

## Volatile Agents Depress Contractility in Children

*To the Editor:*—Rivenes *et al.*<sup>1</sup> have presented evidence that sevoflurane and isoflurane preserve forward output in patients with congenital heart disease. Their conclusion that cardiac output is maintained with little change in contractility with sevoflurane and isoflurane is not accurate. The data in their table 4 indicate that systemic vascular resistance decreases with both agents, whereas cardiac output and preload (left ventricular end-diastolic volume) are unchanged. This result is obtained only if contractility decreases. I used the data in table 4 of Rivenes *et al.*<sup>1</sup> to estimate end-systolic elastance (Ees)<sup>2</sup> for the isoflurane cases using a computer model<sup>3</sup> modified to simulate the characteristics of pediatric hearts. Input variables were heart rate, systemic vascular resistance, and left ventricular end-diastolic volume. The Ees required to generate the ejection fraction (mean value) from table 4 of Rivenes *et al.*<sup>1</sup> for each isoflurane case and the resulting mean arterial pressure and cardiac index are shown in table 1 below.

**Table 1. End-systolic Elastance as a Function of Isoflurane Concentration: Model Predictions**

Case	HR (min <sup>-1</sup> )	SVRI (dyn · cm <sup>-5</sup> · m <sup>-2</sup> )	LVEDVI (ml/m <sup>2</sup> )*	Ees (mmHg/ml)	CI (l · min <sup>-1</sup> · m <sup>-2</sup> )	MAP (mmHg)	EF (%)
0 MAC	112	1,377	69	12.0	4.88	82	63
1 MAC	125	1,022	62	10.1	4.82	59	63
1.5 MAC	128	950	62	8.3	4.70	56	59

The mean arterial pressure (MAP) values in table 1 are greater than the mean values reported in table 4 of Rivenes *et al.*<sup>1</sup> but are within the mean plus 2 SDs. Although cardiac index (CI) is virtually unchanged, contractility (Ees) decreases 16 and 31% at 1 and 1.5 minimum alveolar concentration (MAC), respectively, for isoflurane. Similar results are obtained for sevoflurane. For patients in whom there is sufficient contractile reserve, this degree of depression may not be clinically significant. However, there are patients with marginal reserves for whom any loss of contractile function may be problematic.

SVRI = systemic vascular resistance index; LVEDVI = left ventricular end-diastolic volume index; Ees = end-systolic elastance; EF = ejection fraction.

\* LVEDVI in table 4 of Rivenes *et al.*<sup>1</sup> is echocardiographically measured. LVEDVI × HR × EF should equal CI but is only 70% of measured CI. The LVEDVI here is the actual value. SVI = LVEDVI × EF from table 1 is identical to the SVI values for the isoflurane group in Rivenes *et al.*<sup>1</sup>

*In Reply:*—Dr. McAuliffe uses our data to invoke the Emax method for calculating myocardial contractility. Emax, a load-independent measure of left ventricular contractility, is defined as  $Pes/(Ves - Vd)$ , where Vd is the volume-axis intercept of a linear regression line of multiple end-systolic ventricular pressure-volume data in a given contractile state, Pes is left ventricular (LV) pressure at end systole, and Ves is LV volume at the same time.<sup>1</sup> Emax is determined invasively by measuring Pes with a catheter in the left ventricle. Noninvasive estimates of Emax have been described,<sup>2,3</sup> but to our knowledge, none have been validated by comparison with standard, accepted pediatric echocardiographic methods to quantitate myocardial contractility, such as the Simpson biplane method for ejection fraction (EF),<sup>4</sup> load-independent methods to assess contractility (stress-velocity and stress-shortening indices),<sup>5</sup> or angiographic methods in pediatric patients with normal hearts<sup>4</sup> or with congenital heart disease. In fact, the reliability of Vd and thus Emax as indexes of load independent contractility has been questioned.<sup>6</sup>

The Simpson biplane method has been shown to correlate well with angiographic EF calculations in pediatric patients with congenital heart disease.<sup>4</sup> Using this methodology, we found that sevoflurane changed contractility only at 1.5 minimum alveolar concentration (MAC), resulting in a 15% decrease in EF from base-

**John J. McAuliffe, M.D.**, Cincinnati Children's Hospital and University of Cincinnati, Cincinnati, Ohio. mcauj0@chmcc.org

## References

- Rivenes SM, Lewin MB, Stayer SA, Bent ST, Schoenig HM, McKenzie ED, Fraser CD, Andropoulos DB: Cardiovascular effects of sevoflurane, isoflurane, halothane and fentanyl-midazolam in children with congenital heart disease. *ANESTHESIOLOGY* 2001; 94:223-9
- Suga H, Sagawa K, Kostiuk DP: Controls of ventricular contractility assessed by pressure-volume ratio, Emax. *Cardiovasc Res* 1976; 95:582-92
- Stern RH, Rasmussen H: Left ventricular ejection: Model solution by collocation, an approximate analytical method. *Comput Biol Med* 1996; 26: 255-61

(Accepted for publication October 1, 2001.)

line. EF at 1 MAC sevoflurane and 1 and 1.5 MAC isoflurane did not change from baseline, nor did the shortening fraction (an M-mode measure of contractility) at any concentration of either agent. Our conclusion that isoflurane and sevoflurane maintain systemic cardiac index (CI) with little change in contractility is based on this data (table 4). Dr. McAuliffe offers neither statistical analysis nor similar calculations for halothane.

