonance imaging

scanning without contrast gave us a satisfactory diagnostic certainty, we decided not to expose the patient to an avoidable risk.

**Andrea Albertin, M.D.,\* Chiara Marchetti, M.D., Daniela Mamo, M.D., Davide Poli, M.D., Elisa Dedola, M.D.** \*Vita-Salute University of Milan, IRCCS San Raffaele, Milan, Italy. [albertin.andrea@hsr.it](mailto:albertin.andrea@hsr.it)

### References

1. Albertin A, Marchetti C, Mamo D, Poli D, Dedola E: Intracranial hypotension: A case of spontaneous arachnoid rupture in a parturient. *ANESTHESIOLOGY* 2006; 104:609–10
2. Webb JA, Thomsen HS, Morkos SK, members of Contrast Media Safety Committee of European Society of Urogenital Radiology: The use of iodinated and gadolinium contrast media during pregnancy and lactation. *Eur Radiol* 2005; 15:1234–40
3. Kubik-Huch RA, Gottstein-Aalame NM, Frenzel T, Seifert B, Puchert E, Wittek S, Debatin JF: Gadopentetate dimeglumine excretion into human breast milk during lactation. *Radiology* 2000; 216:555–8

(Accepted for publication August 17, 2006.)

## Is Bilateral Cerebral Subdural Hematoma More Frequent after Epidural Anesthesia than Spinal Anesthesia?

*To the Editor:*—We read with interest the case report of Mashour *et al.*,<sup>1</sup> who reported a bilateral subdural hematoma (SDH) in a parturient after epidural anesthesia. In a previous report,<sup>2</sup> we reviewed 47 cases of cerebral hemorrhage after spinal (26 cases) and/or epidural (21 cases) anesthesia (table 1). Almost half of the patients developed bilateral subdural hematoma after dural puncture by an epidural needle. In contrast, subdural hematoma after spinal anesthesia occurred most frequently on the left side of the brain. It is possible that the increased incidence of bilateral subdural hematoma after epidural (11 of 21) *versus* spinal anesthesia (4 of 26) can be attributed to the greater loss of cerebrospinal fluid volume after inadvertent dural puncture with a large-bore epidural needle. Cerebrospinal fluid leak through a large dural hole might lead to marked cerebral hypotension associated with excessive traction on the bridging veins on both sides of the brain, resulting in bilateral subdural hematoma formation.

**Table 1. Cerebral Subdural Hematoma after Spinal *versus* Epidural Anesthesia**

|                             | Spinal Group | Epidural Group |
|-----------------------------|--------------|----------------|
| Number of patients          | 26           | 21             |
| Bilateral subdural hematoma | 4            | 11             |
| Left subdural hematoma      | 14           | 6              |
| Right subdural hematoma     | 6            | 4              |
| Intracerebral hematoma      | 2            | 2              |
| Pregnant patients           | 6            | 17             |
| Blood patch                 | —            | 8              |

Further analysis of the 47 cases of SDH showed that half of the published cases were in obstetric patients (22 of 47 cases); 6 cases were reported after spinal anesthesia, and 17 cases followed epidural

anesthesia. It is possible that pregnant patients are more liable to develop post-dural puncture subdural hematoma. However, this observation might be attributed, in part, to the frequent use of epidural analgesia during labor.

We agree with Mashour *et al.*<sup>1</sup> that SDH has been found to develop after inadvertent dural puncture even when an epidural blood patch was placed. Analysis of the published cases of SDH (table 1) showed that epidural blood patch was used in 8 of 21 cases to treat post-dural puncture headache, but this treatment did not prevent the formation of SDH. However, SDH was not ruled out before applying the blood patch.

Anesthesiology 2006; 105:1278

Copyright © 2006, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

*In Reply:*—We appreciate the interest of Drs. Zeidan and Baraka in our report and enjoyed reading their articles on the subject.<sup>1,2</sup> Indeed, we previously described the formation of bilateral intracranial subdural hematomas in a parturient who received epidural analgesia and who presumably encountered an occult dural tear.<sup>3</sup> The data presented by Drs. Zeidan and Baraka are compelling: The incidence of bilateral intracranial subdural hematomas seems to be increased in patients receiving epidural catheters in comparison with the spinal anesthesia group. It seems entirely reasonable to conclude that the size of the needle and associated degree of dural tear is the explanation. The reason for preferential formation of left subdural hematomas in patients receiving spinal anesthesia is less obvious to us.

The laterality of intracranial subdural hematoma formation is poorly studied. In chronic hematomas, bilateral location is more common in patients with prolonged coagulation times.<sup>4</sup> Of further interest, the shape of the cranial vault may also contribute to the formation of a bilateral *versus* unilateral hematoma. Patients who have symmetrical crania form bilateral chronic subdural hematomas more frequently than those who have asymmetrical crania.<sup>5</sup> Therefore, the underlying coagulation status and cranial anatomy may potentially be contributing factors in addition to the size of the dural tear.

Anesthesiology 2006; 105:1278-9

Copyright © 2006, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

## To Sleep, Perchance to Decode?

*To the Editor:*—Plourde *et al.*<sup>1</sup> recently reported the effects of propofol on the brain's response to different forms of auditory stimuli during sedation and anesthesia. This holistic approach is the only rational option to understand such phenomena as learning during anesthesia and perioperative dreaming.

One of the most interesting findings from this study is the extreme diminution of cortical response to auditory stimuli during the first episode of "sedation" before anesthesia. The cortical response to auditory stimuli during the period of "sedation" before anesthesia was much less than at baseline or at an equivalent blood level of sedation during recovery. The authors offer the explanation of acute tolerance to propofol in the interpretation of these results, which I would suggest is unnecessary.

