

tive outcome (see our table 4) and are therefore worthy of the clinician's serious consideration. Lebard *et al.* also express surprise at the 19.5% mortality we observed in patients with PPC, finding it high; they suggest that overlapping postoperative cardiovascular complications (CVC) might have played a role. In fact, however, high mortality is not unusual in patients with PPC: mortality was 27% and 21% in two studies by Arozullah *et al.*<sup>3,4</sup> Nonetheless, we did record postoperative CVC in detail in our study, finding them in 36.6% of the patients with a PPC. Thirty-day mortality in this subgroup was 33.3%, which was similar to mortality in the study of Lawrence *et al.*<sup>5</sup> and in sharp contrast with the rate of 11.5% we saw in patients with a PPC but no added CVC. Meanwhile, mortality in patients with a CVC but no PPC was low in our study (3.4%). We therefore think that although the cooccurrence of a PPC and a CVC is an ominous event, the PPC still play a large role in increasing risk of death. We emphasize that, although we analyzed factors associated with PPC, it was not our aim to examine how they might have arisen. Generally speaking, if a patient first develops a PPC, the clinical course that culminates in death may also include the development of cardiovascular or other complication that will influence the outcome. Conversely, if a PPC is not the first complication to appear, its later development nonetheless will play a role.

Marret and Jaber suggest that anesthetic technique may play role in the development of PPC, and they specifically ask about the effect of combining general anesthesia with an epidural block. This subgroup accounted for 8.4% of our study population undergoing general anesthesia ( $n = 1,336$ ) and comprised patients who on average were older, in a poorer state of health, and undergoing more aggressive and longer-lasting surgical procedures. In a *post hoc* analysis of our data, we compared a group of 112 patients who underwent general anesthesia with another group of 112 who received combined general-epidural anesthesia, finding no significant differences in the incidence of PPC (18.8% *vs.* 20.5%,  $P = 0.867$ ) or pain intensity at 24 h (score of 3 or less on a visual analog pain scale, 56.3% *vs.* 67%,  $P = 0.131$ ) (statistical results from the ARISCAT database run on March 1, 2011). Thus, there seems to be no suggestion of a beneficial effect of combined anesthesia, although we must emphasize that our study was not designed to compare anesthetic strategies. We agree with Drs. Marret and Jaber that there is a possible influence of ventilatory settings on the development of PPC. The anesthesiologists in charge of care chose the settings in all cases in our study, and although our database includes recordings of positive end-expiratory pressures, alveolar recruitment maneuvers, and hyperoxygenation, we have no reliable information on tidal volume. Finally, with regard to fluid therapy and postoperative pain, we included both in the list of potential risk factors for PPC, but neither achieved statistical significance in the bivariable analysis. We agree with Drs. Marret and Jaber that different perioperative strategies might reduce risk; nonetheless, so far, systematic analysis has found that only a few have been shown to clearly

or possibly do so,<sup>6</sup> whereas others remain to be tried. We think controlled studies should now be designed to analyze the possible benefit of promising strategies given the impact of PPC on postoperative mortality. Our study has provided evidence of the magnitude of the problem in general surgical populations and the possibility of easily and reliably identifying patients at greater risk of PPC.

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## Halogenated Anesthetics and Intensive Care Unit Sedation: A Note of Caution

### To the Editor:

I read with interest the article by Sackey *et al.*<sup>1</sup> and accompanying editorial<sup>2</sup> discussing the use of volatile anesthetics for sedation in the intensive care unit. Although the points regarding tailoring sedation to individual needs are accurate, there is a developing body of literature that suggests prolonged exposure to volatile anesthetics is unsafe, and I believe that Payen understates the case in the editorial.<sup>2</sup>

It is clear that volatile anesthetics (and all *N*-methyl-D-aspartate receptor antagonists) cause widespread neurode-

This letter was sent to the author of the referenced Editorial, who felt that a reply was not necessary.

