To the Editor—We read with interest the article by Ramsay and Luterman, and accompanying editorial discussing the use of high-dose dexmedetomidine as a single-agent intravenous anesthetic. We have several concerns, both with the technique described and the journal’s editorial position.

As to the case series itself, we wonder what was the basis for the clinical choice to use doses of dexmedetomidine at more than 7 to 50 times the recommended dose range of 0.2–0.7 μg·kg⁻¹·h⁻¹ as the sole anesthetic. Ebert et al.’s work with volunteers was extremely limited and in no way established dexmedetomidine as a safe single-agent anesthetic. Indeed, doses of dexmedetomidine lower than those in the case series have been recently reported as “accidental overdose” and are accompanied by guidelines for the management of same. Although Ramsay and Luterman’s cases imply that the doses were increased when the patients could not tolerate the procedures at lower dose levels, there is no mention of the initial anesthetic plan. Did the authors undertake the anesthetics with the expectation of using dexmedetomidine at massive, unstudied doses? Given the properties of dexmedetomidine at its usual clinical dose range, it is unlikely that patients would be able to tolerate the procedures described without either supplementation or rapid escalation to massive doses, as actually occurred. We find no convincing evidence in the literature to believe that their course of action could be chosen with confidence in its safety and efficacy. The intraoperative management of the cases is also unusual. We fail to understand their need to avoid the use of supplemental oxygen except when absolutely necessary. The argument regarding electrocautery is unconvincing. It is almost as if the decreased margin of safety is used as a demonstration of dexmedetomidine’s properties with respect to maintenance of ventilation. In the two cases that did not receive supplemental oxygen, were the patients subsequently placed on oxygen in the postanesthesia care unit? Finally, we question the assertion that recovery time in these patients was not significantly prolonged when compared with many conventional anesthetic techniques. A recovery time and postanesthesia care unit stay of 2 to 3 h is considered by many to be significantly prolonged and is not a desirable side effect.

We are therefore concerned that Anesthesiology tacitly endorses this anesthetic technique by calling it “another arrow for the clinician’s quiver” in the accompanying editorial. On the basis of Ebert et al.’s two volunteers and the three cases described by Ramsay and Luterman, are we to assume that this is now an acceptable practice? Certainly, we all daily administer many medications “off-label” in a safe and reasonable manner. There comes a point, however, when the off-label use of a drug crosses the line of “reasonable” and becomes a deviation from the standard of care. Until properly controlled, Institutional Review Board or hospital ethics committee was consulted regarding this “case series.” The practice of anesthesiology is neither a contest of skills nor a game of what one can get away with. The necessity of the practice of anesthesiology is the planning and administration of the safest and most efficient anesthetic for a given individual patient using principles grounded in science and controlled clinical studies. An unusual technique that worked in three patients does not rise to this standard and sidesteps the checks and balances of ethical scientific investigation.

Finally, the lack of complete disclosure of conflicts of interest on Dr. Ebert’s part is disturbing. The attestation states, “Dr. Ebert is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this editorial.” This may be true only in the strictest and most limited interpretation of the statement, but ignores Dr. Ebert’s long and close association with Abbott Laboratories (Abbott Park, IL) and previous substantial financial support and honoraria. In fact, the study cited by Ebert in the editorial, examining high-dose dexmedetomidine in volunteers, was itself supported by a grant from Abbott Laboratories. At best, this is disingenuous. The casual reader of the journal should be fully aware that an unproven anesthetic technique, utilizing an expensive drug manufactured by Hospira, Inc. (Lake Forest, IL), a wholly-owned spin-off company of Abbott Laboratories, is advocated by an Abbott-funded investigator and is trumpeted by editorial writers with a long history of close association and support from Abbott Laboratories. It is difficult to understand how one can consider this an objective review of scientific data.

