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In Reply:

The authors wish to thank Dr. Derakhshan for his detailed letter in response to our review,[1] and for reminding the readers that the phenomenology of herniation is complex and may vary between individuals. In his letter, he calls attention to the first descriptions by Kernohan of the falsely localizing hemiparesis; in several cases of patients with supratentorial intracranial lesions and mass effect, the neurologic impairment was found ipsilateral to the side of hemispheric injury rather than the usual contralateral location. This was thought to be due to descent of the ipsilateral uncus of the temporal lobe pushing the brainstem contralateral rather than downward, with a resulting notching of the crus cerebri against the contralateral cerebellar tentorium.[2,3] These findings were of greatest importance in the preimaging era when neurosurgeons needed to be persuaded by clinical findings alone as to which side of the skull to place a burr hole or larger craniotomy.[4]

Although the etiology of ipsilateral *versus* contralateral symptoms and whether the cause is vertical *versus* lateral displacement of brain tissue are still not fully elucidated,[2–5] it is important to note that these signs of neurologic impairment are in no way false and are generally harbingers of significant pathology. Our article attempts to provide the reader with an understanding of how to assess the risk of herniation in patients with differing types of intracranial pathology, and the impact of neuraxial anesthetics in these cases. It does not address the varied neurologic manifestations of brain herniation, which, itself, is the proper subject of a dedicated review.

Specifically, we would like to remind the reader against maneuvers that will acutely lower the cerebrospinal fluid pressure in the lumbar cistern of patients who already have imaging evidence of a shift of brain tissue into neighboring compartments. The laws of physics dictate that when a pressure gradient develops between two compartments, there will be a movement to equilibrate this difference. When this occurs rapidly across the foramen magnum and without ample and free-flowing intracranial cerebrospinal fluid in reserve, brain tissue will shift. This produces neurologic impairment which may progress to stupor or coma if untreated. However, many patients with intracranial lesions with favorable characteristics can safely receive neuraxial anesthetics, as is catalogued in the online supplementary material to our review.[1]

We thank Dr. Derakhshan for reinforcing the point that that not all patients with intracranial lesions will develop devastating neurologic complications from brain herniation, and hope that our article has empowered the reader to be a more thoughtful participant in the conversation about what anesthesia technique is best for individual patients.

Competing Interests

The authors declare no competing interests.

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Association of Intraoperative Hypotension with Postoperative Acute Kidney and Myocardial Injuries in Noncardiac Surgery Patients

To the Editor:

In an observational study including 33,330 noncardiac surgeries performed in 27,381 patients with detailed intraoperative blood pressures, Walsh *et al.*[1] showed that intraoperative mean arterial pressure less than 55 mmHg was associated

with the development of postoperative acute kidney and myocardial injuries. This study makes an important contribution to the effort to define risk factors for acute vital organ injury after surgery. Strengths of this study include the large sample of patients and adjust for most of the known risk factors that can affect acute kidney and myocardial injuries after surgery. Furthermore, the authors openly discuss the limitations of their work. However, in our view, there are several aspects of this study design that should be discussed and clarified.

First, the body mass index and ethnicity were not included in the basic demographic data of patients for analysis and adjustment. It has been shown that in the noncardiac surgery patients, body mass index is independently associated with risk for postoperative acute kidney injury (AKI).[2,3] Furthermore, obesity is an independent predictor of perioperative cardiac adverse events.[4] In a retrospective study including 975,825 patients undergoing colorectal surgery, Masoomi *et al.*[5] find that black race is associated with higher risk of postoperative AKI. Their trial design did also not include the detail about anesthesia techniques and intraoperative managements. Consequently, it is difficult to estimate the extent to which interventions by anesthesiologists might have influenced outcomes. A retrospective analysis including 9,171 patients undergoing joint-replacement operations shows that use of general anesthesia is independently associated with risk for postoperative AKI.[2] Besides the transfusion volume adjusted by this study, other intraoperative managements, such as total vasopressor dose administered, use of a vasopressor infusion, and diuretic administration, have been shown to be independent predictors of postoperative AKI.[3] In addition, intraoperative hypoxemia, tachycardia, and hypertension are associated independently with increased risk of myocardial injury after noncardiac surgery.[6,7] Thus, we cannot exclude the possibility that the above confounding factors would have contributed to final analysis of their results.