We too have noted an increase in brain activation during propofol sedation, most evident in the statistical maps used to define brain activity in neuroimaging studies. During propofol or thiopental sedation, a very visible increase in statistical activation to auditory stimulation is present, although in actuality a small decrease in regional cerebral blood flow occurs.<sup>2</sup> Plourde *et al.* also document a similar discrepancy between blood oxygenation level-dependent signal magnitudes, which remain similar in many regions to baseline, and the

Ahed Zeidan, M.D.,\* Anis Baraka, M.D., F.R.C.A. \*Sahel General Hospital, Beirut, Lebanon. doczeidan@hotmail.com

## References

1. Mashour GA, Schwamm LH, Leffert L: Intracranial subdural hematomas and cerebral herniation after labor epidural with no evidence of dural puncture. *ANESTHESIOLOGY* 2006; 104:610-2
2. Zeidan A, Farhat O, Maaliki H, Baraka A: Does postdural puncture headache left untreated lead to subdural hematoma? Case report and review of the literature. *Int J Obstet Anesth* 2006; 15:50-8

(Accepted for publication August 17, 2006.)

George A. Mashour, M.D., Ph.D.,\* Lisa Leffert, M.D. \*Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts. gmashour@partners.org

## References

1. Zeidan A, Chaaban M, Farhat O, Baraka A: Cerebral rebleeding by spinal anesthesia in a patient with undiagnosed chronic subdural hematoma. *ANESTHESIOLOGY* 2006; 104:613-4
2. Zeidan A, Farhat O, Maaliki H, Baraka A: Does postdural puncture headache left untreated lead to subdural hematoma? Case report and review of the literature. *Int J Obstet Anesth* 2006; 15:50-8
3. Mashour GA, Schwamm LH, Leffert L: Intracranial subdural hematomas and cerebral herniation after labor epidural with no evidence of dural puncture. *ANESTHESIOLOGY* 2006; 104:610-12
4. Oyama H, Ikeda A, Inoue S, Shibuya M: The relationship between coagulation time and bilateral occurrence in chronic subdural hematoma. *No To Shinkei* 1999; 51:325-30
5. Lee KS, Bae WK, Yoon SM, Doh JW, Bae HG, Yun IG: Location of the chronic subdural haematoma: Role of the gravity and cranial morphology. *Brain Inj* 2001; 15:47-52

(Accepted for publication August 17, 2006.)

increase in statistical significance, from roughly  $t = 14$  at baseline to 19 in recovery, clearly visible in their brain map figures. There is no doubt that the subjects in the study of Plourde *et al.* were awake and sedated during recovery, because they remembered some 60% of the stimuli presented to them. Therefore, the phenomenon of increased statistical significance seems to be a marker of the effect of a sedative drug on auditory stimulation in an awake cortex. The new, paradoxical finding in the study of Plourde *et al.*, however, is that this situation is absent in the initial "sedation" condition, where both blood oxygenation level-dependent signal and significance are similar to the anesthesia condition. The only behavioral measure prospectively collected in this study is memory performance, and it too is noticeably absent in the initial "sedation" condition, being the same as during anesthesia. However, at recovery, the memory performance is at the expected 60% of control. As noted by Plourde *et al.*, these sedative concentrations of propofol should produce performance of approximately 50% of baseline/control, as we have documented in our studies.<sup>3</sup>

The most parsimonious explanation of the paradoxical findings during the initial "sedation" condition is that the subjects were indeed asleep, whereas they were awake and truly sedated in the recovery condition. The contention that sedation was equivalent at the begin-

ning and at recovery is based solely on measured concentrations of propofol, not on behavioral state. Clear interpretation of the imaging findings is difficult because volunteers were performing no active behavioral task (e.g., button press to hearing a word) to measure their degree of sedation and responsiveness while inside the scanner. Although the authors state that "it is difficult to fall asleep in the cramped and noisy scanner environment," our experience has been that, even without drug, it is actually easy to fall asleep in a 3-T magnetic resonance scanner in the absence of an active task. Other investigators at our institution have had similar experiences; being confined in a constant position with the arms tucked in under warm blankets, particularly if the eyes are closed, is a situation similar to swaddling a baby to induce sleep. The "close monitoring" of the subjects is not defined, and an "impression" of whether the subject is awake or asleep is difficult to assess while in the scanner, particularly in retrospect. Any subjects sleeping after initial sedation would wake up when moved out of the scanner in preparation for induction of anesthesia.

On another point, some caution must be exercised regarding which auditory processes are affected most by propofol. The authors state that higher level processing for speech and voice is abolished during anesthesia, whereas the response to nonspecific auditory stimuli is not. However, the cortical response to nonspecific auditory stimuli was determined using all measured data *versus* a rest condition, whereas response to speech and voice were measured using only a subset of the data collected, with the comparison being between two active conditions. The effect of this change in data handling is evident in baseline. Whereas maximal *t* values for the nonspecific auditory stimulation are on the order of 14, those of the speech- and voice-related activation are only approximately 3.5 (the significance threshold is 3.2). Congruently, blood oxygenation level-dependent signal magnitudes at baseline for nonspecific auditory stimuli are approximately 30, whereas for speech and voice they are approximately 5. Therefore, the presence of

decreased but still present brain activity in response to voice or speech during anesthesia would not likely be detected in this study.

