

## Cannabinoids for Postoperative Pain

*To the Editor:*—An article published by Holdcroft *et al.*<sup>1</sup> in the May 2006 issue of ANESTHESIOLOGY reported the analgesic and adverse effects of an oral cannabis extract for postoperative pain management. To date, only three other manuscripts investigating the role of cannabinoids in postoperative pain have been published.<sup>2–4</sup> The conclusions from these studies are that cannabinoids are not ideally suited to manage postoperative pain, being either moderately effective,<sup>1,2</sup> not different from placebo,<sup>3</sup> or even antianalgesic at high doses.<sup>4</sup> However, a definitive conclusion of the role of cannabinoids in the postoperative setting cannot yet be made because only 202 patients were studied using different drugs, dosages, routes of administration, and protocols.

In their study, Holdcroft *et al.*<sup>1</sup> used an escalating-dose technique, which leads to two main problems: the lack of blinding and the absence of a placebo group. Furthermore, Holdcroft *et al.* stated, “The study recruited all types of surgical patients” and “Apart from the different distribution of surgical types, the three dose groups were similar at baseline.” This obviously introduces a major problem in the interpretation of their results.<sup>4</sup> Another potential problem with the study by Holdcroft *et al.* is that the 65 patients enrolled in their study were recruited from eight different centers, which does not help to obtain consistent data.

The actual design of the study could also be criticized because patients were only studied for a 6-h period (periods longer than 6 h are advocated)<sup>5</sup> and, more importantly, because the study drug was administered only when clinical evidence showed that patient-controlled analgesia morphine was not necessary anymore. Therefore, the first hours (or days?) immediately following the operation were not studied. The authors do not report the time when patients were in fact recruited and when they were given the cannabis extracts. This information is crucial to understanding when the study took place. Furthermore, in real life, using the so-called multimodal analgesia approach, patients should receive adjuvant analgesics (acetaminophen, nonsteroidal antiinflammatory drugs) at the beginning of the postoperative period and not after morphine administration has been stopped. Fi-

nally, pain on movement was measured, but no details were given on how these assessments were made considering the many types of surgery performed.

A last comment is on the choice of Cannador (IKF, Berlin, Germany) as the cannabinoid of choice for this study. Although it contains tetrahydrocannabinol, its association with cannabidiol and other cannabis extracts (which ones and in what proportions?) is certainly another variable that potentially complicates the interpretation of the results.

Despite these limitations, the authors must be congratulated because this research area is not easy: there are difficulties in funding such trials, an unfavorable political climate, and societal and institutional concerns related to the use of cannabinoids. It is reasonable to question why there has been so little research conducted in this area, and it is possible that obstacles to the conduct of such research continue to exist.

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*In Reply:*—We thank Pierre Beaulieu for his interest in our study of cannabinoids for postoperative pain. However, we cannot concur with his view that cannabinoids are only moderately effective analgesics. We found that, across different surgeries and institutions, pain relief equivalent to the best available postoperative analgesia was achieved. We agree that results from one type of cannabinoid may not be comparable to those from another type and that larger studies are needed. However, we found that our stringent entry criteria, intended to exclude patients with serious medical conditions, made it essential to recruit from a large number of centers.

Our study was designed to measure the effectiveness of cannabinoids alone without the advantage of other analgesic combinations, as occurs in clinical practice.<sup>1</sup> Hence, the time to escape analgesia was an important outcome. In comparison with the study of Beaulieu,<sup>2</sup> in which the outcome measure was morphine consumption, we can be sure that the effects we measured were from cannabinoids, not the result of synergistic effects from an opioid-cannabinoid combination, as has been described in preclinical studies.<sup>3</sup> Our aim was to investigate whether cannabinoids were analgesic when administered as the sole agent and to find their most effective dose; our results provide confirmatory evidence for analgesia at the higher doses we used.

Interestingly, the duration of our study was determined in pretrial

workshops by the same authors that Beaulieu cites as advocating durations longer than 6 h. The rationale was that this was the first time that cannabinoids had been used postoperatively, in fasting patients, and a single-dose study was safest; furthermore, a 24-h study would have required waking the patient at night to obtain regular pain scores, which might have made recruitment even less attractive. In retrospect, the times to rescue analgesia also support this view. Because total pain relief and pain intensity differences summary measures carry forward the final value before rescue analgesia, sensitivity would be lost if assessments continued until all patients requested escape analgesia. In addition, the use of an oral preparation precluded early administration after major surgery, and the single dose was delivered to most patients within 24 h of surgery. This regimen was similar to that used clinically in the study centers for orally administered analgesics.

Beaulieu asks how pain on movement was measured. The protocol for the study standardized these movements for each type of surgery to establish conformity across sites; our method was comparable to his. He also requests justification for and content of Cannador (IKF, Berlin, Germany). Most of these details are in the article. In addition, the study was conducted in parallel with the CAMS study<sup>4</sup> because postoperative pain and multiple sclerosis were both considered to be important areas to investigate the medicinal uses of cannabis.

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## Paravertebral Blocks in Thoracoscopy: Single No, Continuous Yes

*To the Editor:*—We read with great interest the article by Hill *et al.*<sup>1</sup> regarding the analgesic efficacy of single-dose, multilevel paravertebral nerve blockade (PVB) for thoracoscopic surgery. Given our own experience with PVBs (160-200 patients per month using both single and continuous, unilateral and bilateral PVBs for a wide variety of cases) in thoracoscopic surgery, we find their results most believable. Single-shot PVB analgesia is *not* long-lasting, and pain after thoracoscopic surgery is actually quite significant in the first 24 h and even beyond (especially with the continued presence of a chest tube). Our quarrel with these authors is not with their methods or their findings, but with their conclusions. It is akin to concluding that, because single-dose nerve blocks do not provide prolonged analgesia after total knee replacement, peripheral nerve blocks are of no use for this surgery. Clearly that would be a perverse extrapolation, and most would recognize that such findings indicate the need for continuous blockade.

