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In Reply:

We wish to thank Drs. Wicker and Bronheim for their interest in our recent publication[1] and welcome the opportunity to address their concerns. They question whether the impact of early initiation of β-blocker may have confounded our analysis. This is entirely appropriate because it is possible that metoprolol is preferentially used in acute administration, a population that has been shown to be associated with increased cardiovascular outcomes.

First, we would point out that our recent article was not simply arrived at through a data-mining process but carried out to investigate a specific hypothesis: β-receptor selectivity increased stroke rates. Our hypothesis was firmly based on the physiologic changes that we had observed in several previous animal studies.[2–4] These experimental investigations, started in 2005, were on the basis of several signals that we had observed in both animal models of stroke[5] and a meta-analysis of noncardiac surgical patients.[6] Thus, with publication of our recent article,[1] there are now both physiologic rationale and human data supporting the *THESIS* that β selectivity is one of the several possible mechanisms mediating the increase in stroke rates with β receptor antagonists. It is also irrefutable that perioperative β-receptor antagonism is a major patient safety issue.

Although we think that the issue of timing is an important component of β-blocker safety, we do not believe that it is the primary reason behind the increased incidence in β-blocker–mediated perioperative stroke. The issue of timing has been addressed now in at least five different articles, all using separate databases, and varied outcome measures, outcomes that are not equivalent. The first report, Flu *et al.*[7] used data from Erasmus Medical Centre. This group and its data resources are currently the object of intense scrutiny. In this article, the only outcome that was different at 30 days was an increased rate of detectable troponin T.* Ellenberger *et al.*[8] showed a difference in number of patients with detectable troponin I. Neither of these studies used the universal definition or screened for myocardial infarction. In addition, neither report show a difference in 30-day mortality rates. More recently, London *et al.*,[9] using the Veteran Affairs Surgical database, could not show a difference in mortality based on the initiation within the 7 days compared with those initiated within 30 days of surgery (etable 15). Wijeysundera *et al.* have shown that early *versus* late initiation of β-blockers is associated with a 50% risk-adjusted increase in mortality. Neither myocardial infarction nor stroke rate (using International Statistical Classification of Diseases and Related Health Problems 10 coding) was shown to be different based on the timing of drug.[10] Importantly, this analysis, using a large administrative database in more than 47,000 Medicare patients, found little difference in the proportion of patients initiating metoprolol or bisoprolol early *versus* those who were chronically β-blocked (table 2 in reference 1).[1] Thus, our data do not support the idea that metoprolol is preferentially the drug used clinically in acutely starting perioperative β-blockers. In addition, the cumulative data, in these five reports, do not support the notion that timing is important to postoperative stroke.

Third, we also agree that a discussion relating to the dosage of β-blockers is relevant. However, Drs. Wicker and Bronheim are mistaken, the dosages of the three major β-blockers were presented (see line 1 of table 1 in reference 1).[1] The median outpatient dosages found in our population reflect the package insert instruction for use of these β-blockers as antihypertensive and antiangina medications. The variability in dose we present reflects what we consider to be the advantage of chronic dosing; that is, dose titration. Moreover, the doses in our study are identical to the outpatient dosages of metoprolol found in the Wallace study.[11] We would also point out that the higher the dose of a β-blocker the less likely it would be for the drug will maintain a relative β1 selectivity.

As we state in the original article, we agree entirely that this thesis should be subject to further investigation, preferably using a blinded randomized design. Our analysis was intended, and we think reconfirms the possibility that, the physiologic phenomena we demonstrated in animal models of stroke may be active in humans. We are actively seeking support for this proposed randomized trial and invite all interested parties to contact us to get involved in this important investigation.

* Table 2 in the referenced article suggests that stroke is also different; however, there were five strokes in the early group and two strokes in the late group, which displays a fragile result.

Competing Interests

The authors declare no competing interests.

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Thoracic Epidural Anesthesia in Abdominal Aortic Surgery: Use and Advantages

To the Editor:

We read with interest the prospective, randomized, controlled trial by Lindholm *et al.*[1] where they compare the troponin T release after elective major vascular surgery in two groups of patients: one group with fentanyl–sevoflurane anesthesia and the other with propofol–remifentanil anesthesia. These authors concluded that sevoflurane-based anesthesia did not reduce myocardial injury, evaluated by troponin T release, compared with total intravenous anesthesia, suggesting that volatile anesthesia is no more protective than total intravenous anesthesia in elective abdominal aortic surgery. In this study, authors indicate that epidural catheter was introduced at thoracic level T6–T10 and epidural analgesia was started after opening the aortic cross-clamp in the two groups of patients.

In our opinion, the use of thoracic epidural analgesia (TEA) in the two groups of patients included in this trial could be an important issue regarding the obtained results. It has been suggested that intraoperative combination of general and epidural anesthesia with continuing postoperative epidural analgesia could be beneficial in high-risk surgical patients undergoing major noncardiac surgery.[2] The effects of TEA are produced by the blockade of cardiac sympathetic efferent nerve fibers that have their origin in segments T1–T5.[3] Activation of these fibers results in the stimulation of α- and β-adrenergic receptors, leading to an increased inotropy, chronotropy, vasoconstriction of epicardial coronary arteries, and systemic vasoconstriction, increasing myocardial oxygen demand. Previous studies have shown that combination of TEA and general anesthesia decreases heart rate, myocardial contractility, and systemic vascular resistance, resulting in potential benefits such as an improved balance of myocardial oxygen supply demand and greater intraoperative hemodynamic stability in patients with coronary artery disease undergoing surgery.[3,4] TEA has been reported to improve the status of nonsurgical patients with unstable angina and myocardial ischemia,[5] but we must note that studies on cardiac surgery have failed to find significant differences in troponin levels after TEA although this difference could be explained by the varying etiology and pathophysiology of the perioperative ischemia during coronary artery bypass graft surgery.[6] To this way, Jackobsen *et al.*[7] found that thoracic epidural anesthesia patients had higher stroke volume index, higher cardiac index, higher venous pressures, and lower systemic vascular resistance index perioperatively and postoperatively in cardiac surgical patients. Therefore, it seems logical to suggest that TEA could have decreased myocardial ischemia in patients included in the two groups of this intersesting study and this may have biased the results of this trial. We wonder that what would had happened to the results whether thoracic epidural anesthesia had not been added to the patients included in the two groups of this trial.

Competing Interests

The authors declare no competing interests.

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