Although Dr. McAuliffe's calculations using Emax show that LV ejection into the aorta may decrease, his analysis does not provide consideration of the effect of intracardiac shunting. Twenty-one of the patients in our study had left-to-right intracardiac shunting at the ventricular level, with some of the LV stroke volume ejected into the right ventricle, not the aorta. Ten patients had right-to-left intracardiac shunting at the ventricular level, resulting in a net reduction in the total amount of blood ejected from the left ventricle during systole. This presumably is the reason that left ventricular end-diastolic volume (LVEDVI) × heart rate (HR) × EF from our data equals only 70% of the calculated CI in our study. In our group of patients as a whole, a significant portion of the LV stroke volume is not ejected into the aorta. This is why we chose to calculate CI by measuring stroke volume (SV) into the proximal aorta by the pulse-wave, Doppler-derived, velocity-time integral (VTI) method:  $CI = SV \times HR$ , where  $SV = VTI \times$

cross-sectional area of aorta (see Web Enhancement, www.anesthesiology.org, February 2001, for all formulae for hemodynamic calculations). This method measures LV ejection into the aorta only and has been shown to have a strong correlation ( $r = 0.98$ ) to Fick CI values during cardiac catheterization<sup>7</sup> in children.

Although Dr. McAuliffe is correct in contending that contractility in normal hearts must decrease if SVRI decreases and CI and preload (LVEDVI) are unchanged, this again may not be the case for patients with intracardiac shunting, in whom under different conditions varying proportions of the LV stroke volume may be ejected into the aorta, allowing contractility to be preserved with lower SVRI.

We appreciate Dr. McAuliffe's perspective but maintain that our methods of calculating contractility and CI with well-validated echocardiographic methods give an accurate idea of the effects of anesthetics on myocardial contractility and hemodynamics in patients with congenital heart disease.

**Dean B. Andropoulos, M.D.,\*** **Stephen A. Stayer, M.D.,** **Shannon M. Rivenes, M.D.** \*Texas Children's Hospital, Baylor College of Medicine, Houston, Texas. dra@bcm.tmc.edu

Anesthesiology 2002; 96:1274-5

## Do Sevoflurane and Desflurane Differ in Upper Airway Reactivity?

*To the Editor:*—Klock *et al.*<sup>1</sup> report that equivalent minimum alveolar concentration (MAC) fractions of sevoflurane and desflurane yielded different responses to endotracheal tube manipulation. We identify three problems in their report.

First, the statistical analysis is questionable. The primary comparison is the incidence of a moderate or severe response to inflation of an endotracheal tube cuff (2 of 32 subjects with sevoflurane *vs.* 8 of 32 subjects with desflurane). The authors claimed statistical significance using the chi-square test. The *P* value for the chi-square test with the Yates continuity correction is 0.08; only the uncorrected chi-square test yielded a statistically significant value ( $P = 0.04$ ). The convention in statistics is that for a  $2 \times 2$  table (*i.e.*, two groups and two possible outcomes, as in the current study), the Yates correction should be applied. According to Zar,<sup>2</sup> "when one calculates the chi-square statistic, the theoretical chi-square distribution is being approximated. This approximation is a very acceptable one, except when  $\nu = 1$  [*i.e.*, one degree of freedom, as in a  $2 \times 2$  table] (in which case the Yates correction for continuity usually should be employed)." The *P* value obtained from the Fisher exact test (which does not rely on an approximation to the theoretical chi-square distribution) is 0.08. Should Klock *et al.* choose to report a nonstandard statistical approach, they have an obligation to their readers to reveal and justify this decision.

Second, Klock *et al.* state, "The slope of the regression curve between severity of coughing and heart rate increase was significantly greater for desflurane than for sevoflurane (coefficient of correlation  $\pm$  SE of the coefficient was  $4.4 \pm 2.0$  for desflurane and  $2.3 \pm 1.04$  for sevoflurane,  $P < 0.01$ )." If by "coefficient of correlation" the authors mean "correlation coefficient," their statement does not make sense: correlation coefficients are bounded between  $-1$  and  $1$ . More likely, the authors used incorrect terminology, intending "coefficient of correlation" to mean "slope." If so, their analysis is flawed: this difference is not statistically significant.

Finally, MAC fractions imposed in the two experimental groups were probably not equivalent, evidence for another bias in experimental design. Klock *et al.* calculated anesthetic doses using a MAC value of 6% for desflurane; this value is in the range typically reported. Their MAC value for sevoflurane, 2.05%, the largest of the seven values reported for that age range<sup>3</sup> (others range from 1.58 to 1.95%),<sup>4-9</sup> is 11% above the average of all the values. The opportunity for bias can be understood by considering the relation between anesthetic dose

## References

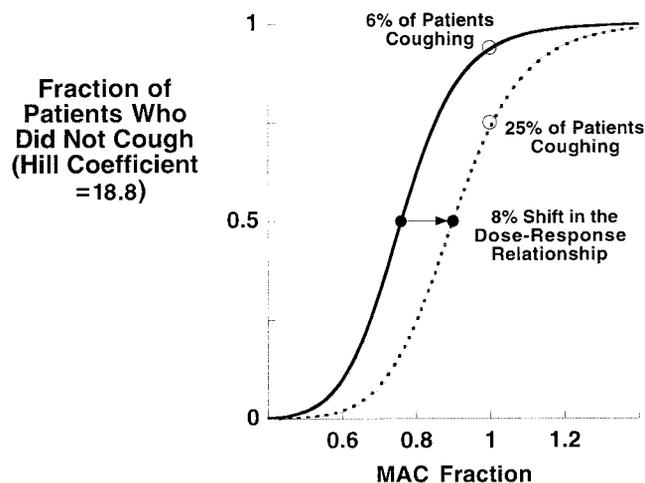
1. Suga H, Sagawa K, Kostiuk DP: Controls of ventricular contractility assessed by pressure-volume ratio. *Emax. Cardiovasc Res* 1976; 10:582-92
2. Alpert BS, Benson L, Olley PM: Peak left ventricular pressure/volume (Emax) during exercise in control subjects and children with left-sided cardiac disease. *Cathet Cardiovasc Diagn* 1981; 7:145-53
3. Stern RH, Rasmussen H: Left ventricular ejection: model solution by collocation, an approximate analytical method. *Comput Biol Med* 1996; 26:255-61
4. Silverman NH, Ports TA, Snider AR, Schiller NB, Carlsson E, Heilbron DC: Determination of left ventricular volume in children: Echocardiographic and angiographic considerations. *Circulation* 1980; 62:548-57
5. Holzman RS, van der Velde ME, Kaus SJ, Body SC, Colan SD, Sullivan LJ, Soriano SG: Sevoflurane depresses myocardial contractility less than halothane during induction of anesthesia in children. *ANESTHESIOLOGY* 1996; 85:1260-7
6. Crottoni AJ, Willshaw P, Barra JG, Armentano R, Cabrera Fischer EI, Pichel RH: Inconsistency of the slope and the volume intercept of the end-systolic pressure-volume relationship as individual indexes of inotropic state in conscious dogs: Presentation of an index combining both variables. *Circulation* 1987; 76:1115-26
7. Alverson DC, Eldridge M, Dillon T, Yabek SM, Berman W Jr: Noninvasive pulsed Doppler determination of cardiac output in neonates and children. *J Pediatr* 1982; 101:46-50