Our approach to postoperative pain management after thoracoscopic surgery includes routine preoperative placement of a single paravertebral catheter at a level of T5 or T6. This is much more time efficient and comfortable for the patient than placing multiple blocks. We have found no loss of analgesic efficacy by eliminating the single-shot blocks at multiple levels and have observed both clinically and with contrast dye injection that the sole catheter does indeed provide for multiple levels of paravertebral blockade. Besides simplicity and a minimum of side effects, the advantages of a single continuous paravertebral catheter are its effectiveness, its flexibility, and its adaptability. A PVB catheter allows for titration of the local anesthetic and extension of nerve blockade as needed. With further bolus dosing and adjustment of infusion rates, PVB analgesia is individualized before patient discharge from the postanesthesia care unit. In fact, our post-

anesthesia care unit nurses work closely with our acute interventional postoperative pain service and are most comfortable working with peripheral nerve block infusions. By having a catheter in place, we can also continue the nerve blockade until removal of the chest tube (typically the determining factor in timing of hospital discharge after thoracoscopic surgery), thus minimizing pain and opiate consumption for the duration of this period. Moreover, in the event that the thoracoscopic procedure turns into an open thoracotomy, the PVB catheter is already in position to readily provide postoperative analgesia and adjust it to the patient's needs.

It has been suggested that thoracic PVB may replace the thoracic epidural technique as the gold standard for providing analgesia for patients undergoing thoracotomy.<sup>2</sup> In our institution, this has been the case for some time, and it has had a profound and positive impact. We urge our colleagues to move forward in learning and applying continuous PVB in their practices.

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*In Reply:*—The search for the optimal pain management technique after thoracoscopic surgery remains a clinically important undertaking. Although I support the enthusiasm of Drs. Ben-David, Merman, and Chelly for the development of safe and effective postoperative analgesia, I disagree with their assessment of our clinical trial. Because the mode for hospital length of stay in my institution after thoracoscopic surgery is 1 day, we evaluated single-dose, multilevel paravertebral nerve blockade in a randomized, double-blind, placebo-controlled clinical trial using postoperative patient-controlled morphine usage as our primary endpoint. We found a significant reduction in narcotic requirement for the first 6 h after block placement, but the benefit did not persist. Therefore, we concluded, "Single-dose paravertebral nerve blockade with bupivacaine is effective in reducing pain following thoracoscopic surgery, but only during the first 6h after nerve blockade. Due to the limited duration of effect with currently available local anesthetic agents, our data suggest that, at present, this technique is

not indicated in the setting of thoracoscopic surgery."<sup>1</sup> We did not study continuous paravertebral local anesthetic infusion, nor did we conclude that this technique would be ineffective.

Whereas I support continued study of paravertebral catheter placement with continuous local anesthetic infusion, I caution against advocacy for a therapeutic intervention with associated risk and expense based on clinical experience in a series of patients without adequate study in a randomized, double-blind, placebo-controlled clinical trial. Before our trial, I was enthusiastic about the technique and was of the opinion that the results of the study would be unequivocally positive. I had observed that patients seemed to wake up with less pain and required less narcotic administration in the recovery area. Although these observations proved to be correct, patients were less comfortable after leaving the recovery room. From 6 to 12 h after nerve blockade, the treatment group used more patient-controlled morphine than the control group, making the cumulative morphine dose indis-

tinguishable between groups by the 12th h. Although morphine usage may be an imperfect endpoint, we were unable to explain the increased narcotic requirement in any way other than loss of paravertebral block efficacy. Although adverse events were mild and similar between groups, increased narcotic usage by patients undergoing pulmonary resection after leaving the closely monitored recovery area could potentially lead to respiratory complications. Our results do suggest that continuous paravertebral local anesthetic infusion could be a superior technique for this patient population. However, investigator bias can only be eliminated by well-designed clinical trials. Therefore, I suggest further randomized, double-blind, placebo-controlled studies of continuous thoracic paravertebral nerve blockade

before promoting this technique as the analgesic gold standard in thoracoscopic surgery.

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## Depolarizing Block Is an Endplate-Muscular Block, Not a Neuromuscular Block

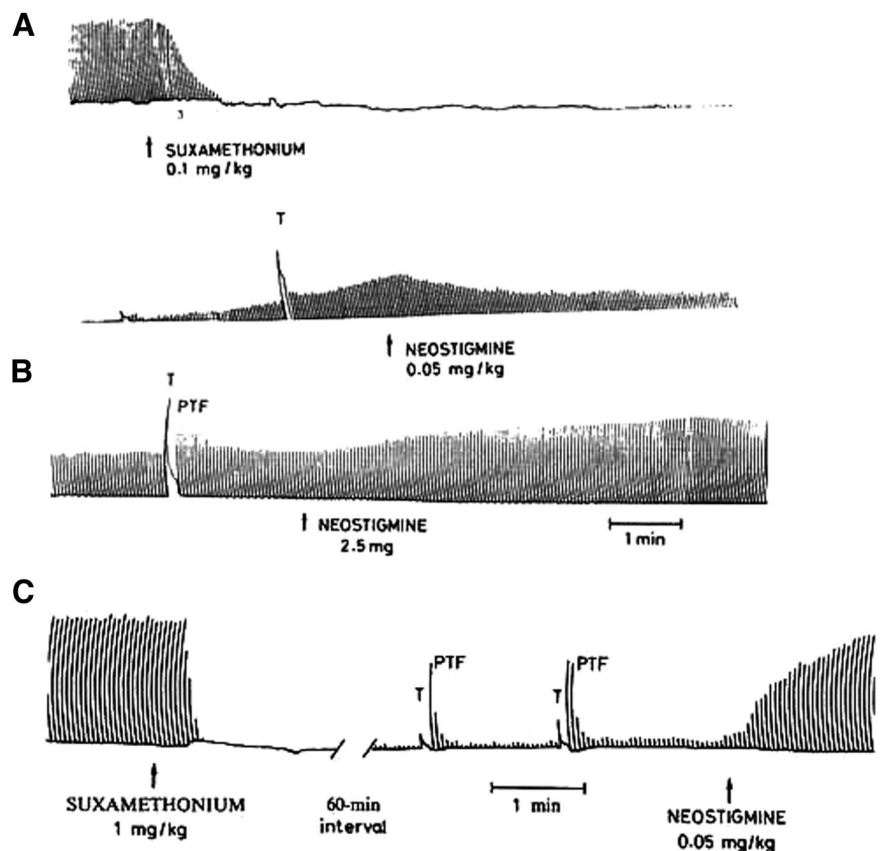
*To the Editor:*—The excellent article by Jonsson *et al.*<sup>1</sup> provides biophysical insight into the mechanism of action of succinylcholine on the muscle-type acetylcholine receptors. They conclude that succinylcholine activates these receptors followed by desensitization.