generation in both rodent and primate models.<sup>3,4</sup> What is unclear is the relevance of these models to humans. To quote an occasionally used phrase, “rats are funny people,” and a prolonged exposure of 10-day-old rat pups to isoflurane, while mimicking the gestational age of a 36-week premature infant, may not be applicable to the relatively brief exposure of humans to volatile agents in a typical operating room setting. Prolonged use in the intensive care unit (ICU), however, is far different and comes closer to the exposure duration of the animal models.<sup>3,4</sup> Even Sackey *et al.* mention reversible symptoms of ataxia, tremor, and clonus in children in whom volatile anesthetics have been used for sedation.<sup>1</sup> Although the potential harm to patients exhibiting these symptoms is unclear, their presence is unlikely to be beneficial. Similarly, the aging brain may be vulnerable to yet-to-be elucidated neurotoxic effects of volatile anesthetics. Postoperative cognitive dysfunction in the elderly is a well-known phenomenon whose precise etiology is elusive, but again, animal studies suggest a possible correlation with expressions of Alzheimer-like pathology in rodents after volatile anesthetic exposure.<sup>5</sup> As is the case in studies of the developing brain, the relevance of animal models to human clinical care is unclear, but the prolonged exposure to volatile anesthetics in a scenario of ICU sedation approaches experimental conditions in animal studies. Finally, the mutagenic effects of volatile anesthetic exposure continue to be debated in the literature with some evidence to support acceleration of cancers after anesthesia.<sup>6</sup>

The use of benzodiazepines, narcotics, and intravenous hypnotic agents such as propofol for ICU sedation is well established with an acceptable safety profile. As with any pharmaceutical therapy, there are side effects and challenges associated with their long-term administration, especially when relying on clinical guidance for management when muscle relaxants are used and without Bispectral Index or other monitors of depth of anesthesia. In the report by Sackey *et al.*, it is likely that the same therapeutic goals could have been accomplished with better titration of intravenous agents and use of Bispectral Index or similar technology and without the use of volatile anesthetics. It is increasingly clear that prolonged exposure to volatile anesthetics, especially in the immature, elderly, and compromised brain (the patients most likely to be in an ICU), may be associated with significant risk that is not justified by the clinical benefit of their use for ICU sedation. Until more definitive studies are done, I believe the use of volatile anesthetics for prolonged sedation should be approached with great caution, if at all.

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## In Reply:

We appreciate Dr. Mychaskiw's cautioning words regarding possible negative effects of volatile anesthetics for intensive care unit (ICU) sedation. Perhaps they reflect the apprehension that many anesthetists/intensivists feel regarding the growing body of evidence revealing possible injurious effects of sedatives and anesthetics on the central nervous system. Because these medications are indispensable in modern medicine, we seem to be “damned if we do, damned if we don't.” This may be particularly true in our most vulnerable patients: the very young and very old. We hope to further the discussion with some additional reflections here.

The main purpose of our article was to highlight the clinical impact of sedation strategies on patient outcomes.<sup>1</sup> This specific case using isoflurane illustrates that volatile anesthetics may be a therapeutic option for deep sedation of intubated ICU patients. Although we grant that isoflurane is relatively unproven for this indication, we would tend not to agree with the assertion that “the use of benzodiazepines, narcotics and intravenous hypnotics, like propofol, for ICU sedation is well-established with an acceptable safety profile.” The cited and worrisome recent findings of neurodegenerative and apoptotic effects have been found to apply as well to barbiturates, ketamine, benzodiazepines, and propofol.<sup>2–4</sup> To our knowledge, only the  $\alpha$ -2-agonists have not been found to cause these changes. Dr. Mychaskiw rightly wonders what significance these animal findings bear on clinical medicine, but at least in the pediatric setting Wilder *et al.* have revealed in a large cohort that relatively modest exposure to general anesthesia before the age of 4 yr was related to increased risk of learning disability later in life.<sup>5</sup> Unfortunately, at our current level of knowledge there is nothing to say that risk is lessened by using one class of drug over another or that inhaled anesthetics are more harmful than intravenous.