(Accepted for publication October 1, 2001.)

© 2002 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

and airway responsiveness. A published report<sup>10</sup> indicates that the concentration-effect relation for coughing is steep. Based on the data of Neelakanta and Miller,<sup>10</sup> we determined that the Hill coefficient exceeds 18. Applying this Hill coefficient to the data of Klock *et al.* indicates that the ED<sub>50</sub>s for cough suppression for the two anesthetics differ by only 8% (fig. 1). Correcting for the 11% bias in MAC values negates this potential difference in potency.

We conclude that the three experimental flaws compromise the conclusions of Klock *et al.* regarding differences in the effects of sevoflurane and desflurane on the response to airway stimulation.



**Fig. 1.** Coughing response (open circles) *versus* anesthetic dose (expressed as a fraction of minimum alveolar concentration [MAC]). Using a Hill coefficient of 18.8 (estimated from the data of Neelakanta and Miller<sup>10</sup>), the data of Klock *et al.*<sup>1</sup> (6% of patients coughed while inhaling 1 MAC sevoflurane [thick line] compared with 25% of patients inhaling 1 MAC desflurane [thin line]) can be fit to a sigmoid curve. The resulting values for ED<sub>50</sub> (closed circles) differ by only 8%, smaller than the 11% bias in anesthetic concentrations used by Klock *et al.*

The authors thank Edmond I Eger, M.D. (Department of Anesthesia, University of California, San Francisco, California), for his insights.

**James Sonner, M.D.,\* Dennis M. Fisher, M.D.** \*University of California, San Francisco, California. sonnerj@anesthesia.ucsf.edu

## References

1. Klock PA Jr, Czeslick EG, Klapfta JM, Ovassapian A, Moss J: The effect of sevoflurane and desflurane on upper airway reactivity. *ANESTHESIOLOGY* 2001; 94:963-7
2. Zar JH: *Biostatistical Analysis*, 2nd edition. Englewood Cliffs, Prentice-Hall, 1984, p 49
3. Scheller MS, Partridge BL, Saidman IJ: MAC of sevoflurane in humans and the New Zealand white rabbit. *Can Anaesth Soc J* 1988; 35:153-6
4. Inomata S, Yaguchi Y, Toyooka H: The effects of clonidine premedication on sevoflurane requirements and anesthetic induction time. *Anesth Analg* 1999; 89:204-8

*Anesthesiology* 2002; 96:1275-6

*In Reply:*—My coauthors and I thank Drs. Sonner and Fisher for their careful reading of our manuscript. We believe it is imperative to clarify the issues they have raised. Regarding two points that are central to the article, we provide strong support for our methodology and conclusions. On a third point, we acknowledge that an error occurred. We will review our position and methodology for each issue.

First, Drs. Sonner and Fisher question the statistical analysis performed comparing the rate of coughing after tracheal stimulation in patients anesthetized with 1 minimum alveolar concentration (MAC) sevoflurane or 1 MAC desflurane. We respond on several levels, first summarizing the data. In our study, 8 of 32 subjects anesthetized with 1 MAC desflurane had a severe coughing response after tracheal stimulation. Of the 32 subjects anesthetized with 1 MAC sevoflurane, 1 had a moderate coughing response, and only 1 had a severe response to tracheal stimulation. The chi-square test comparing these rates is significant at  $P = 0.04$ . Drs. Sonner and Fisher state that this significance level is erroneous because a continuity correction (which yields  $P = 0.08$ ) was not used.

We have consulted two statisticians in our institution, and we now understand that the automatic use of the continuity correction is controversial in the statistics community. A seminal collection of articles outlining the issues was published 25 yr ago,<sup>1</sup> and the debate continues, including recent discussion articles by Haviland<sup>2</sup> and Agresti.<sup>3</sup> Although no one can argue against the fact that using the correction results in conservative significance tests, both the continuity-corrected chi-square statistic and Fisher exact test tend to be misleadingly conservative when applied in circumstances for which they were not designed, such as the circumstances of this study. The Fisher exact test or continuity-corrected chi-square is appropriate when all four margins of the  $2 \times 2$  table are fixed in advance. In our study, only the number of patients who received each agent was fixed (32 and 32); the number of patients showing moderate or severe cough response was observed, not fixed in advance. Under these circumstances, even the uncorrected chi-square tends to be conservative when the samples are small.<sup>4</sup> For these reasons, some standard statistical packages purposely do not calculate the continuity corrections (e.g., Stata; Stata Corporation, College Station, TX). Drs. Sonner and Fisher quote a single statistical textbook stating that the Yates correction "usually should be employed" in  $2 \times 2$  tables. At least one other reputable biostatistics book chooses not to use the correction at all, stating that it is too conservative.<sup>5</sup>

In reviewing the statistics sections of *Clinical Investigations* published in issues 1-6 of volume 94 of *ANESTHESIOLOGY*, we found that the chi-square test had been used in 15 studies other than ours.\* None of

\* Chi-square noted in volume 94, pp 33, 60, 196, 220, 409, 434, 448, 555, 563, 575, 594, 762, 768, 800, 1000.