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2. Ebert T, Maze M: Dexmedetomidine: Another arrow for the clinician’s quiver. Anesthesiology 2004; 101:568–70

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In Reply—I believe Dr. Mychaskiw and Dr. Badr indicate four areas of concern in their Letter to the Editor. The first relates to the clinical choice of using extremely high doses of dexmedetomidine, the second refers to case management and oxygen therapy, the third is the perception that the Journal endorses the technique of “off-label” use of dexmedetomidine, and the fourth has to do with my conflict of interest disclosure. I believe the first two concerns are questions about the editorial review process. Clearly, expert reviewers provided sufficient enthusiasm to have the case reports published. I was not involved in the review and cannot comment except on one area of concern; my personal belief is oxygen is generally good for patients, even during spontaneous ventilation.

I do wish to comment on the third issue of the Journal’s perceived “endorsement” of the “off-label” use of dexmedetomidine in the clinical care of several difficult cases. Case reports are meant to “draw attention to important and novel clinical situations, treatments, and

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complications." I commend the *Journal for* asking for expert commentary on the described use of dexmedetomidine with a focus on further education and safety. Without the editorial by Dr. Maze and myself,¹ the clinician might not have been aware of the "caveats" and "potential side effects of large concentrations of dexmedetomidine" described in detail in our editorial. The concerns we expressed were: 1) reports of apnea from bolus administration of dexmedetomidine in patients with a history of sleep apnea; 2) hypertension, both pulmonary and systemic; and 3) bradycardia. Clearly an endorsement of "off-label" use of dexmedetomidine was not intended or given. However, the off-label use of anesthesia-related drugs is extensive. Consider a careful read of the Food and Drug Administration labeling of drugs such as the use of the antiepileptic drug gabapentin for pain syndromes, dexamethasone for postoperative nausea and vomiting, intrathecal use of fentanyl, meperidine for shivering, and many drugs used in the pediatric population. The list of accepted drug usages that are not supported by Food and Drug Administration labeling is lengthy. With each unapproved use came case reports followed by controversy (e.g., letters to editors), followed by controlled studies and ultimately accepted practice when the risk/benefit ratio was proven despite package labeling. Finally, Drs. Mychaskiw and Badr express concern with my attestation that I maintain no financial interest or commercial activity in the topic of our editorial and further perceive that I have received "substantial financial support and honoraria" from Abbott Laboratories (Abbott Park, IL). Perhaps a careful review of my income statements would have eliminated their adjective "substantial." Importantly, Hospira Inc. (Lake Forest, IL) owns and markets dexmedetomidine, and they claim no financial relationship to Abbott Laboratories and are listed as a separate company on the New York Stock Exchange. I have not received research funding from Hospira Inc. and do not speak on their behalf. Previously, Abbott Laboratories had marketed dexmedetomidine; my last support from them for a dexmedetomidine study was in 1999. The volunteer studies I refer to in our editorial were funded in the early 1990s. Based on the lack of support for studies with dexmedetomidine for 5 yr and the absence of speaking on this topic on behalf of Hospira Inc, I stand by the strict interpretation of my attestation at the time of the publication of our editorial.

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In Reply—I certainly understand the concerns of Mychaskiw and Badr regarding the case reports in which we described the administration of high "off-label" doses of dexmedetomidine to patients with critical airway related problems.¹ This was certainly not a recommendation for those practitioners inexperienced in the use of dexmedetomidine to attempt this anesthetic technique. The administration of these doses of dexmedetomidine was only performed after extensive experience with the use of this drug over a long period of time and in carefully monitored patients. This technique was utilized in scenarios where current anesthetic methods have significant drawbacks. I described the use of high doses of dexmedetomidine in three patients where current anesthesia techniques presented a significant risk/benefit challenge.

There are a number of published accounts on the administration of high doses of dexmedetomidine. Venn et al. have found that doses of up to 2.5 µg·kg⁻¹·h⁻¹ are necessary to control agitation in critically ill medical intensive care unit patients.² There were no reports of adverse hemodynamic or other unwanted events. Jordan et al. have published a review of a number of cases where inadvertent overdoses of dexmedetomidine have been administered.³ These included patients who had dexmedetomidine administered in doses of up to 20 µg·kg⁻¹·h⁻¹. The only adverse effects noted were extreme sedation and loss of airway control in some of the patients, a clinical scenario very similar to my report of patient #2, who received a maximum of 10 µg·kg⁻¹·h⁻¹ and who required a "chin-lift" during the procedure. The infusion rates in my case reports were very carefully controlled and could have been reduced or stopped at any time if any concerns were raised. The hemodynamic changes associated with the administration of dexmedetomidine have been well described and may be ameliorated effectively if the patient is closely monitored and early intervention is made.