Plourde *et al.* have presented a more refined evaluation of auditory processing during sedation and anesthesia than has heretofore been published. The interesting questions raised by these findings clearly elucidate paths for further study. However, the conclusions drawn from the current study are limited by lack of behavioral data and by issues of statistical significance. I would suggest that the evidence for acute tolerance to propofol is confounded by sleeping subjects. The issue of inhibition of higher order but not general auditory processes by propofol is still an open one. It seems likely that decoding of auditory stimuli during anesthesia is still functioning at some level, because numerous studies have demonstrated at least an implicit form of memory for these stimuli, albeit in much larger sample sizes (e.g., Deepröse *et al.*<sup>4</sup>).

**Robert A. Veselis, M.D.**, Memorial Sloan-Kettering Cancer Center and Weill Medical College of Cornell University, New York, New York. veselisr@mskcc.org

## References

1. Plourde G, Belin P, Chartrand D, Fiset P, Backman SB, Xie G, Zatorre RJ: Cortical processing of complex auditory stimuli during alterations of consciousness with the general anesthetic propofol. *ANESTHESIOLOGY* 2006; 104:448-57
2. Veselis RA, Feshchenko VA, Reinsel RA, Beattie B, Akhurst TJ: Propofol and thiopental do not interfere with regional cerebral blood flow response at sedative concentrations. *ANESTHESIOLOGY* 2005; 102:26-34
3. Veselis RA, Reinsel RA, Feshchenko VA, Wronski M: The comparative amnesic effects of midazolam, propofol, thiopental, and fentanyl at equisedative concentrations. *ANESTHESIOLOGY* 1997; 87:749-64
4. Deepröse C, Andrade J, Harrison D, Edwards N: Unconscious auditory priming during surgery with propofol and nitrous oxide anaesthesia: A replication. *Br J Anaesth* 2005; 94:57-62

(Accepted for publication August 17, 2006.)

Anesthesiology 2006; 105:1279-80

Copyright © 2006, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

*In Reply:*—We thank Dr. Veselis for his insightful comments on our article.<sup>1</sup> His first point is that the lack of specific auditory activation during the light sedation stage was most probably caused by physiologic sleep. The interactions we had with the subjects during the experiment and the informal debriefing between runs make us think this is unlikely: Subjects after the light sedation run seemed more "chatty" than sleepy. In addition, as we point out in the article, normal sleep does not abolish responses to complex sounds. Hence, even if the subjects had fallen asleep, this would not *per se* explain the lack of auditory responses. Despite these arguments and as indicated in our article, we agree that we have no way to unambiguously demonstrate that subjects were not sleeping during the light sedation recordings. In future experiments, we will have to monitor subjects' level of arousal more closely, although even asking subjects to perform an active task might not be sufficient. Lack of response would not necessarily indicate sleep; it could also indicate attentional, motivational, motor, or memory alterations due to the anesthesia, for example. The most objective means is probably monitoring of an ongoing electroencephalograph, a complicated task in a magnetic resonance imaging suite.

Irrespective of the sleep issue, we still believe the evidence of increased neural excitability (or disinhibition) after anesthesia with propofol because the level of activation during recovery (propofol plasma concentration: 0.64 µg/ml) significantly exceeded baseline levels. The critical question is, Does the development of this hyperexcitability require previous exposure to a higher concentration of propofol? Veselis believes that the answer is no, based on a study<sup>2</sup> that revealed a visible increase in statistical activation to auditory stimula-

tion during sedation (not preceded by exposure to higher concentration) with propofol or thiopental. The statistical significance of that effect was not reported. We proposed acute tolerance as the most likely explanation for the increased excitability seen during recovery in our study because we have observed an analogous phenomenon with the 40-Hz auditory steady state response: The amplitude during recovery from propofol anesthesia significantly exceeded baseline amplitude.<sup>3</sup> This phenomenon was not observed during propofol sedation not preceded by exposure to a higher concentration<sup>4</sup> or during prolonged recordings in nonanesthetized subjects (unpublished observations, Gilles Plourde, M.D., M.Sc., Professor, Department of Anesthesia, Montreal Neurologic Hospital, Montreal, Quebec, Canada, 2002). We believe that this topic deserves further inquiry.

Dr. Veselis' second point is that we were not able to demonstrate higher level processing during anesthesia because of insufficient power. We did discuss in the article the factors that could have led to a relative loss of signal during the anesthesia and hence affected our ability to pick up a signal. However, we disagree that the lack of response during anesthesia for higher level processing is explained on the basis of a lack of power:

First, we did have sufficient power to detect speech- and voice-related responses during baseline (and recovery). During anesthesia, we showed, using the same functional magnetic resonance imaging sampling protocol, that these responses were absent with mean signal amplitudes very close to zero and one-sample *t* tests yielding  $P > 0.2$ . Naturally, neither we nor anyone else can prove the null hypothesis of no activation, regardless of how large a sample is studied or how many data points are acquired. However, as we also point out in the article,

our conclusion is consistent with electrophysiologic data from higher order visual cortex in monkeys.

Second, and perhaps more important, we successfully demonstrated significant *negative* activation during anesthesia in the words-*versus*-scrambled words contrast. This suggests that the protocol had adequate sensitivity, because with the same number of trials, we picked up an atypical response difference between the two stimulus classes. If the lack of normal positive response to words or voice stimuli were simply due to low signal and/or high noise, we would not have detected the unusual negative response either.

Third, the reduced level of significance for the words *versus* scrambled words and vocal *versus* nonvocal stimuli was expected because we were comparing activations produced by different classes of stimuli (instead of a stimulus *vs.* silent baseline). This is therefore not an indication of inadequate signal acquisition.