5. Suzuki A, Katoh T, Ikeda K: The effect of adenosine triphosphate on sevoflurane requirements for minimum alveolar anesthetic concentration and minimum alveolar anesthetic concentration-awake. *Anesth Analg* 1998; 86:179-83

6. Katoh T, Kobayashi S, Suzuki A, Iwamoto T, Bito H, Ikeda K: The effect of fentanyl on sevoflurane requirements for somatic and sympathetic responses to surgical incision. *ANESTHESIOLOGY* 1999; 90:398-405

7. Katoh T, Ikeda K: The effects of fentanyl on sevoflurane requirements for loss of consciousness and skin incision. *ANESTHESIOLOGY* 1998; 88:18-24

8. Katoh T, Ikeda K: The minimum alveolar concentration (MAC) of sevoflurane in humans. *ANESTHESIOLOGY* 1987; 66:301-3

9. Kimura T, Watanabe S, Asakura N, Inamata S, Okada M, Taguchi M: Determination of end-tidal sevoflurane concentration for tracheal intubation and minimum alveolar anesthetic concentration in adults. *Anesth Analg* 1994; 79:378-81

10. Neelakanta G, Miller J: Minimum alveolar concentration of isoflurane for tracheal extubation in deeply anesthetized children. *ANESTHESIOLOGY* 1994; 80: 811-3

(Accepted for publication November 30, 2001.)

© 2002 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

these articles stated whether the continuity correction had been applied. We recognize Dr. Fisher's expertise in this area but are uncertain why this article should use different techniques than those used in similar studies and recommended by leading authorities. Given that all of the relevant data were presented in our article, the question of Drs. Sonner and Fisher regarding the continuity correction comes down to a matter of philosophy of inference rather than a matter of knowledge.

Drs. Sonner and Fisher also state that the patients anesthetized with 2.05% sevoflurane received a larger MAC dose than those anesthetized with 6.0% desflurane. The MAC values that we chose are commonly accepted.<sup>6</sup> The package insert for sevoflurane states the MAC for 40 yr-olds is 2.1% (the average age for subjects receiving sevoflurane in our study was 43 yr). The package insert for desflurane states that the MAC for 45-yr-old patients is 6.0% (the average age for desflurane subjects was 44 yr). According to the package inserts,<sup>7,8</sup> if any error in dosing was made, the patients randomized to sevoflurane received a relatively lower dose. The doctors then reference a study examining the MAC for tracheal extubation in children anesthetized with isoflurane<sup>9</sup> and use statistical gymnastics to conclude, "the three experimental flaws compromise the conclusions of Klock *et al.* regarding differences in the effects of sevoflurane and desflurane on the response to airway stimulation."

Drs. Sonner and Fisher correctly identify a reporting error regarding the relation between coughing and heart rate. The slopes comparing cough response and heart rate increase are not significantly different. Fortunately, this result was not central to the conclusions of the article and does not affect the principal findings of the study. We apologize for this error.

In summary, we stand by our experimental design and the statistical validity of the chi-square statistic and its  $P$  value that we report.

**P. Allan Klock, Jr., M.D.,† Elke G. Czeslick, M.D., Jerome M. Klapfta, M.D., Andranik Ovassapian, M.D., Jonathan Moss, M.D., Ph.D.** †University of Chicago Hospitals, Chicago, Illinois. aklock@airway2.uchicago.edu

## References

1. Conover WJ: Some reasons for not using the Yates continuity correction on  $2 \times 2$  contingency tables (comment/rejoinder, pp 376-82). *J Am Stat Assoc* 1974; 69:374-6
2. Haviland MG: Yates's correction for continuity and the analysis of  $2 \times 2$  contingency tables (comment/rejoinder, pp 369-83). *Stat Med* 1990; 9:363-7
3. Agresti A: A survey of exact inference for contingency tables (Discussion, pp 153-77). *Statistical Science* 1992; 7:131-53
4. Starmer CF, Grizzle JE, Sen PK: Comments on "Some reasons for not using the Yates continuity correction on  $2 \times 2$  contingency tables." *J Am Stat Assoc* 1974; 69:376-8

5. Scheffler WC: Statistics for Health Professionals. Reading, Massachusetts, Addison-Wesley, 1984, p 228
6. Koblin DD: Mechanisms of action, Anesthesia, 5th edition. Edited by Miller RD. Philadelphia, Churchill Livingstone, 2000, p 59
7. Ultane (sevoflurane) [package insert]. North Chicago: Abbott Laboratories; 2000

8. Suprane (desflurane) [package insert]. Deerfield: Baxter Healthcare; 2001
9. Neelakanta G, Miller J: Minimum alveolar concentration of isoflurane for tracheal extubation in deeply anesthetized children. ANESTHESIOLOGY 1994; 80: 811-3

(Accepted for publication November 30, 2001.)

Anesthesiology 2002; 96:1276

© 2002 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

## Does Nitrous Oxide Really Induce c-Fos Expression Related to Its Analgesic Effect?

*To the Editor:*—I read with much interest the recent report by Hashimoto *et al.*<sup>1</sup> regarding the analgesic mechanism of nitrous oxide in the spinal cord. They found that inhalation of nitrous oxide itself induced the c-Fos protein expression in the rat spinal dorsal horn (especially in laminae III and IV).