This was not a clinical research project but individual patient care given in the patients' best interest by physicians well experienced in the use of dexmedetomidine; therefore Institutional Review Board permission was not necessary nor was written patient consent. However, the anesthetic technique was discussed in detail with the patients before the procedure. The administration of an approved drug in a way that is not approved by the Food and Drug Administration is not research if it is done in the patients' best interest and in the practitioner's experience represents the safest approach to care. Labeling is not intended to preclude the practitioner using his best medical judgment in the interest of the patient. The Food and Drug Administration regulates the manufacture, labeling, and promotion of drugs; it does not regulate the use of drugs by physicians. The Food and Drug Administration’s approval of a new drug is based on data submitted by the manufacturer; this particular case was based on sedation for the postsurgical patient, initially mechanically ventilated. It is not surprising that the label does not reflect all possible uses of the drug. It is not only commonplace to go off-label but in many incidences this may represent the preferred therapy.

Mychaskiw and Badr criticized the time these patients spent in the postanesthesia care unit. One patient (patient #3) acted as his own control; we compared historical data for the same procedure on the same patient. This patient always stayed approximately 6 h in postanesthesia care unit because of the significant amounts of postoperative opioids required in this opioid-dependant patient. On this admission no postoperative opioids were necessary and the time to discharge was reduced by 4 h.

Patient #1 had severe respiratory compromise and if I was forced to use an anesthetic technique that required tracheal intubation and mechanical ventilation the weaning period may have been prolonged, as was witnessed after his recent pneumonia.

The second patient with the tracheal stenosis that was fulgurated by laser therapy would traditionally have been a postoperative admission to the intensive care ward in my institution rather than a routine postanesthesia care unit admission. The recovery period from dexmedetomidine for this patient was certainly more prolonged than would have been seen with a more conventional propofol technique, but the intraoperative course was notable for the lack of any major airway problems and also for the excellent analgesia with no need for opioid supplementation in the perioperative period.

The lack of oxygen supplementation was primarily to make the pulse oximeter a very sensitive monitor of respiratory depression; at no time did any of these patients require intervention with supplementary oxygen, and only one patient, as described in the report, required a "chin-lift." Oxygen was of course readily available if needed.

The accompanying editorial suggested extreme caution in using this anesthetic technique and did not endorse it in any way.² Ebert and Maze described three major caveats to this anesthetic technique, and only
in the last sentence of the editorial did they offer the suggestion that dexmedetomidine may have a place in the management of the difficult airway. They recommended further comparative studies to establish the clinical role of dexmedetomidine in difficult airway algorithms. I certainly agree that three case reports are not even enough data to claim an "outcomes" clinical trial; these reports were just observations. However, I am collecting more case reports to add to my initial database. I am also involved in a multicenter prospective clinical trial that is including the use of higher doses of dexmedetomidine than currently on the label and administering them for longer periods of time.

I wholeheartedly support the notion of evidence-based medicine following rigorous randomized controlled clinical trials, but the low incidence of the types of cases we reported will make this difficult to achieve in this patient population.

The "off-label" use of drugs is not unusual in the practice of anesthesiology, especially in some of our more sensitive patient groups such as the pediatric population. I agree with Mychaskiw and Badr that the use of "off-label" drugs needs to be done with extreme caution and is only justified when current therapies are less than optimal.

We thank Drs. Mychaskiw and Badr for raising a cautionary note about the use of these high doses of dexmedetomidine and we certainly emphasize that this should only be done by those practitioners with extensive experience with this drug in well-controlled circumstances and where current technologies are less than ideal. However, as our experience with dexmedetomidine increases, its role in the management of the difficult airway may well become "Another Arrow in the Clinician’s Quiver!"