The initial phase of activation results in an endplate potential that opens the adjacent voltage-gated sodium channel, resulting in repetitive waves of action potentials that manifest as initial muscle fasciculations. Because succinylcholine is not metabolized by the specific cholinesterase at the endplate, the succinylcholine-induced depolarization is maintained, and the outer voltage-gated sodium channel remains open. However, the inner time-dependent sodium gate will close, resulting in an endplate-muscular block. Because the

depolarizing block is beyond the endplate, it is not characterized by tetanic fade or posttetanic facilitation and is potentiated by neostigmine (fig. 1A).

Prolonged exposure of the endplate to succinylcholine will result in progressive desensitization to the depolarizing action of succinylcholine, as well as to the chemical transmitter acetylcholine; hence, the block will gradually change from a depolarizing endplate-muscular block (Phase I) into a desensitizing Phase II neuromuscular block, which is characterized by progressive tetanic fade and posttetanic facilitation. The neuromuscular block may be antagonized by neostigmine. The degree of reversal by neostigmine is proportional to the extent of fade and posttetanic facilitation (fig. 1, B and C).<sup>2</sup>

**Fig. 1.** Tracings of the twitch response to ulnar nerve stimulation in three patients with homozygote atypical plasma cholinesterase. (A) Administration of succinylcholine 0.1 mg/kg resulted in a depolarizing block characterized by minimal tetanic fade (T) and no posttetanic facilitation (PTF). Neostigmine 0.05 mg/kg potentiated block. (B) Twitch response in a second patient with atypical esterase showing recovery of the twitch response after succinylcholine 0.1 mg/kg, associated with moderate tetanic fade and posttetanic facilitation. Neostigmine 2.5 mg accelerated recovery. (C) The twitch response in a third patient with atypical esterase. Injection of succinylcholine 1 mg/kg resulted in a very prolonged neuromuscular block. After 90 min, recovery started and was associated with marked tetanic fade and posttetanic facilitation. Administration of neostigmine 0.05 mg/kg could completely reverse the block. Modified from Baraka.<sup>2</sup>



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*In Reply:*—We thank Dr. Baraka for his insightful comments on our article.<sup>1</sup> As Dr. Baraka pointed out, one of our findings is that the muscle-type nicotinic acetylcholine receptor, when expressed in *Xenopus* oocytes, is desensitized by succinylcholine after an initial activation. Because we have not studied the neuromuscular junction with all its components, we cannot from this type of study fully investigate the mechanism of action by succinylcholine-induced neuromuscular block.

To the best of our knowledge, succinylcholine seems to cause neuromuscular blockade due to a prolonged depolarization of the endplates,<sup>2</sup> which might include both desensitization of the muscle nicotinic acetylcholine receptors and inactivation of voltage-gated sodium channels. In addition, we suggest that the low affinity of succinylcholine for the presynaptic  $\alpha 3\beta 2$  nicotinic acetylcholine receptor

subtype explains the lack of tetanic and train-of-four fade during succinylcholine-induced neuromuscular block.<sup>1</sup>

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## Anemia-induced Neurocognitive Dysfunction: Is Oxygen the Only Player?

*To the Editor:*—Investigations dealing with blood transfusions and their components have recently been more and more focused on the risk-to-benefit issue. This has led to the investigation of specific organ functions under isovolemic anemia to define rational transfusion triggers. From these results, investigators have tried to define physiology-based parameters for transfusion triggers.<sup>1-7</sup>

In their recent article, Weiskopf *et al.*<sup>8</sup> showed that erythrocytes stored for 3 weeks are almost as efficacious as are fresh erythrocytes for reversing the cognitive functions. Based on these results, the authors reject the current opinion that stored erythrocytes off-load oxygen less than fresh erythrocytes do.

As Spahn and Madjpour argued in the corresponding editorial,<sup>9</sup> the authors did not prove a direct correlation between better neurologic function and oxygen release by 2,3-diphosphoglycerate in the central nervous system. Spahn and Madjpour emphasize that factors other than 2,3-diphosphoglycerate are responsible for the oxygen off-load.

These findings raised questions. Oxygen transport and release have been the main topic of research in this field. However, evidence is mounting<sup>8,9</sup> that factors other than hemoglobin and 2,3-diphosphoglycerate are involved in explaining the benefits of blood transfusions. This is supported by the literature from the gynecological field.

It is well known that iron has functions other than hematologic functions. A common symptom, such as postoperative fatigue, can be explained by an iron deficiency: iron supplementation improves aerobic adaptation<sup>10</sup> and endurance capacity<sup>11</sup> in young iron-depleted but nonanemic women. Knee extensor exercise in nonanemic but iron-depleted women is also improved after iron supplementation.<sup>12</sup> In the context of Weiskopf *et al.*'s investigation, it is of great interest to note that iron supplementation has been shown to improve some cognitive functions in nonanemic iron-depleted adolescent girls.<sup>13</sup>

Withdrawing one blood unit (450 ml), as described by the authors, corresponds to 250 mg of iron, which is almost 10% of the volunteer's (mean weight 64 kg) functional iron. One unit has been withdrawn 4-5

weeks before the first experimental day (to gain stored blood for the experiments). Further blood units (iron included) were withdrawn to induce isovolemic anemia without (mentioned) iron substitution. According to previous articles,<sup>1-3</sup> hemoglobin levels were roughly halved by withdrawing further blood in 450-ml steps for each experiment. Halving the hemoglobin concentration goes hand in hand with remarkable additional iron depletion. Unfortunately, no data concerning the volunteers' iron status have been given.