We look forward to additional research on this topic from Dr. Veselis' group and others, because much clearly remains to be learned from the study of neural responses during anesthesia.

Gilles Plourde, M.D., M.Sc.,\* Pascal Belin, Ph.D., Robert J. Zatorre, Ph.D. \*McGill University, Montreal, Quebec, Canada. gilles.plourde@staff.mcgill.ca

## References

1. Plourde G, Belin P, Chartrand D, Fiset P, Backman SB, Xie G, Zatorre RJ: Cortical processing of complex auditory stimuli during alterations of consciousness with the general anesthetic propofol. *ANESTHESIOLOGY* 2006; 104:448-57
2. Veselis RA, Feshchenko VA, Reinsel RA, Beattie B, Akhurst TJ: Propofol and thiopental do not interfere with regional cerebral blood flow response at sedative concentrations. *ANESTHESIOLOGY* 2005; 102:26-34
3. Garcia-Asensi A, Backman SB, Deschamps A, Chartrand D, Fiset P, Picton TW, Plourde G: Attenuation of the 40 Hz auditory steady-state response (ASSR) during general anesthesia reflects impairment of cortical activity. Society for Neuroscience 33rd Annual Meeting, New Orleans, Society for Neuroscience, 2003, p 486.2
4. Bonhomme V, Plourde G, Meuret P, Fiset P, Backman SB: Auditory steady-state response and bispectral index for assessing level of consciousness during propofol sedation and hypnosis. *Anesth Analg* 2000; 91:1398-403

(Accepted for publication August 17, 2006.)

Anesthesiology 2006; 105:1280

Copyright © 2006, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

## Role of a Reduction of Cytokine Levels in Isoflurane-mediated Protection from Endotoxin-induced Lung Injury

*To the Editor:*—Reutershan *et al.*<sup>1</sup> reported on the finding of reduced endotoxin-induced acute lung injury in mice pretreated with isoflurane. In their investigation of the underlying cause of this phenomenon, the authors focused on neutrophil recruitment and chemokine concentrations. They found a reduction of neutrophil recruitment and CXCL1 and CXCL2/3 chemokine concentrations in the lungs of isoflurane-treated mice. Previous studies have not established a causal link between chemokine levels or the associated neutrophil accumulation and endotoxin-induced lung injury. There is, however, evidence that the cytokines tumor necrosis factor and interleukin 1 are involved in a reduction of alveolar ion and the associated fluid transport and hence pulmonary edema clearance.<sup>2,3</sup> Particularly tumor necrosis factor has been strongly implicated in the pathogenesis of pulmonary edema, and its effect is mediated by nitric oxide.<sup>2,4</sup> Tumor necrosis factor-induced nitric oxide leads thereby to a reduction of the activity of the alveolar epithelial sodium channel and the basolateral sodium potassium adenosine triphosphatase, which are essential for alveolar sodium and fluid transport.<sup>2</sup> Isoflurane has been shown to reduce plasma interleukin 1 $\beta$  and tumor necrosis factor levels significantly in endotoxemic rats.<sup>5</sup> The underlying cause for this effect has been investigated and found to be an inhibition of nuclear transcription factor KB.<sup>6</sup> The reduction in chemokine levels and subsequently neutrophil accumulation may be only a reflection of this inhibition of nuclear transcription factor KB rather than causally related to lung injury reduction, because chemokine genes are part of the array of genes regulated by this transcrip-

tional factor.<sup>7</sup> Future studies on the protective effect of isoflurane against lung injury must correlate its effect on tumor necrosis factor and interleukin-1 levels with measures of pulmonary edema clearance.

Michael Eisenhut, M.D., Institute of Child Health, University of Liverpool, Liverpool, United Kingdom. michael\_eisenhut@yahoo.com

## References

1. Reutershan J, Chang D, Hayes JK, Ley K: Protective effects of isoflurane pretreatment in endotoxin-induced lung injury. *ANESTHESIOLOGY* 2006; 104:511-7
2. Eisenhut M: Changes in ion transport in inflammatory disease. *J Inflamm (Lond)* 2006; 3:5
3. Braun C, Hamacher J, Morel DR, Wendel A, Lucas R: Dichotomous role of TNF in experimental pulmonary edema reabsorption. *J Immunol* 2005; 175:3402-8
4. Johnson A, Ferro TJ: Nitrovasodilator repletion increases TNF-alpha-induced pulmonary edema. *J Appl Physiol* 1996; 80:2151-5
5. Hofstetter C, Flondor M, Boost KA, Koehler P, Bosmann M, Pfeilschifter J, Zwissler B, Muhl H: A brief exposure to isoflurane (50s) significantly impacts on plasma cytokine levels in endotoxemic rats. *Int Immunopharmacol* 2005; 5:1519-22
6. De Rossi LW, Brueckmann M, Rex S, Barderschneider M, Buhre W, Rossaint R: Xenon and isoflurane differentially modulate lipopolysaccharide-induced activation of the nuclear transcription factor KB and production of tumor necrosis factor-alpha and interleukin-6 in monocytes. *Anesth Analg* 2004; 98:1007-12
7. Tian B, Brasier AR: Identification of a nuclear factor kappa B-dependent gene network. *Recent Prog Horm Res* 2003; 58:95-130

(Accepted for publication August 17, 2006.)