However, I did not find such induction of c-Fos expression in my experiment.<sup>2</sup> Sun *et al.*<sup>3</sup> also showed no increase of c-Fos expression by inhalation of nitrous oxide. Although Sun *et al.* and I investigated the effect of nitrous oxide on c-Fos expression evoked by noxious stimuli, we found no changes in the control side, namely the nonstimulated side. I found that nitrous oxide suppressed c-Fos expression evoked by noxious stimulation only in the deeper layer, whereas in laminae III and IV, there were few Fos-like immunoreactive cells, even with noxious stimulation, and no changes were observed in this region. Is the induction of c-Fos expression by nitrous oxide due to the difference in species? I used Wistar rats and Sun *et al.* used Sprague-Dawley rats, whereas Hashimoto *et al.* used Fischer rats.

Second, many anatomic and electrophysiologic studies confirmed that generally neurons, which exist in laminae III and IV, which receive only proprioceptive inputs and do not involve noxious input processing. Hunt *et al.*<sup>4</sup> showed that noxious stimuli evoked c-Fos expression on neurons in laminae I, II, and V, whereas nonnoxious stimuli evoked c-Fos expression on neurons in laminae III and IV, which also supports the concept of functional organization in the spinal dorsal horn. Furthermore, immunohistochemical studies<sup>5,6</sup> revealed that there are many noradrenergic terminals in laminae I and II but few in laminae III and IV. Consequently, even c-Fos expression would be induced by inhalation of nitrous oxide; it would not involve pain processing or descending noradrenergic control.

Third, many reports (Hunt *et al.*,<sup>4</sup> Bullitt,<sup>7</sup> Menétrey *et al.*,<sup>8</sup> and others) showed that there were no or few Fos-like immunoreactive neurons in the control animals in the spinal cord. Bullitt wrote that

almost no immunoreactivity was present in the lumbar or cervical spinal cord in normal controls, whereas Hashimoto *et al.* reported that a fair number of Fos-like immunoreactive neurons existed in the control animals. What is the difference between those previous reports and that of Hashimoto *et al.*? Is it because of the difference in species or characteristics of antibodies used in the experiments?

**Satoshi Hagihira, M.D., Ph.D.,** Osaka Prefectural Habikino Hospital, Osaka, Japan. hagihira@masui.med.osaka-u.ac.jp

### References

1. Hashimoto T, Maze M, Ohashi Y, Fujinaga M: Nitrous oxide activates GABAergic neurons in the spinal cord in Fischer rats. ANESTHESIOLOGY 2001; 95:463-9
2. Hagihira S, Taenaka N, Yoshiya I: Inhalation anesthetics suppress the expression of c-fos protein evoked by noxious somatic stimulation in the deeper layer of the spinal cord in the rat. Brain Res 1997; 751:124-30
3. Sun WZ, Shyu BC, Shieh JY: Nitrous oxide or halothane, or both, fail to suppress c-fos expression in rat spinal cord dorsal horn neurones after subcutaneous formalin. Br J Anaesth 1996; 76:99-105
4. Hunt SP, Pini A, Evan G: Induction of c-fos-like protein in spinal cord neurons following sensory stimulation. Nature 1987; 328:632-4
5. Westlund KN, Bowker RM, Ziegler MG, Coulter JD: Noradrenergic projections to the spinal cord of the rat. Brain Res 1983; 263:15-31
6. Hagihira S, Senba E, Yoshida S, Tohyama M, Yoshiya I: Fine structure of noradrenergic terminals and their synapses in the rat spinal dorsal horn: An immunohistochemical study. Brain Res 1990; 526:73-80
7. Bullitt E: Expression of c-fos-like protein as a marker for neuronal activity following noxious stimulation in the rat. J Comp Neurol 1990; 296:517-30
8. Menétrey D, Gannon A, Levine JD, Basbaum AI: Expression of c-fos protein in interneurons and projection neurons of the rat spinal cord in response to noxious somatic, articular, and visceral stimulation. J Comp Neurol 1989; 285: 177-95

(Accepted for publication December 29, 2001.)

Anesthesiology 2002; 96:1276-7

© 2002 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

*In Reply:*—In response to the letter to the editor by Dr. Hagihira regarding our manuscript entitled “Nitrous Oxide Activates GABAergic Neurons in the Spinal Cord in Fischer Rats,” we offer the following point-by-point response.

First, Hagihira writes that neither he<sup>1</sup> nor Sun *et al.*<sup>2</sup> found “increase of c-Fos expression by inhalation of nitrous oxide.” However, neither examined the effect of nitrous oxide *alone* on c-Fos expression in the spinal cord as we did in our study. Also, their experimental designs were not capable of eliciting the antinociceptive effect of nitrous oxide. Hagihira *et al.*<sup>1</sup> administered nitrous oxide *after* formalin injection, although it takes 15–30 min for nitrous oxide to show a significant antinociceptive effect. In the study by Sun *et al.*,<sup>2</sup> nitrous oxide was administered 20 min before formalin injection but was discontinued 5 min after formalin injection, although noxious stimuli by formalin last at least 1 h. Therefore, it is understandable why both studies failed to show a significant effect of nitrous oxide on formalin-induced nociceptive behavior and c-Fos expression.

Second, Hagihira comments that “. . . neurons exist in laminae III and IV receive only proprioceptive inputs and do not involve noxious input processing,” which we do not contest. Our finding that nitrous oxide induces c-Fos expression in laminae III and IV are consistent with this fact because it is the  $\gamma$ -aminobutyric acid-mediated interneurons that are affected by nitrous oxide and not the primary afferent neurons conveying nociceptive input. Hagihira cites two studies (one published by Westlund *et al.*<sup>3</sup> in 1983 and another by himself<sup>4</sup> in 1990) to substantiate his statement that “. . . there are many noradrenergic terminals in laminae I and II but few in laminae III and IV.” However, he ignores many other studies that have shown that noradrenergic neurons are widely distributed within the entire spinal cord, including the motor neurons (*e.g.*, Commission<sup>5</sup> [1983], Aramant *et al.*<sup>6</sup> [1986], Rajaofetra *et al.*<sup>7</sup> [1992]).