Based on this view and supported by the literature,<sup>10-13</sup> one could argue that, with the authors' protocol, iron was withdrawn and retransfused in comparable amounts in both groups ("fresh" and "stored"). Iron could have been one of "the important" factors explaining the observed results, which are comparable to the cognitive test results reported by Bruner *et al.*<sup>13</sup> Thus, one may wonder whether the results observed in Weiskopf *et al.*'s investigation could be partly explained by transient iron deficits.

For the future, it will be of great interest to investigate parameters other than hemoglobin levels and oxygen release by 2,3-diphosphoglycerate when dealing with the question of whether to transfuse blood or not.

Symptoms like fatigue or dizziness, which are frequently observed in postoperative orthopedic surgery, could be greatly reduced by improving iron status—preoperative and postoperative prescription—instead of postoperative blood transfusions.

**Hans Jutzi, M.D., Markus Risch, M.D., Stephan Blumenthal, M.D., Alain Borgeat, M.D.\*** \*Balgrist University Hospital, Zurich, Switzerland. alain.borgeat@balgrist.ch

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*In Reply:*—We thank Drs. Jutzi, Risch, Blumenthal, and Borgate for their interest in the report of our finding that erythrocytes stored for 3 weeks are as efficacious as fresh erythrocytes (3.5 h storage) in reversing anemia-induced cognitive function deficits in healthy humans.<sup>1</sup> The measured hemoglobin P<sub>50</sub> at the time of cognitive testing, a few minutes after transfusion, support the lack of a physiologically significant increase in the stored erythrocytes' P<sub>50</sub> from the measured low value of 15 mmHg, as is to be expected from the measured *in vivo* rate of regeneration of 2,3-diphosphoglycerate in erythrocytes stored in citrate-phosphate-dextrose-adenine.<sup>2</sup> This is not in agreement with the conjecture<sup>3</sup> based on 2,3-diphosphoglycerate data from erythrocytes stored in acid-citrate-dextrose and transfused more slowly.<sup>4</sup>

Jutzi *et al.* suggest that the neurocognitive deficit created by isovolemic anemia was secondary to iron deficiency and that the reversal of the cognitive deficit for erythrocytes of both storage durations was produced by transfusion of iron, rather than an increase of oxygen delivery by transfused hemoglobin. Although our results do not seem to be consistent with an inability of 2,3-diphosphoglycerate-depleted erythrocytes to release oxygen from hemoglobin, we do not believe that there is evidence to support the suggestion of Jutzi *et al.*

Beutler has concluded that it is unclear whether "iron deficiency without anemia" can cause symptoms.<sup>5</sup> As pointed out by Beutler, the lack of clarity is, at least in part, owing to the difficulty in separating these experimentally.<sup>5</sup> When iron is administered to patients with a "normal" hemoglobin concentration (*i.e.*, at the lower end of the normal range), the latter, nevertheless, can increase.<sup>6</sup> Although Jutzi *et al.* cite work showing that iron therapy improves exercise capacity and endurance, fatigue, and cognition in weeks to months, other studies have failed to find such improvement.<sup>5</sup> Most importantly, the improvement found in those studies was among patients with chronic, not acute, iron deficiency, and the reported improvements occurred after weeks to months of therapy. We are unaware of reports of such improvement in the few-minute time frame of our study, or even within a few days. A systematic review found "no convincing evidence" of an effect of iron therapy on improvement of psychomotor development and cognitive function 5-11 days from the commencement of therapy.<sup>7</sup> The sole study cited by Jutzi *et al.* as having demonstrated improved cognitive effects reported a very small effect in only one of four subanalyses (by multiple linear regression but not analysis of variance), but not the overall evaluation, after 8 weeks of iron therapy, with a concomitant increase in hemoglobin concentration that resulted in a greater hemoglobin concentration than in the control group.<sup>8</sup>

Decreased blood oxygen content and delivery caused by hypoxia decreases maximal oxygen consumption (exercise capacity) immediately,<sup>9</sup> and acute isovolemic anemia to hemoglobin concentration of 5

g/dl alters central processing<sup>10</sup> and cognitive function<sup>11</sup> and increases fatigue,<sup>12</sup> whereas increasing oxygen content at this critical level reverses these effects. Chronic iron-deficiency anemia alters central processing as determined by P300 latency,<sup>13</sup> and 90 days of iron therapy reverses the iron deficiency and improves the anemia but does not improve the prolonged P300 latency.<sup>13</sup> Increasing hemoglobin concentration immediately normalizes acute anemia-induced prolongation of P300 latency.<sup>10</sup> Breathing oxygen for 5 min, without alteration of iron stores, completely reverses anemia-induced cognitive deficits.<sup>11</sup> These results indicate that oxygen, not iron, is responsible for the improved cognitive function. Acute anemia to the identical degree does not alter peripheral or central nerve conduction,<sup>14</sup> which also argues against an immediate direct neural effect of an acute decrease in blood iron content.

As we stated in our article, we do not have data to support or refute the several possible explanations we discussed.<sup>1</sup> However, we do not feel compelled to add iron deficiency and replacement as a possible cause of our findings.

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## Desflurane and Density

*To the Editor:*—I read with interest the report from Nyktari *et al.* on the interaction between the physical properties of halogenated vapors and pulmonary resistance.<sup>1</sup> Their observations have important implications on the choice of anesthetic agents in selected patient populations.