Anesthesiology 2006; 105:1280-1

Copyright © 2006, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

*In Reply:*—In our study,<sup>1</sup> we investigated the role of isoflurane on recruitment of neutrophils (polymorphonuclear leukocytes [PMNs]) in a model of lipopolysaccharide-induced lung injury. We found that pretreatment with isoflurane reduced PMN recruitment and protected from lung damage when administered within certain time windows. We revealed that chemoattractants CXCL1 and CXCL2/3 in the bronchoalveolar lavage fluid were reduced when mice inhaled isoflurane 1 h before lipopolysaccharide exposure and suggested that isoflurane might affect the release of these chemokines.

In his letter, Dr. Eisenhut suggests that tumor necrosis factor  $\alpha$ - and interleukin 1-dependent formation of pulmonary edema might be primarily responsible for lipopolysaccharide-induced lung damage and that nuclear transcription factor KB might be the main target for the antiinflammatory effects of isoflurane observed in our study.

Although increased vascular permeability and PMN recruitment are two key factors in lung injury, there is evidence that regulation of both is different and one might occur without the other.<sup>2</sup> For example, vascular protein leakage is dependent on inducible nitric oxide syn-

these from alveolar macrophages; however, PMN recruitment is not.<sup>3</sup> In our model, lipopolysaccharide inhalation results in a rapid PMN accumulation in the vascular bed within 1 h,<sup>4</sup> whereas vascular protein leakage is not seen until 6 h after lipopolysaccharide exposure. Lung injury in our model is completely dependent on PMN recruitment as demonstrated in CXCR2-deficient mice,<sup>5</sup> suggesting that vascular leakage might be a secondary event.

Chemoattractants are essential in acute lung injury. Functional blocking of chemokines or their receptors curbs lung damage.<sup>6</sup> In our model, CXCL1 and CXCL2/3 account for approximately 70% of the chemotactic activity in lipopolysaccharide-exposed bronchoalveolar fluid.<sup>5</sup> Tumor necrosis factor  $\alpha$  and interleukin 1 may also contribute, although tumor necrosis factor  $\alpha$ - and interleukin 1-independent production of CXCL1 and CXCL2/3 has been reported.<sup>7</sup> Although type II cells are involved, alveolar macrophages seem to be the major source of chemokines in the lung as shown by depletion studies. Our data do not allow distinguishing between effects of isoflurane on either cell type. The concept of cytokine-dependent fluid transport across alveolar epithelial cells is interesting and may well promote lung damage. This pathway could involve nuclear transcription factor-KB activation and might be particularly relevant for the delayed, CXCL1- and CXCL2/3-independent protection observed in our study.

We agree that future studies should further characterize the mechanisms underlying the antiinflammatory effects of isoflurane in lung injury.

Jörg Reutershan, M.D.,\* Daniel Chang, B.S., John K. Hayes, Ph.D., Klaus Ley, M.D. \*University of Tübingen, Tübingen, Germany. joerg.reutershan@uni-tuebingen.de

## References

1. Reutershan J, Chang D, Hayes JK, Ley K: Protective effects of isoflurane pretreatment in endotoxin-induced lung injury. *ANESTHESIOLOGY* 2006; 104:511-7
2. Chignard M, Balloy V: Neutrophil recruitment and increased permeability during acute lung injury induced by lipopolysaccharide. *Am J Physiol Lung Cell Mol Physiol* 2000; 279:L1083-90
3. Farley KS, Wang LF, Razavi HM, Law C, Rohan M, McCormack DG, Mehta S: Effects of macrophage inducible nitric oxide synthase in murine septic lung injury. *Am J Physiol Lung Cell Mol Physiol* 2006; 290:L1164-72
4. Reutershan J, Basit A, Galkina EV, Ley K: Sequential recruitment of neutrophils into lung and bronchoalveolar lavage fluid in LPS-induced acute lung injury. *Am J Physiol Lung Cell Mol Physiol* 2005; 289:L807-15
5. Reutershan J, Morris MA, Burcin TL, Smith DF, Chang D, Saprito MS, Ley K: Critical role of endothelial CXCR2 in LPS-induced neutrophil migration into the lung. *J Clin Invest* 2006; 116:695-702
6. Belperio JA, Keane MP, Burdick MD, Londhe V, Xue YY, Li K, Phillips RJ, Strieter RM: Critical role for CXCR2 and CXCR2 ligands during the pathogenesis of ventilator-induced lung injury. *J Clin Invest* 2002; 110:1703-16
7. Call DR, Nemzek JA, Ebong SJ, Bolgos GR, Newcomb DE, Wollenberg GK, Remick DG: Differential local and systemic regulation of the murine chemokines KC and MIP2. *Shock* 2001; 15:278-84

(Accepted for publication August 17, 2006.)

Anesthesiology 2006; 105:1281

Copyright © 2006, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

## Hypotension, Heart Rate Variability, and Altered Autonomic Function

*To the Editor:*—The elegant studies by Hanss *et al.*<sup>1,2</sup> demonstrate that alterations in heart rate variability (HRV) may predict hypotension after spinal anesthesia. The authors found a significant association between an increased ratio of low-frequency HRV (LF) to high-frequency HRV (HF) (*i.e.*, LF/HF) and subsequent hypotension. A less predictive but still significant relation was found between decreased HF and subsequent hypotension.<sup>1</sup>

In their discussion, the authors briefly compare their results with our previous results<sup>3</sup> investigating altered autonomic function and hypotension after induction of general anesthesia. Both of these studies demonstrated an association between decreased HF and subsequent hypotension. Although the stronger relation that we found with decreased HF and subsequent hypotension may simply reflect obvious differences in the study conditions (*e.g.*, general anesthesia *vs.* spinal anesthesia, different patient populations), it might also relate to the different methods used to quantitate HF.

