In Reply:

We appreciate Manning *et al.*'s comments about our article[1] and the issues surrounding withholding of Angiotensin Converting Enzyme Inhibitors (ACEis) and Angiotensin II Receptor Blockers (ARBs) before noncardiac surgery. We agree that large, international, randomized trials are required to optimally inform the effects of medications in the perioperative period; however, we do not agree that there is a compelling reason to conduct separate trials for ACEi and ARB medications in the surgical setting. The authors suggest that, based on some differences in their mechanisms of action, the withholding of these medications before surgery may produce different effects on major outcomes and should be considered separately. The Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) Study did not differentiate between ACEi and ARB medications and cannot inform whether there was a difference in effect between these drugs.

In general cardiology, the issue of whether the differences in mechanisms of action of ACEi and ARB medications results in differential clinical effects has been explored. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) randomized 8,576 patients to receive ramipril (an ACEi) 10 mg per day and 8,542 patients to receive telmisartan (an ARB) 80 mg per day and followed patients for a median of 56 months.[2] The primary composite outcome (a composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure) occurred in 1,412 patients (16.5%) assigned ramipril and 1,423 patients (16.7%) assigned telmisartan (relative risk, 1.01; 95% CI, 0.94 to 1.09). Moreover, there was no difference across the treatment groups in any of the individual components of the composite outcome.

The authors suggest that perioperative discontinuation of ACEi or ARB medications may potentially cause rebound hypertension and that this, too, may differ between these drug classes. A trial of 526 patients randomized to withhold or continue their ACEi or ARB before noncardiac surgery (approximately half of the patients were taking an ACEi and the other half an ARB) demonstrated that the withholding of these medications did not increase preoperative or postoperative hypertension.[3] Although there were no separate analyses for ACEi and ARBs, we would expect at least some trend toward an increased risk of hypertension if the discontinuation of either medication produced this effect.

The authors suggest that the duration for which patients have been taking an ACEi before surgery also may modify the effect of preoperative withholding because of the angiotensin escape phenomenon. We did not collect data regarding the duration of preoperative ACEi therapy; however, the escape phenomenon manifested within days to two weeks of initiating ACEi therapy.[4] We believe few patients would have initiated an ACEi within days to two weeks before surgery because of prior concerns in the literature about the use of ACEi in the perioperative setting.

We agree with the authors that large trials should inform the treatment effects of perioperative medications. Until such a trial occurs, we believe that—based on data from the VISION Study—physicians should consider withholding ACEi and ARB medications in patients undergoing noncardiac surgery.

Competing Interests

Dr. Roshanov declares no competing interests. Dr. Devereaux declares grants from Roche-Diagnostics (Mannheim, Germany) and Abbott-Diagnostics (Abbott Park, Illinois) during the conduct of the study, and grants from Octopharma (Lachen, Switzerland), Philips Healthcare (Amsterdam, The Netherlands), Stryker (Hamilton, Ontario, Canada), Covidien (Minneapolis, Minnesota), and Boehringer Ingelheim (Ingelheim am Rhein, Germany) outside the submitted work.

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The Isolated Forearm Paradox: Why Never a Response to Command in the Completely Unparalyzed?

To the Editor:

Sanders *et al.*[1] have carefully performed an international study by a distinguished consortium that I am sure was not

easy to organize. That said, the fact that apparently suitably anesthetized patients move during isolated forearm test (IFT) after induction and tracheal intubation is well established and unsurprising. Long reported, with systematic review showing 31 previous papers with more than 1,300 patients studied,[2] a positive response to IFT is easily reproducible by any anesthesiologist, anywhere, at any time. There is some modest interest in the now reported response rate (~5%)[1] being lower than the aggregate of these previous studies (~40%),[2] but it is difficult to see what else is novel about this latest report.

Pryor and Veselis[3] offer important advice for the direction of future research and I would like to add two suggestions based on paradoxes in the observations. By paradox I mean responses that appear difficult to reconcile, given the stimulus. During the IFT, when we observe the patient moving only to verbal command but not to the obvious, ongoing, and greater stimulus of surgery, we properly regard that as surprising enough to develop sophisticated theories of dysanesthesia,[4,5] connected consciousness,[1] or cognitive unbinding.[6] Yet, when a patient during IFT fails to move to verbal command, but makes other spontaneous movements that appear purposeless, we dismiss these movements as reflex or light anesthesia. We do not seem equally surprised that a patient light enough to move will not also respond to command. Perhaps it is time to study also this second apparent paradox in more detail, especially if brain imaging coupled with IFT is a way forward, as Pryor and Veselis suggest.[3]

A much more important paradox is why the finding cannot be reproduced in the nonparalyzed (*i.e.*, patients who have received no neuromuscular blockade). I have already reported on the impossibility of eliciting a positive IFT response to verbal command during surgery in these circumstances.[7] Even when patients retain the ability to move spontaneously to stimuli, they fail to respond to verbal command if unparalyzed, even when they have received the same anesthetic doses and are at similar bispectral index levels as those reported in previous studies. Why this paradox? Why do things change when they are (save the isolated forearm) paralyzed? This distinguished and experienced team has the infrastructure now to explore this paradox more robustly than I previously reported. So, in good spirit I challenge Sanders *et al.*[1] to harness their international collaboration and report a single case of positive IFT in an apparently suitably anesthetized but unparalyzed patient, anywhere in the world. Or, if they are unable to do so, to explain why this is impossible and how this paradox fits into existing theories of a positive IFT response.

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This letter was sent to the authors of the original article referenced above, who declined to respond.—Evan D. Kharasch, M.D., Ph.D., Editor-in-Chief

Competing Interests

The author declares no competing interests.

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Current Status of Neuromuscular Reversal and Monitoring: Posttetanic Neuromonitoring and Other Considerations

To the Editor:

The recent comprehensive review article by Drs. Brull and Kopman[1] outlines the challenges and opportunities of the current status of neuromuscular reversal and monitoring. Their superlative and informative review is clearly destined to be a go-to reference on the subject. Importantly, it should serve as a rallying point for advancing future neuromuscular blockade (NMB) and function monitoring.

Several aspects of this article do warrant additional comment, however. First, the article deals with many important concepts in NMB monitoring and reversal, including not only perioperative considerations, but issues pertinent to the intensive care unit (ICU) where residual neuromuscular blockade, and associated patient awareness, has occasionally been reported.[2] Given that the article will rightly take its place as a definitive article on the subject, and as an advocate for postpublication peer-review, I was curious as to why