These results are consistent with modeling their experimental apparatus as a simple orifice. Flow through an orifice is directly proportional to the square root of the pressure gradient across the orifice and inversely proportional to the square root of the density of the gas. This is shown in the following equation

$$Q \propto \sqrt{\frac{\Delta P}{\rho}}, \quad (1)$$

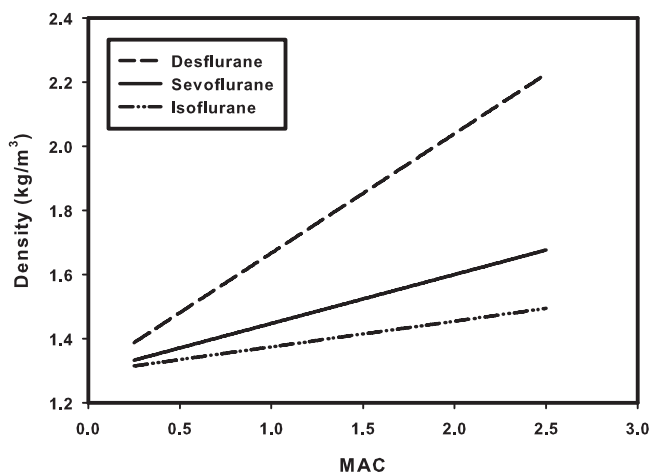
where  $Q$  is the volumetric flow,  $\Delta P$  is the pressure gradient, and  $\rho$  is the density. As the authors calculated resistance from the pressure gradient needed to deliver a constant flow, equation 1 can be modified by squaring both sides and rearranging terms into a form analogous to Ohm's law ( $V = IR$ ):

$$\Delta P \propto Q \times (Q\rho). \quad (2)$$

In equation 2, the term  $Q\rho$  corresponds to the resistance; when the flow is held constant, as in the described experiment, the resistance will increase linearly with the density of the gas. Plotting the density (calculated as the weighted sum of the molecular weights divided by the molar gas volume at standard temperature and pressure) of a mixture of various minimal alveolar concentration (MAC)-multiples of desflurane, sevoflurane, and isoflurane diluted in 25% oxygen and 75% nitrogen produces a graph that is strikingly similar to the authors' figure 4 (see fig. 1). Using only the mean values in the authors' figure 4, there is a strong linear relationship between MAC-multiple and resistance (isoflurane,  $P = 0.060$ ,  $r^2 = 0.88$ ; sevoflurane,  $P = 0.067$ ,  $r^2 = 0.87$ ; desflurane,  $P = 0.002$ ,  $r^2 = 0.995$ ). These relationships would have been even more significant had all the data points available from their figure 3 been included in the regression. The linear relationship between MAC-multiple and resistance is masked in figure 4 by the authors' decision to make the interval from baseline (MAC = 0) to 1 MAC the same as that between 1 and 1.5 MAC and between 1.5 and 2 MAC.

In addition to resistance for orifice flow, the critical velocity (the volumetric flow velocity at which flow transitions from laminar to turbulent) is also inversely proportional to density. Thus, low-potency agents may also increase the likelihood of airway turbulence at lower gas velocities, further increasing resistance.

These physical principles are the justification for the use of helium, a



**Fig. 1.** Density at standard temperature and pressure (0°C and 1 atm) of admixtures of various minimal alveolar concentration (MAC)-multiples of isoflurane, sevoflurane, and desflurane in 25% oxygen and 75% nitrogen.

low-density gas, in patients with stenotic airways. As such, desflurane should probably be used with caution in patients with airway obstruction, even ignoring its propensity to aggravate airway reflexes. Despite the authors' note that desflurane has been successfully used in spontaneously breathing patients, it should be recognized that desflurane will, through its effects on gas density, increase the work of breathing in patients with a native glottis (facemask or laryngeal mask airway), in which the vocal cords act as an orifice. The final decision as to whether these considerations are of clinical significance awaits further study, but the authors should be congratulated for bringing this issue to our attention.

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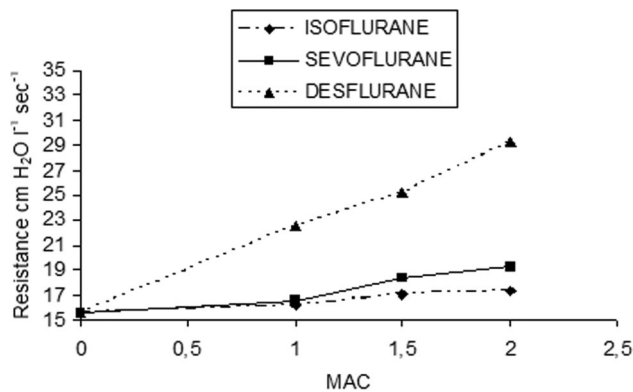
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*In Reply:*—We thank very much Dr. Gunter for his useful and kind comments on our article.<sup>1</sup> His observation that in our figure 4 the interval from baseline minimal alveolar concentration (MAC = 0) to MAC 1 is the same as that between 1 and 1.5 MAC and between 1.5 and 2 MAC is precise. This is a point that has been overlooked by the

authors, but it does not alter the figure significantly (fig. 1). We decided to use only the mean values in our original figure 4 to keep it simple and easily apprehensible. Furthermore, because of the use of a laboratory model, the variations of the measurements of resistance were minimal.



**Fig. 1.** Comparison of the effect of different volatile anesthetics at equivalent concentrations on total pulmonary resistance. At 1 minimal alveolar concentration (MAC), only desflurane significantly increased pulmonary resistance compared with isoflurane and sevoflurane ( $P < 0.001$  for both comparisons). The difference between isoflurane and sevoflurane was not statistically significant ( $P = 0.15$ ). At 1.5 MAC, sevoflurane significantly increased total pulmonary resistance compared with isoflurane ( $P = 0.015$ ), whereas desflurane caused a more pronounced increase compared with isoflurane and sevoflurane ( $P < 0.001$  for all comparisons). The same findings apply at 2 MAC concentrations. Sevoflurane significantly increased pulmonary resistance compared with isoflurane ( $P < 0.001$ ), and desflurane caused a significant increase compared with the other two volatile agents ( $P < 0.001$  for both comparisons).