Heart rate variability measurements in the study by Hanss *et al.*<sup>1</sup> are presented using *normalized* units, where the power in a specific frequency band (*e.g.*, HF) is *normalized* by the total power in the HRV spectrum (total HRV) for that patient (*i.e.*, HF in normalized units = [HF in absolute units]/[total HRV in absolute units]). A patient with decreased HF expressed in *absolute* units might have a normal value of HF when expressed in *normalized* units if the total HRV in his or her HRV power spectrum is also reduced (which is often the case in patients with autonomic dysfunction from multiple causes). For this reason, we used *absolute* measurements of HRV in our study. We found both a significant predictive value of decreased HF for postinduction hypotension and a strong correlation between HF and other measures of autonomic dysfunction. Historically, both absolute and normalized measurements of HRV have been used by different investigators.<sup>4</sup> Normalized units have advantages when HRV is used to examine “sympathovagal balance” (a major focus of the study of Hanss *et al.*<sup>1</sup>), whereas absolute units have advantages when reflex integrity or “gain” (a major focus of our study) is examined.

Did the authors of the current study<sup>1</sup> examine any possible relation between *absolute* measurements of HF and subsequent hypotension (or is such an analysis possible with their data)? The relation that they observed with postspinal hypotension and *normalized* measurements of HF might be even stronger using *absolute* measurements of HF. A stronger relation, if it exists, would argue that preexisting alterations in reflex integrity or gain might also play a role in hypotension after spinal anesthesia (similar to previous findings with general anesthesia<sup>3,5</sup>). Furthermore, if a significant predictive relation between absolute measurements of HF and postspinal hypotension does exist, fairly simple clinical tests of autonomic function (*e.g.*, the change in heart rate with six vital capacity breaths, which is highly correlated with absolute measures of HF<sup>3</sup>) might also have significant predictive value.

Terry W. Latson, M.D., Dallas, Texas. latson@charter.net

## References

1. Hanss R, Bein B, Weseloh H, Bauer M, Cavus E, Steinfath M, Scholz J, Tonner PH: Heart rate variability predicts severe hypotension after spinal anesthesia. *ANESTHESIOLOGY* 2006; 104:537-45
2. Hanss R, Bein B, Ledowski T, Lehmkuhl M, Ohnesorge H, Scherkl W, Steinfath M, Scholz J, Tonner PH: Heart rate variability predicts severe hypotension after spinal anesthesia for elective cesarean delivery. *ANESTHESIOLOGY* 2005; 102:1086-93
3. Latson TW, Ashmore TH, Reinhart DJ, Klein KW, Giesecke AH: Autonomic reflex dysfunction in patients presenting for elective surgery is associated with hypotension after anesthesia induction. *ANESTHESIOLOGY* 1994; 80:326-37
4. Latson T: Principles and applications of heart rate variability analysis, *Clinical Cardiac Electrophysiology*. Edited by Lynch C III. Philadelphia, JB Lippincott, 1994, pp 307-49
5. Burgos LG, Ebert TJ, Asiddao C, Turner LA, Pattison CZ, Wang-Cheng R, Kampine JP: Increased intraoperative cardiovascular morbidity in diabetics with autonomic neuropathy. *ANESTHESIOLOGY* 1989; 70:591-7

(Accepted for publication August 18, 2006.)

*In Reply:*—We thank Dr. Latson for and appreciate his interesting comment on our study. As he stated, we demonstrated that the ratio of low frequency (LF) to high frequency (HF) of heart rate variability (HRV) predicts postspinal hypotension with high sensitivity and specificity.<sup>1,2</sup> These findings were confirmed in the control group of another study.<sup>3</sup> In addition, we demonstrated significant differences of normalized HF spectral power before subarachnoid block. These results may indicate that baseline HF is of predictive value as well, confirming the conclusions of Latson *et al.*<sup>4</sup>

We agree with the author that the type of HRV analysis may crucially influence the results. Latson *et al.* investigated absolute values, whereas we analyzed the different frequency bands of the power spectrum as normalized units.

Currently, HRV-derived data are processed and presented in different ways. First, absolute HRV values are frequently analyzed and, as the author stated, may have advantages in the analysis of autonomic reflex integrity. Nevertheless, total power of HRV and its different parts decrease with increasing age, underlying cardiovascular disease, and impaired autonomic regulation.<sup>5-7</sup> Thus, an absolute HF of, for example, 1,000 ms<sup>2</sup>/Hz may be considered as below normal in young and healthy patients, normal in older healthy patients, and even above normal range in patients with coronary artery disease. Therefore, absolute values do not reflect the specific impact of the parasympathetic or the sympathetic activity of the autonomic regulation. Second, HRV data are normalized to total power. If the total power is high (*e.g.*, 10,000 ms<sup>2</sup>/Hz), an HF of 1,000 ms<sup>2</sup>/Hz is only 10%, reflecting a low parasympathetic activity in the individual. If the total power is only 2,000 ms<sup>2</sup>/Hz, the same absolute HF value would reflect a considerably higher parasympathetic activity. The aim of our studies was to identify a general predictor of postspinal hypotension; therefore, we investigated the different frequencies in normalized units and cannot comment on absolute HF values in our patients. Absolute values were analyzed as well, but demonstrated only a trend toward higher HF in normotensive patients compared with hypotensive patients. Therefore, we cannot recommend the analysis of absolute values for prediction of postspinal hypotension based on our data.