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In Reply—We thank Drs. Lichtor and Takizawa et al. for their interest in our study and thought-provoking observations. Dr. Lichtor points out that in settings of hypotensive extremis from blood loss i) perfusion to the brain can be compromised to the point of significantly altering electrical activity in the brain and ii) delivering an anesthetic that results in brain isoelectricity is clearly excessive. It is interesting to note that in our experimental protocol, we performed a series of pilot studies directed at characterizing the impact of our hemorrhage and resuscitation protocol on a processed measure of brain electrical activity, the Bispectral Index score, in the presence of isoflurane. Although hemorrhage was severe (+2 ml/kg) and resuscitation restored hemodynamic parameters to near-baseline levels, we observed no significant change in the Bispectral Index score (i.e., no Bispectral Index decrease beyond that initially produced by isoflurane). We point out, however, that in our protocol, the mean arterial blood pressure never dropped below 40 mmHg and resuscitation was initiated just at the onset of cardiovascular decompensation. The clinical correlates here are twofold: 1) although hypotensive, compensatory mechanisms most likely maintained adequate cerebral perfusion to sustain brain electrical activity, and 2) resuscitation was initiated before going beyond a time that loosely coincides with the end of the “golden hour.” Once in a severely hypotensive (i.e., less than a mean arterial blood pressure of 40 mmHg) or in a decompensated cardiovascular state (e.g., beyond the “golden hour”), brain electrical activity may be dramatically altered, as suggested by the studies referenced in Dr. Lichtor’s letter.

Dr. Lichtor also points out that although the dose response of blood loss to changes in the Bispectral Index is not well defined, Bispectral Index can be useful in titrating an anesthetic. We concur with his recommendations that monitoring brain electrical activity during surgeries associated with excessive hemorrhage may offer a pragmatic approach to titrating the appropriate dose of anesthetic when the consequences of overdosing can be unpredictable.

In a previous study, we reported that blood loss alone led to a dramatic change in the pharmacokinetics and pharmacodynamics of accompanying hemorrhage—especially followed by crystalloid resuscitation.

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To the Editor.—We report the case of a 68-yr-old obese male patient that was admitted to our university hospital for scheduled elective left carotid endarterectomy under regional anesthesia. Past medical history was significant, with controlled ischemic (four coronary artery bypass grafts at the age of 56 yr) and hypertensive cardiopathy and sleep apnea syndrome balanced with nocturnal ventilation support. Preoperative physical examination detected no abnormality. The patient received a deep cervical plexus block using a single-injection (15 ml 0.5% bupivacaine and 15 ml 2% lidocaine) nerve stimulator-assisted technique. The patient developed acute ventilatory distress associated with bilateral diaphragm paralysis symptoms 15 min after the block was placed. Facemask noninvasive titrated inspiratory pressure-support ventilation resulted in normal breathing pattern and oxygen parameters. After an uneventful surgical procedure the patient was transferred to the ward 2 h after postanesthesia care unit admission. Postoperative ambulatory arterial blood gas analysis and pulmonary functional tests were considered subnormal but phrenic conduction measurements confirmed severe right phrenic nerve conduction alteration.

In this report the patient experienced acute ventilatory failure probably attributable to bilateral diaphragm weakness. Epidural or subarachnoid injection might have promoted similar clinical features. However, the deep cervical plexus block we performed remained strictly ipsilateral to the puncture side. The block concerned left C2-C4 sensory dermatomes but preserved distal motor function of the arm. Then, we believe that the spread of deep cervical plexus block promoted a left phrenic block, resulting in ventilatory failure because of preexisting contralateral phrenic damage. Usually, extension of the

block to the phrenic nerve is common during cervical blocks but without significant clinical problems, in patients with preexisting lung disease. In the present case, unrecognized coronary artery bypass graft-induced right phrenic nerve damage was revealed by the extension of left deep cervical plexus block.

Because up to 10% of cardiac surgery patients may suffer from postoperative electrophysiological abnormal phrenic nerve conduction, we recommend anesthesiologists performing cervical blocks in postcardiac surgery patients remain vigilant attending the patient, with the capacity to supply ventilatory failure.

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First, find out if they truly had a general anesthetic. Second, do not make assurances of memory ablation if you do not plan a general anesthetic and even then be careful what you promise. Third, talk with your colleagues in the endoscopy and catheterization laboratories. I think they are making well-intentioned assurances of memory ablation and are unaware of how often they fail to provide the amnesia they wish to give.

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