The lung model used for the experiment simulates the central part of the respiratory system, mainly the trachea and the main bronchi, and our results are not explained by modeling the laboratory lung as a simple orifice. Nevertheless, our findings suggest that desflurane can increase the work of breathing in patients with upper airway obstruction. The respiratory system is much more complicated than our laboratory model, and many factors affect the overall pulmonary resistance. Because desflurane may possess a degree of bronchodilatory properties, we should await further studies in humans to clarify the clinical relevance of our observation.

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(Accepted for publication October 23, 2006.)

## Use of Macintosh Laryngoscope No. 2 for Adult Patients with a Short Thyromental Distance

*To the Editor:*—We read with great interest the article by Tripathi and Pandey<sup>1</sup> reporting that the use of the Macintosh laryngoscope No. 3 (Mac #3) in patients with a short thyromental distance was associated with great difficulty in laryngoscopy and intubation compared with the Mac #2. We previously assessed the laryngeal aperture fiberoptically during direct laryngoscopy with the Mac #3 in 17 patients whose glottis was invisible under direct vision (difficult laryngoscopy).<sup>2</sup> In one fourth of these patients, the laryngoscope could not provide an adequate fiberoptic view of the laryngeal aperture because of an inability to lift the collapsed laryngeal tissues caused by general anesthesia and the muscle relaxant.<sup>3</sup> That is, in these patients, it is difficult to place the blade tip of the Mac #3 in the position necessary to lift the epiglottis and the laryngeal soft tissues. The authors clarified this problem by measuring the intubation distance and overcame it by using the Mac #2 with its thinner flange and greater curvature of the spatula. We respect their ideas. However, adult patients whose airway is predicted as difficult by a short thyromental distance have a small mandible, but the size of their maxilla is usually normal (defined as micrognathia), which is different from pediatric patients. Moreover,

they often have protruding upper incisors. Thus, we are concerned that when the Mac #2, which is 1.5–2 cm shorter than the Mac #3, is used with these patients, the whole blade gets into the oral cavity, and a good laryngoscopic view is not obtained even if the blade tip reaches the optimal position required to lift the laryngeal soft tissues.

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(Accepted for publication October 23, 2006.)

*In Reply:*—We appreciate the comments of Drs. Takenaka and Aoyama about our article regarding the use of Macintosh blade No. 2 to be used for better laryngeal view in adult patients with a short (<5 cm) thyromental distance, who may be difficult to intubate with a

regular blade.<sup>1</sup> They suggest that, because of the normal size of maxilla in adults with micrognathia, the Macintosh blade No. 2 might get into the oral cavity at the point of placement for optimal position required to lift the laryngeal soft tissues and could fail to give a good view for

intubation. We have found that, when placed correctly in preepiglottic space from the right side of the tongue, displacing the whole tongue to the left of blade, the Macintosh curved blade No. 2 can be easily rested on the left premolars. We emphasize that the laryngoscopy method by making a fulcrum on the teeth is not recommended, as it can contribute to broken teeth or damage to enamel. The correct way is to pull the laryngoscope anteriorly and the soft tissue up in the mandibular space to visualize the glottis. The whole blade can only get into the oral cavity if the blade is placed over the tongue and not by the side of it. We do agree that if the blade completely gets into the oral cavity, the view might be difficult, but we have not encountered this problem.

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## Questioning the Length of Airway Exchange Catheters

*To the Editor:*—The recent letter by Fetterman *et al.* on esophageal misplacement of a size 14-French Cook airway exchange catheter (Cook Critical Care, Bloomington, IN) highlights potential complications of this equipment.<sup>1</sup> We believe that the length of these catheters may be excessive. Cook airway exchange catheter sizes 11-, 14-, and 19-French have a length of 83 cm; however, because they are intended for use with single-lumen endotracheal tubes, we believe that a length of approximately 56 cm (double the length of most adult single-lumen endotracheal tubes and the same length as the Cook Aintree catheter) is all that is really needed.

Many of the complications associated with airway exchange catheter use result from overly deep placement of these catheters<sup>2</sup>; a length of 83 cm far exceeds the length necessary for safe endotracheal tube exchange and may lead to overly deep airway exchange catheter

placement by inexperienced users who inadvertently ignore the guide marks. Whereas we realize that a length of 56 cm can still allow for complications, we believe that reducing the length of these catheters may help to reduce the incidence of such complications. Finally, we would like to echo the authors' recommendations on capnographic confirmation of tracheal airway exchange catheter placement.

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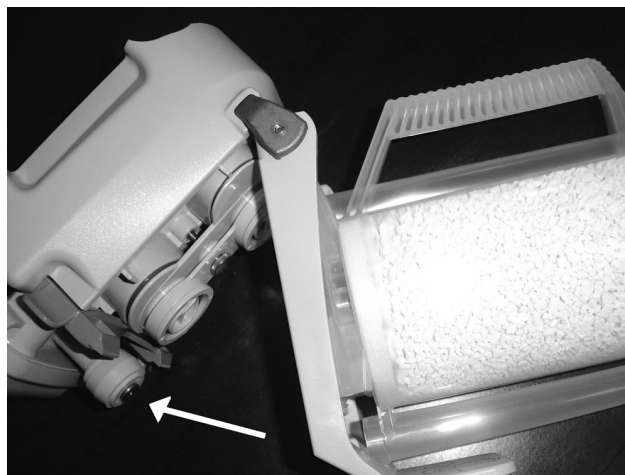
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## Malfunction of the New Aisys<sup>®</sup> Anesthesia Machine

*To the Editor:*—We recently replaced most of our anesthesia machine fleet with the newly available Aisys<sup>®</sup> Carestation (GE Healthcare, Waukesha, WI). In the course of using these second-generation electronic machines, we have encountered two clinically significant problems that have each occurred on more than one unit.