The guidelines of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology do not favor any one of the mathematical techniques, and each may have advantages and disadvantages.<sup>8</sup>

However, the ratio of LF to HF was demonstrated to be the most valuable parameter of HRV in terms of prediction of postspinal hypotension.<sup>1-3</sup> This parameter reflects the balance of the auto-

nomous nervous system and is independent of relative or absolute values because the ratio of absolute and normalized values is mathematically identical. Risk stratification based on the analysis of this autonomic balance was demonstrated to successfully guide prophylactic therapy.<sup>3</sup>

We conclude that in a homogenous group of patients, analysis of absolute values of HRV parameters is probably the best method to determine reflex integrity or "gain." If the trial's patient population demonstrates a large variation with respect to age, sex, and underlying diseases, relative values may be more appropriate. LF to HF ratio may be particularly useful for HRV analysis because it is independent of this difference.

**Robert Hanss, M.D.,\* Jens Scholz, M.D., Berthold Bein, M.D.**  
\*University-Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany.  
hanss@anaesthesie.uni-kiel.de

## References

1. Hanss R, Bein B, Ledowski T, Lehmkuhl M, Ohnesorge H, Scherkl W, Steinfath M, Scholz J, Tonner PH: Heart rate variability predicts severe hypotension after spinal anesthesia for elective cesarean delivery. *ANESTHESIOLOGY* 2005; 102:1086-93
2. Hanss R, Bein B, Weseloh H, Bauer M, Cavus E, Steinfath M, Scholz J, Tonner PH: Heart rate variability predicts severe hypotension after spinal anesthesia. *ANESTHESIOLOGY* 2006; 104:537-45
3. Hanss R, Bein B, Francksen H, Scherkl W, Bauer M, Doerges V, Steinfath M, Scholz J, Tonner PH: Heart rate variability-guided prophylactic treatment of severe hypotension after subarachnoid block for elective cesarean delivery. *ANESTHESIOLOGY* 2006; 104:635-43
4. Latson TW, Ashmore TH, Reinhart DJ, Klein KW, Giesecke AH: Autonomic reflex dysfunction in patients presenting for elective surgery is associated with hypotension after anesthesia induction. *ANESTHESIOLOGY* 1994; 80:326-37
5. Bonnemeier H, Richardt G, Potratz J, Wiegand UK, Brandes A, Kluge N, Katus HA: Circadian profile of cardiac autonomic nervous modulation in healthy subjects: Differing effects of aging and gender on heart rate variability. *J Cardiovasc Electrophysiol* 2003; 14:791-9
6. Wennerblom B, Lurje L, Tygesen H, Vahisalo R, Hjalmarson A: Patients with uncomplicated coronary artery disease have reduced heart rate variability mainly affecting vagal tone. *Heart* 2000; 83:290-4
7. Burger AJ, Charlab M, Weinrauch LA, D'Elia JA: Short- and long-term reproducibility of heart rate variability in patients with long-standing type I diabetes mellitus. *Am J Cardiol* 1997; 80:1198-202
8. Heart rate variability: Standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* 1996; 93:1043-65

(Accepted for publication August 18, 2006.)

## What Sunrise Might Reveal

*To the Editor:*—I read with great interest the article by Hanss *et al.*<sup>1</sup> in which the authors elegantly demonstrate a relation among heart rate variability, the risk of hypotension after spinal anesthesia for cesarean delivery, and the effectiveness of prophylactic measures such as prehydration and vasopressor use in terms of heart rate variability as well as clinical outcome.

However, I am puzzled by the fact that there was no control for the time of day when the experiments were performed. The authors did their baseline assessments between 18:00 and 20:00, which might be totally different from the values obtained during the experiments. Chassard and Bruguerolle<sup>2</sup> recently reviewed the ef-

fects of time of day as a synchronizer for different processes and bodily functions such as drug metabolism, cortisol levels, and hepatic blood flow. Therefore, it should not be surprising to see different results depending on the time of day when the experiments were performed. A clinical observation is that early morning elective cesarean deliveries tend to have a higher incidence of hypotension than afternoon deliveries. This may represent a multifactorial problem, however, after the results of Hanss *et al.*<sup>1,3</sup> Heart rate variability might be a good representation of one of the main factors influencing postspinal hypotension: sympathetic relative overactivity, which might be synchronized with the time of day.

**Hector J. Lacassie, M.D.**, Pontificia Universidad Católica de Chile, Santiago, Chile. lacassie@med.puc.cl or hlacassie@gmail.com

## References

1. Hanss R, Bein B, Francksen H, Scherkl W, Bauer M, Doerges V, Steinfath M, Scholz J, Tonner PH. Heart rate variability-guided prophylactic treatment of

severe hypotension after subarachnoid block for elective cesarean delivery. *ANESTHESIOLOGY* 2006; 104:635-43

2. Chassard D, Bruguerolle B. Chronobiology and anesthesia. *ANESTHESIOLOGY* 2004; 100:413-27

3. Hanss R, Bein B, Ledowski T, Lehmkuhl M, Ohnesorge H, Scherkl W, Steinfath M, Scholz J, Tonner PH. Heart rate variability predicts severe hypotension after spinal anesthesia for elective cesarean delivery. *ANESTHESIOLOGY* 2005; 102:1086-93

(Accepted for publication August 18, 2006.)