Third, Hagihira is concerned about the high “background” c-Fos expression in the spinal cord of our study (*i.e.*, approximately 40 cells per section), higher than that seen in previous studies (Hunt *et al.*<sup>8</sup> in

1987, Menétrey *et al.*<sup>9</sup> in 1989, and Bullitt<sup>10</sup> in 1990). We can only comment that the sensitivity of antibodies and imaging have increased over this period; support for this contention is the fact that in the report by Hunt *et al.*<sup>8</sup> in 1987, there was considerably less c-Fos induction by noxious stimuli. Unlike other investigators, we have not confined our examination only to the dorsal horn of one half of the spinal cord but have examined the entire gray matter of both halves of the spinal cord, which results in a higher number of c-Fos-positive cells in the control samples.

**Masahiko Fujinaga, M.D.,\* Mervyn Maze, M.B., Ch.B.** \*Chelsea and Westminster Hospital, Imperial College Faculty of Medicine, London, United Kingdom. m.fujinaga@ic.ac.uk

## References

1. Hagihira S, Taenaka N, Yoshiya I: Inhalation anesthetics suppress the expression of c-fos protein evoked by noxious somatic stimulation in the deeper layer of the spinal cord in the rat. *Brain Res* 1997; 751:124-30
2. Sun WZ, Shyu BC, Shieh JY: Nitrous oxide or halothane, or both, fail to

suppress *c-fos* expression in rat spinal cord dorsal horn neurones after subcutaneous formalin. *Br J Anaesth* 1996; 76:99-105

3. Westlund KN, Bowker RM, Ziegler MG, Coulter JD: Noradrenergic projections to the spinal cord of the rat. *Brain Res* 1983; 263:15-31

4. Hagihira S, Senba E, Yoshida S, Tohyama M, Yoshiya I: Fine structure of noradrenergic terminals and their synapses in the rat spinal dorsal horn: An immunohistochemical study. *Brain Res* 1990; 526:73-80

5. Commissiong JW: Development of catecholaminergic nerves in the spinal cord of the rat. *Brain Res* 1983; 264:197-208

6. Aramant RB, Giron LT Jr, Ziegler MG: Postnatal development of dopamine- $\beta$ -hydroxylase-immunoreactive fibers of the spinal cord of the rat. *Dev Brain Res* 1986; 25:161-71

7. Rajaofetra N, Poulat P, Marlier L, Geffard M, Privat A: Pre- and postnatal development of noradrenergic projections to the rat spinal cord: An immunocytochemical study. *Brain Res Dev Brain Res* 1992; 67:237-46

8. Hunt SP, Pini A, Evan G: Induction of *c-fos*-like protein in spinal cord neurons following sensory stimulation. *Nature* 1987; 328:632-4

9. Menétrey D, Gannon A, Levine JD, Basbaum AI: Expression of c-fos protein in interneurons and projection neurons of the rat spinal cord in response to noxious somatic, articular, and visceral stimulation. *J Comp Neurol* 1989; 285:177-95

10. Bullitt E: Expression of c-fos-like protein as a marker for neuronal activity following noxious stimulation in the rat. *J Comp Neurol* 1990; 296:517-30

(Accepted for publication December 29, 2001.)

Anesthesiology 2002; 96:1277

© 2002 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

## Obtaining Informed Consent

*To the Editor:*—As an anesthesiologist who became a medical malpractice defense attorney, I read with interest the article by Tait *et al.*<sup>1</sup> as well as the accompanying editorial by Coté.<sup>2</sup> The issue of informed consent came to mind.

When practicing anesthesiology, I thought I did a fair job of obtaining informed consent from the patient. Now that I am defending physicians, I realize the importance of communication regarding informed consent. A large number of lawsuits are filed because the patient believes the physician did not spend enough time discussing procedures, alternatives, risks, or benefits of the planned medical intervention.

Dr. Coté offers an excellent example when he says he makes “a note in the record that these issues have been discussed with both the surgeon and the family and that everyone has been informed of the risks and has agreed to proceed.” A written record in the chart is evidence that informed consent has been obtained. Be aware that evidence is not true or false; it simply is offered to prove the existence or nonexistence of a fact. The jury will determine whether the patient truly gave informed consent based only partly on this written evidence of documentation in the chart. Testimony by the physician, patient, and any other third parties present will also be considered as evidence of whether informed consent was obtained.

Documentation of informed consent in the chart should not be considered solely as an exercise to “keep the lawyers at bay.” Informed consent is an interaction between the physician and the patient that truly educates the patient and allows both parties to participate in care decisions. Most patients want to know what is going to happen and what adverse events could occur. Patients often research medical conditions on the Internet and wish to discuss their thoughts with their physicians. It is important for physicians to consider patients’ input.

When applying informed consent concepts to the child with an upper respiratory tract infection, the study by Tait *et al.* can provide a basis for discussion. The anesthesiologist should explain that there are certain risk factors for perioperative respiratory events in children with upper respiratory tract infections. A discussion of the risk factors and the anesthesiologist’s assessment of them should be discussed. It should be stated that although children with acute and recent upper respiratory tract infections are at greater risk for respiratory complications, most of these children can undergo elective procedures without a significant increase in adverse anesthetic outcomes. The anesthesiologist and the parents of the child can then weigh the risks *versus* the benefits. This informed consent discussion should then be documented in the chart. In some cases, the parents may wish to delay the surgery in spite of the anesthesiologist’s confidence in a good outcome. It is a wiser choice to cancel the case than to proceed; a bad outcome could predictably end up in an attorney’s office.