The first problem relates to the EZchange absorber bracket. This component should create a gas-tight seal between the anesthesia machine and absorbent canister. It is also designed to automatically seal the circuit when the absorbent canister is removed, as during absorbent canister changes. We found instances in which a significant leak existed both with and without the canister in place (with one case even requiring patient ventilation with a manual resuscitator to achieve adequate tidal volumes.) The problem was localized to the interconnect valve between the canister and EZchange (fig. 1). The problem seemed to be intermittent and, in some instances, was not detected or appreciated during automated checkout. The exact cause of failure of this connection is still unclear and, according to a company representative, is under investigation by the manufacturer. A solution has been to remove the EZchange assembly and mount the canister directly to the machine.

The second problem involves the built-in spirometry sensors. When this problem occurred, warning messages (*e.g.*, tidal volume not achieved, check flow sensors, system leak) appeared, and the



**Fig. 1.** EZchange assembly and associated absorbent canister. The white arrow identifies the component found to leak during system failures.

calculated expired tidal volumes were well below those actually delivered. Further analysis revealed that excess moisture in the



breathing system (suggested by the condensation seen in the expiratory valve assembly) may lead to such malfunction of the sensors, which are located near the inspiratory and expiratory valves. A solution to this has been to switch to the backup D-Lite spirometry module included on the machines, which uses separate pressure tubing and seems to be less vulnerable to the effects of moisture in the circuit. (The machine will still give an alarm indicating that the volume sensors disagree, but the flow volume loops will appear

normal.) We are also adding expiratory limb filters to our circuits to help to protect the sensors.

Users should be aware of these potential problems and solutions until the manufacturer offers definitive solutions.

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*In Reply:*—GE Healthcare would like to thank ANESTHESIOLOGY for the opportunity to respond to the Letter to the Editor by Drs. Wax and Neustein.

In their letter, the authors discuss two issues pertaining to the Aisys<sup>®</sup> machine. The first concerns the function of the EZchange absorber manifold, the second concerns the effect of water on the inspiratory and expiratory flow sensors.

We have been able to reproduce the leak described by the authors. The breathing circuit leaks experienced at Mt. Sinai (New York, NY) were the result of an inadequate seal between the manifold and the absorber canister; small frays on the drain port of the disposable absorber canister produced the inadequate seal. This issue may be identified during the Aisys<sup>®</sup> automatic system checkout procedure; we have verified this with affected canisters. Of course, if the canister is changed in the middle of a case, there would be no additional system checkout and a leak may result.

We have not been able to reproduce a system leak when the EZchange manifold is in place without a disposable canister because the leak exists where the manifold and the disposable absorber canister connect, as suggested by the authors.

We have taken a two-pronged approach to resolving this issue. First, we are addressing the root cause, the disposable absorber canister, by working with the third-party supplier to remedy the issue with the drain port flashing. Second, we are currently revising the drain seal on the EZchange module so this flashing, even if unchanged, will not affect the seal between the canister and the manifold.

With respect to the moisture and flow sensor issue, the root cause was most likely the impact that moisture or water may have on the function of the flow sensor. Our flow sensors are a vital component of the Aisys<sup>®</sup> ventilator. Like anesthesia practice, these sensors have

undergone extensive evolution since they were first introduced. As clinical anesthesia has moved toward lower and lower fresh gas flows, the impact of the increased humidity has necessitated a redesign of the basic flow sensor. At the time of the events, Mt. Sinai was using an earlier version of the flow sensor. The current flow sensor incorporates an offset in the area of the flow sensor flap that helps to overcome the issue associated with high moisture or water. This version can be readily recognized by the presence of grooves on the bezel of the flow sensor closest to the patient.

The final issue the authors describe is the use of the D-Lite sensor to obtain spirometry instead of using the flow sensors. The D-Lite sensor and the direct patient monitoring of respiratory mechanics the use of the D-Lite may provide are a design feature of the Aisys<sup>®</sup>. Using the D-Lite will not resolve alarm issues produced by the inspiratory and expiratory flow sensor. The authors' description of the ventilator alarms suggests that the old-style flow sensors they were using at the time may have either had some moisture on the inspiratory sensor or may not have been calibrated.

The flow sensors should be calibrated daily simply by removing the flow sensor module, waiting for the "no insp flow sensor" and "no expiratory flow sensor" messages to appear, and then reattaching the flow sensor module. The alarm messages reported by Mt. Sinai would not have occurred with calibrated offset flow sensors.

GE Healthcare commends the authors for their insightful and accurate Letter to the Editor.

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## Propofol: A Novel Treatment for Breaking Migraine Headache

*To the Editor:*—A small number of open-label trials<sup>1,2</sup> and case reports<sup>3,4</sup> support the use of intravenous propofol in subanesthetic doses for the management of chronic severe intractable migraine headache. The largest of these, which included 77 patients, reported an average reduction in headache intensity of 95.4%. In this study, 63 of 77 patients reported complete resolution of headache symptoms after receiving 120 mg of propofol delivered over 30 min.

We report the case of a 54-yr-old woman who was admitted to the hospital with 2 weeks of severe, intractable migraine headache, complicated by severe hemicranial pain, photophobia, phonophobia, and a new left eyelid droop. After completing a full neurologic work-up, which was negative, the patient was diagnosed with status migrainous. Multiple medications, including gabapentin, pregabalin, sumatriptan,

carisoprodol, promethazine, ketorolac tromethamine, and morphine sulfate, were all attempted with limited success.

Our anesthesiology service was consulted by the patient's neurologist for a subanesthetic trial of propofol, as reported by Krusz *et al.*<sup>1</sup> On the visual analog scale of 0-10, the patient reported a score of 6 for frontal head-pain and experienced significant photophobia just before the injection of propofol. She then received 20 mg IV every 5 min to a maximum of 120 mg over 30 min. Within 5 min, the patient's pain scale score decreased to 5. By 20 min (80 mg), she reported a score of 2 and stated that she could not remember the last time she felt this good. By 30 min (120 mg), she reported a pain score of 0 and commented that she could remove her dark glasses without any photophobia and that her headache was gone. Five hours later, and after 5 days in the hospital, the patient was discharged home without pain.