Anesthesiology 2006; 105:1283

Copyright © 2006, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

*In Reply:*—We thank Dr. Lacassie for and appreciate his valuable comment on our study.<sup>1</sup> We agree with his statement that if prophylactic treatment of postspinal hypotension is based on measurement of heart rate variability (HRV), timing of the analysis is crucial. Measurement of HRV is performed to analyze autonomic nervous system regulation. It was clearly demonstrated by Chassard and Bruguerolle<sup>2</sup> as well as Takase *et al.*<sup>3</sup> that autonomic nervous system activity demonstrates circadian rhythm. Therefore, timing of the measurement is important and should be comparable in all patients. In our previous studies, baseline analysis of HRV on the day of surgery directly before volume preload and regional block was demonstrated to identify patients at risk of hypotension in the course of subarachnoid block,<sup>4,5</sup> whereas the analysis on the day before surgery did not correlate with postspinal hypotension.

Events of the current study were defined based on these findings. Baseline analysis identifying patients at risk was the analysis on the day of surgery before volume preload and anesthesia. Because cesarean deliveries were performed at 8:00 AM, all analyses were performed at the same time. The measurement on the day before surgery was performed according to our previous studies and confirmed that there was no correlation between HRV parameters at that event and postspinal hypotension. We conclude that HRV changes during a 24-h period. Therefore, under study conditions, analyses should be performed at the same time to secure comparability of results, as was done in our study.

**Robert Hanss, M.D.,\* Jens Scholz, M.D., Berthold Bein, M.D.**  
\*University-Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany. hanss@anaesthesie.uni-kiel.de

## References

1. Hanss R, Bein B, Francksen H, Scherkl W, Bauer M, Doerges V, Steinfath M, Scholz J, Tonner PH: Heart rate variability-guided prophylactic treatment of severe hypotension after subarachnoid block for elective cesarean delivery. *ANESTHESIOLOGY* 2006; 104:635-43

2. Chassard D, Bruguerolle B: Chronobiology and anesthesia. *ANESTHESIOLOGY* 2004; 100:413-27

3. Takase B, Kitamura H, Noritake M, Nagase T, Kurita A, Ohsuzu F, Matsuoka T: Assessment of diabetic autonomic neuropathy using twenty-four-hour spectral analysis of heart rate variability: A comparison with the findings of the Ewing battery. *Jpn Heart J* 2002; 43:127-35

4. Hanss R, Bein B, Ledowski T, Lehmkuhl M, Ohnesorge H, Scherkl W, Steinfath M, Scholz J, Tonner PH: Heart rate variability predicts severe hypotension after spinal anesthesia for elective cesarean delivery. *ANESTHESIOLOGY* 2005; 102:1086-93

5. Hanss R, Bein B, Weseloh H, Bauer M, Cavus E, Steinfath M, Scholz J, Tonner PH: Heart rate variability predicts severe hypotension after spinal anesthesia. *ANESTHESIOLOGY* 2006; 104:537-45

(Accepted for publication August 18, 2006.)

Anesthesiology 2006; 105:1283

Copyright © 2006, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

## ProSeal™ Laryngeal Mask Airway Size and Fiberoptic Endotracheal Intubation

*To the Editor:*—The ProSeal™ laryngeal mask airway (PSLMA; Laryngeal Mask Company Limited, Mahe, Seychelles) is not designed as an intubation device. However, we may need to intubate the trachea with a PSLMA in place, using it as an intubation conduit with fiberoptic guidance. This situation may occur in an unanticipated difficult intubation, when a PSLMA is used to ventilate the patient. The PSLMA might then be preferred to the LMA-Classic™ when a potentially full stomach is a concern.<sup>1-3</sup>

On the LMA North America Web site,\* which includes PSLMA specifications, it is mentioned that it is possible to introduce a 4.5-mm-ID uncuffed endotracheal tube into a size 1.5 or 2 PSLMA. We tested this information with a 4.5 uncuffed Mallinckrodt (MMJ S.A. de C.V., a Mallinckrodt Company, Juarez, Mexico) tube, and we realized that this tube does not fit into a size 1.5 PSLMA. Moreover, a size 2 PSLMA is also too small to accept easily a 4.5 uncuffed tube. However, it is possible to introduce a 4.0 uncuffed tube into a 1.5 or 2 PSLMA.

Support was provided solely from institutional and/or departmental sources. After numerous failed attempts to acquire a manufacturer reply to this letter, it is being published without a response. —Michael M. Todd, M.D., Editor-in-Chief

\* Available at: www.lmana.com. Accessed July 3, 2006.

We believe that the problem may be related to variations in the outer diameter of endotracheal tubes from one company to another, inner diameter being the same.

In our opinion, this misinformation on the LMA North America Web site should be corrected because many anesthesiologists transcribe it on their difficult airway chart for emergency airway management.

**Marie-José Colas, M.D., F.R.C.P.C.,† René Martin, M.D., F.R.C.P.C.** †University of Sherbrooke, Sherbrooke, Quebec, Canada. marie-jose.colas@usherbrooke.ca

## References

1. American Society of Anesthesiologists Task Force on Management of the Difficult Airway: Practice guidelines for management of the difficult airway: An updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *ANESTHESIOLOGY* 2003; 98:1269-77

2. Cook TM, Brooks TS, Van der Westhuizen J, Clarke M.: The ProSeal LMA is a useful rescue device during failed rapid sequence intubation: Two additional cases. *Can J Anaesth* 2005; 52:630-3

3. Matic A, George A: Intubation using the ProSeal laryngeal mask airway and a Cook airway exchange catheter set (letter). *Can J Anaesth* 2001; 48:932

(Accepted for publication June 28, 2006.)