Having been in solo anesthesiology private practice for 7 yr, I understand the perceived need to keep the operating schedule moving. However, a few extra minutes obtaining informed consent preoperatively are “cost effective” when weighed against the months, if not years, of aggravation and the emotional turmoil of a lawsuit.

**Robert A. Herbert, M.D., J.D., M.B.A.,** Sheurman, Martini & Tabari, San Jose, California. rherbert@prodigy.net

## References

1. Tait AR, Malviya S, Voepel-Lewis T, Munro HM, Siewert M, Pandit UA: Risk factors for perioperative adverse respiratory events in children with upper respiratory tract infections. *ANESTHESIOLOGY* 2001; 95:299-306

2. Coté CJ: The upper respiratory tract infection (URTI) dilemma: Fear of a complication or litigation? *ANESTHESIOLOGY* 2001; 95:283-5

(Accepted for publication December 31, 2001.)

Anesthesiology 2002; 96:1278

© 2002 American Society of Anesthesiologists, Inc. Lippincott Williams &amp; Wilkins, Inc.

*In Reply:*—We appreciate the comments made by Dr. Herbert regarding the importance of disclosure in informed consent and the documentation thereof in the medical record. Dr. Herbert cites our study regarding anesthesia for the child with an upper respiratory tract infection<sup>1</sup> as a good example of the importance of fully discussing the elements of consent (*i.e.*, risks, benefits, procedures, and alternatives) with the patient, his or her surrogate, or both. The importance of informed consent as a process has been highlighted in some of our research. Recently, we presented an abstract at the annual meeting of the American Society of Anesthesiologists that examined parental understanding of informed consent for pediatric anesthesia research.<sup>2</sup> Results of this study showed that only 61.7% of parents had complete understanding of the risks of the study, 55.8% had complete understanding of the benefits, 54.8% completely understood the protocol, and 82.8% understood the alternatives. Although our study addressed understanding of consent for research, the elements and the requirements for disclosure are essentially the same as those required for anesthesia and surgery. Clearly, consent for anesthesia (and anesthesia-related research) offers a unique perspective given that consent may be sought just before surgery, in a less than private setting, and at a time

when the patient (or subject) is most anxious. Therefore, as Dr. Herbert suggests, it is critical from both an ethical and a legal perspective for the physician to discuss the elements of informed consent frankly with the patient or surrogate, to ensure that they fully understand the information, and to provide documentation that the elements of consent have been discussed.

**Alan R. Tait, Ph.D.,\* Shobha Malviya, M.D., Terri Voepel-Lewis, M.S.N., R.N.** \*University of Michigan Health Systems, Ann Arbor, Michigan. atait@umich.edu

## References

1. Tait AR, Malviya S, Voepel-Lewis T, Munro HM, Siewert M, Pandit UA: Risk factors for perioperative adverse respiratory events in children with upper respiratory tract infections. *ANESTHESIOLOGY* 2001; 95:299–306
2. Tait AR, Voepel-Lewis T, Robinson A, Malviya S: Parental understanding of informed consent for pediatric anesthesia research (abstract). *ANESTHESIOLOGY* 2001; 95:A1216

(Accepted for publication December 31, 2001.)

Anesthesiology 2002; 96:1278

© 2002 American Society of Anesthesiologists, Inc. Lippincott Williams &amp; Wilkins, Inc.

## Successful Resuscitation after Maternal Cardiac Arrest by Immediate Cesarean Section in the Labor Room

*To the Editor:*—We report the case of a healthy, multiparous parturient who experienced cardiac arrest in the labor room. Cardiopulmonary resuscitation was not successful; therefore, after approximately 15 min, an emergent cesarean delivery was performed in the labor room, and after delivery of the baby, the mother was successfully resuscitated.

A healthy, 35-yr-old, gravida 5 para 3 woman was admitted to the labor suite in active labor at 8:35 AM. The patient was at 39 weeks' gestational age, and her cervix was dilated 4 cm. At 10:00 AM, a lumbar epidural catheter was placed uneventfully. The test dose results were negative, and the catheter was dosed with a mixture of 10 ml bupivacaine, 0.125%, with 120 µg fentanyl. During this time, systolic maternal blood pressure remained greater than 100 mmHg, and fetal heart rate (FHR) was reactive between 130 and 140 beats/min. The patient was comfortable with a T10 dermatome level bilaterally, and a continuous epidural infusion of 0.125% bupivacaine with 2 µg/ml fentanyl was started.

At 11:40 AM, the obstetrician uneventfully ruptured the patient's membranes. Eight minutes later, the patient reported nausea and fatigue, and FHR decreased to 90 beats/min. Chest auscultation revealed decreased breath sounds, and oxygen was administered *via* face mask. Intravenous oxytocin and the continuous epidural infusion were stopped. FHR improved to 140 beats/min with a change of the mother's position. Within minutes, the patient became unresponsive, and FHR decreased to less than 90 beats/min. At 11:58 AM, intubation was performed successfully, and breath sounds were confirmed. At 12:00 PM, FHR decreased to 80 beats/min, and the patient experienced a

cardiac arrest. A wedge was placed under the patient's hip, and a hard, wooden board was placed underneath the patient's back to facilitate chest compressions. The electrocardiogram revealed a sinus bradycardia, but no pulse was palpable, and 1 mg epinephrine was administered intravenously. With chest compressions, oxygen saturation was measured intermittently at 90%, but no pulse was palpated. At approximately 12:09 PM, a second dose of epinephrine was administered, and FHR remained at 60 beats/min. Because the mother was too unstable for transport, the decision was made to perform an immediate cesarean delivery on the patient's bed. The nursing staff transported the surgical equipment to the labor room, and the fetus was delivered *via* a classic cesarean delivery at 12:15 PM. Apgar scores at 1 and 5 min were 4 and 5, respectively. After delivery, radial pulse became immediately palpable, maternal blood pressure was 120/80 mmHg, and oxygen saturation improved to 98%. Cardiopulmonary resuscitation was discontinued, and the patient was transferred to the intensive care unit. Postoperatively, the patient experienced severe coagulopathy and was treated for the presumed diagnosis of amniotic fluid embolism.