Although existing studies are small, this case report, in conjunc-

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tion with smaller studies reported elsewhere, supports the use of propofol in subanesthetic doses for the treatment of severe migraine headache. These observations also suggest the involvement of the  $\gamma$ -aminobutyric acid type A receptor in the etiology of migraine headaches. It seems that a large-scale trial to examine the efficacy of propofol, at least for acute headache control, is warranted.

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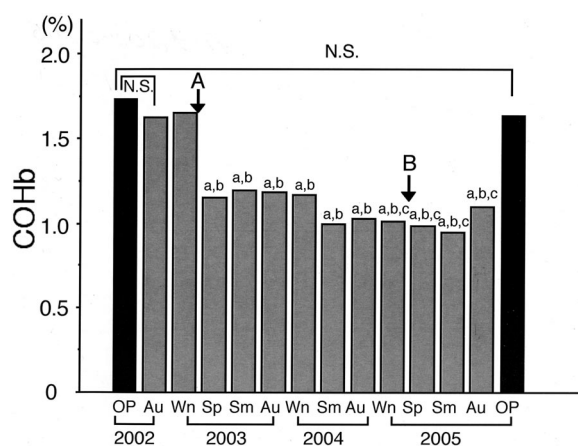
## Implementation of Smoke-free Policy in University Hospital Decreases Carboxyhemoglobin Level in Inpatients Undergoing Surgery

*To the Editor:*—Over the past two decades, many hospitals in advanced countries have declared a “smoke-free hospital,” and adoption of such a policy has recently, albeit very belatedly, begun in Japan. Because cigarette smoking is a risk factor for mortality and morbidity, this implementation may be expected to produce measurable benefits for the majority of patients, provided it effectively reduces smoking in the hospital environment.<sup>1</sup> In cigarette smokers, as well as in passive smokers, blood carboxyhemoglobin concentration (COHb) is known to be elevated.<sup>2</sup> Herein we report a significant reduction in COHb values in surgical inpatients following the implementation of such a policy.

We compared COHb values before and after the implementation of a smoke-free hospital (on April 1, 2003) after more than a year's preparation. We collected all arterial blood oxymetry data (measured using an ABL700, Radiometer, Copenhagen, Denmark) obtained from those inpatients undergoing surgery who had an arterial puncture or an arterial line in place for collection of arterial blood samples in the operating room. Arterial blood samples taken just before or after the induction of anesthesia were immediately subjected to the measurement of arterial blood gas tensions and COHb. The implementation of a smoke-free university campus was begun on April 1, 2005. Differences in COHb were examined *via* a one-way analysis of variance with an unpaired *t* test (with a Bonferroni correction) being used for *post hoc* comparisons.

As shown in figure 1, the mean values COHb were  $1.65 \pm 0.87\%$  ( $n = 656$ , mean  $\pm$  SD) over the 3 months before the implementation of a smoke-free hospital and  $1.15 \pm 0.50\%$  ( $n = 614$ ) just after the implementation, and this decreased COHb level remained stable. After the implementation of a smoke-free university campus (April 2005), it showed a slight decrease to  $0.98 \pm 0.40\%$  ( $n = 713$ ) over the next 3 months. There was no difference in age distribution, hemoglobin concentration, or arterial oxygen tension ( $P_{aO_2}$ ) before and after the implementation. Whereas in 2002 the percentage of surgical patients who were smokers was 26.9% and the average hospital stay before surgery was approximately 6.7 days, in 2005, these were smaller (22.5% and 5.4 days, respectively). Among outpatients, the mean COHb values were  $1.74 \pm 0.94\%$  ( $n = 1,069$ ) for 12 months before the implementation of the smoke-free hospital and  $1.64 \pm 0.72\%$  ( $n = 1,475$ ) after the implementation of a smoke-free university campus.

These data document that the implementation of a smoke-free hospital caused a dramatic decrease in COHb values among surgical inpatients. It is unlikely that upon implementing a smoke-free hospital, all patients who smoked had stopped before admission. However, such patients were no longer able to smoke in the hospital buildings and had



**Fig. 1.** Changes in the blood levels of blood carboxyhemoglobin concentration (COHb; %) in inpatients undergoing surgery before and after the implementation of a smoke-free hospital on April 1, 2003 (A). Sp = spring (April to June), Sm = summer (July to September), Au = autumn (September to December), Wn = winter (January to March). No data are available for spring 2004 because of moving to the new hospital. The implementation of a smoke-free university campus was begun on April 1, 2005 (B). a =  $P < 0.01$  compared with autumn 2002; b =  $P < 0.01$  compared with winter 2003; c =  $P < 0.01$  compared with outpatients (OP) 2005; N.S. = not significant.

an approximately 6-day period of forced abstinence or reduction of smoking before surgery after the policy implementation. These data could also preclude the possibility that seasonal variations in COHb among the population admitted to our hospital might have affected the results, as COHb did not significantly change during the observation period, except the timing of the implementation of the smoke-free hospital. The implementation of a smoke-free policy may have made smokers abstain from smoking or prevented inpatients from passive smoke. Thus, such a policy seems to be an effective way of reducing smoke pollution in the hospital environment and lowers the carbon monoxide concentration in the blood of inpatients.

Although COHb may not be the sole factor in determining smoke-induced morbidity and mortality, smokers are at higher risk of cardiopulmonary<sup>3</sup> and wound-related postoperative complications than non-smokers,<sup>4</sup> and high COHb levels are associated with high mortality.<sup>5</sup> Thus, this first observation of a decrease in hospital-wide COHb warrants further study to evaluate the potential benefits to patients resulting from admission to a smoke-free hospital, as well as to people in a smoke-free community.

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

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The authors thank Mr. H. Jintoku (Radiometer, Copenhagen, Denmark) for his help collecting part of the data.

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