In the scenario of sudden cardiovascular collapse, regardless of the etiology of the arrest, successful resuscitation in late pregnancy is frequently unsuccessful until after the fetus is delivered. In this case, expedient emergency cesarean delivery in the labor room allowed both mother and baby to survive fully intact.

**Helene Finegold, M.D.,\* Aladdin Darwich, M.D., Ryan Romeo, M.D., Manuel Vallejo, M.D., Sivam Ramanathan, M.D.** \*Magee Womens Hospital, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania. Finegoldh@anes.upmc.edu

(Accepted for publication January 3, 2002.)

Support was provided solely from institutional and/or departmental sources.

Anesthesiology 2002; 96:1279

© 2002 American Society of Anesthesiologists, Inc. Lippincott Williams &amp; Wilkins, Inc.

## Another Reason to Choose the Left Molar Approach of Laryngoscopy: To Spare the Incisor Teeth

*To the Editor:*—The *left molar approach of laryngoscopy* is an unconventional technique in which the blade is inserted from the left corner of the mouth. The approach has been shown to provide a better view of the glottis than the conventional midline approach in cases of difficult intubation.<sup>1</sup> We appreciate this approach for another reason, that is, to spare the incisor teeth, and would like to present our case.

A 58-yr-old woman was scheduled to undergo upper lobectomy of the right lung. The preoperative visit by an anesthesiologist revealed that her upper incisors (numbers 7-9) were mobile, even with a light touch, and her other upper teeth, with the exception of number 4, were dentures. The patient was informed that her incisors could be damaged during laryngoscopy and tracheal intubation, and verbal consent was obtained for possible damage, but she also requested that we make our best effort to spare her incisor teeth. In the operating room, general anesthesia was induced with intravenous propofol supplemented with fentanyl. After muscle relaxation was obtained with intravenous vecuronium, direct laryngoscopy was performed with a Macintosh blade. On the first attempt, approaching from the right of her incisor teeth, her tongue could not be appropriately displaced leftward because her loose upper incisors prohibited liberal use of the laryngoscopic blade. Only a part of glottis could be seen (Cormack and Lehane<sup>2</sup> grade II) with manual external manipulation of the larynx, and several attempts to put a left-sided endobronchial tube (35-French Bronchocath<sup>®</sup>; Mallinckrodt Japan, Tokyo, Japan) through her glottis were unsuccessful. Next, we tried the left molar approach because the patient had no left upper teeth with her dentures removed. Because the incisor teeth did not limit the manipulation of the Macintosh blade with this approach, upward force to visualize the glottis could be optimally applied. With external laryngeal manipulation, most of the glottis was visible (Cormack and Lehane grade I). The endobronchial tube was advanced from the left side of the tongue without disturbing the incisor teeth. The tube was successfully placed in her trachea after a couple of attempts to align the tube tip to the glottic opening. Her

Support was provided solely from institutional and/or departmental sources.

incisor teeth did not undergo any damage during laryngoscopy and tracheal intubation.

Dental injury is a well-known complication of laryngoscopy and tracheal intubation. Teeth on the patient's right side or in the middle are injured in most cases, with the upper incisors at the highest risk.<sup>3,4</sup> To prevent injury, tooth guards or mouth protectors can be used, but they may make the intubation difficult.<sup>5</sup> Protectors, which should be attached on the laryngoscope blade, are also reported,<sup>6</sup> but they must be prepared beforehand. The left molar approach with a Macintosh blade has the advantages that it may facilitate the laryngoscopic view of the glottis<sup>1</sup> and that no special preparation is needed. Considering that avoidance of the maxillary structure may be the reason for an improved glottic view in the left molar approach,<sup>1</sup> it is logical that the approach spares the upper incisors at the same time. We conclude that the left molar approach of laryngoscopy may be a good choice when the incisor teeth or teeth on the right side are vulnerable or valuable.

Norihito Sato, M.D.,\* Koh Shingu, M.D. \*Kansai Medical University, Moriguchi, Japan. saton@takii.kmu.ac.jp

### References

1. Yamamoto K, Tsubokawa T, Ohmura S, Itoh H, Kobayashi T: Left-molar approach improves the laryngeal view in patients with difficult laryngoscopy. *ANESTHESIOLOGY* 2000; 92: 70-4
2. Cormack RS, Lehane J: Difficult tracheal intubation in obstetrics. *Anaesthesia* 1984; 39:1105-11
3. Gaiser RR, Castro AD: The level of anesthesia resident training does not affect the risk of dental injury. *Anesth Analg* 1998; 87:255-7
4. Warner ME, Benenfeld SM, Warner MA, Schroeder DR, Maxson PM: Peri-anesthetic dental injuries: frequency, outcomes, and risk factors. *ANESTHESIOLOGY* 1999; 90:1302-5
5. Aromaa U, Pesonen P, Linko K, Tammisto T: Difficulties with tooth protectors in endotracheal intubation. *Acta Anaesthesiol Scand* 1988; 32:304-7
6. Ghabash MB, Matta MS, Mehanna CB: Prevention of dental trauma during endotracheal intubation. *Anesth Analg* 1997; 84:230-1

(Accepted for publication January 15, 2002.)