Second, this study assessed occurrence of acute kidney and myocardial injuries within 7 days after surgery. However, the authors did not mention specific measurement times of serum creatinine, troponin T, and creatinine kinase-MB after surgery. In addition, the study design did not include the detail about postoperative recovery and managements of patients. Thus, this study cannot provide enough evidence to support that all kidney and myocardial injuries occurred within 7 days after surgery are attributed to intraoperative hypotension. Actually, serum troponin appears at 30 min to 6 h after myocardial injury.[8] Although serum creatinine lags behind acute changes in renal function, but AKI (defined by a 50% or more increase in serum creatinine) by intraoperative causes can be often detected between 1 and 3 days after surgery.[9] For early detection of the potential kidney and myocardial injuries by intraoperative factors, we would suggest that the related serum biomarkers be measured as soon as possible after surgery, especially for patients who are at high risk of kidney and myocardial injuries. To prevent new kidney and myocardial injuries or avoid aggravation of existing organ injury by postoperative low perfusion, we emphasize that perioperative hemodynamic optimization of noncardiac surgery patients should be continued to the postoperative period, modifying prognosis of patients.

Finally, 506 patients (1.5%) died within 30 days of surgery in this study. The authors should provide the detailed reasons of all death cases through analyzing death certificates, medical records, and autopsy reports, as described in previous studies.[7,10] We would like to know how many of patients with postoperative AKI received kidney-replacement treatment, and how many of deaths are directly related to postoperative acute kidney and myocardial injuries. In addition, the authors should assess association between severity of postoperative acute vital organ and 30-day mortality. All these will help explore whether there is a causal relationship between postoperative acute vital organ injury and mortality or whether acute vital organ injury merely indicates a worse outcome.

Competing Interests

The authors declare no competing interests.

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In Reply:

Xue *et al.* point out that not all potential variables were considered in our analyses and suggest that body mass index and ethnicity may confound the association between hypotension and organ injury. Revised models that include these two variables demonstrate no important effect on the relationship between hypotension and our outcomes (table 1).

Xue *et al.* also wonder whether organ injury results from the hypotension or its treatment. As we discussed in our article, this certainly needs to be considered when interpreting our results.[1] However, including vasopressor use in our analyses is unlikely to be helpful. The issue of indication bias (*i.e.*, the severity of hypotension is correlated to the likelihood of receiving vasopressors and the dose of vasopressor received) is extremely difficult to resolve even with advance statistical techniques. Randomized, controlled trials to prevent hypotension are likely the only sufficiently robust method of determining whether a mean arterial pressure less than 55 mmHg is injurious. Importantly, our work informs the definition of hypotension for any such trial and thereby improves the likelihood treatment can be studied safely and with maximum likelihood of demonstrating a benefit.

Xue *et al.* also question the timing of creatinine and cardiac enzyme determinations in relation to the time of surgery. We defined the outcome as within 7 days of surgery, and our sensitivity analyses restricting the definition to within 3 days of surgery demonstrated no material differences. We agree that early detection of organ injury, particularly in the first 3 days after surgery, is a crucial first step in discovering effective treatments for perioperative events. The Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) study demonstrated that more than half of myocardial injuries would be missed without routine postoperative troponin monitoring during the initial 3 postoperative days.[2] Older studies suggest that more than 80% of acute kidney injury, which is usually clinically silent, also typically occurs in a similar time frame and this is corroborated by our study in which 82% of acute kidney injury occurred in the first 3 days after surgery.[3] Further researches to establish effective treatments after perioperative complications such as renal and cardiac injury are urgently needed.

Xue *et al.*'s final comment suggests that we need to determine the cause of death and its relatedness to organ injury. This information is not available in our dataset; furthermore, we do not believe that relatedness can be reliably determined or likely to be immediately helpful. Take for example the following hypothetical scenario. A patient suffers a silent intraoperative myocardial injury that results in postoperative delirium and fatigue and mild acute kidney injury. This results in immobility and ultimately in a venous thromboembolism. The ensuing chest pain is treated with narcotics which along with the some mild thrombotic event results in some pulmonary function compromise. This predisposes the patient to a hospital-acquired pneumonia which is ultimately fatal. Had any one of these factors been avoided, the patient may have survived. However, attributing the cause of death to any single complication of surgery ignores the contributions of the others. Because of the complicated nature of the causal pathways to postoperative death, we do not believe that it is appropriate to examine specific causes of death in analyses such as ours.

Competing Interests

The authors declare no competing interests.

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Table 1. Adjusted Odds Ratios for Clinical Outcomes with a Mean Arterial Pressure <55 mmHg Lasting >20 min Compared with 0 min

Outcome	Original Adjusted Odds Ratio	New Adjusted Odds Ratio	Relative Difference
Acute kidney injury	1.51 (1.24–1.84)	1.44 (1.16–1.80)	–4.6%
Myocardial injury	1.82 (1.31–2.55)	1.81 (1.25–2.62)	–0.5%
Cardiac complication	1.95 (1.46–2.60)	1.84 (1.32–2.56)	–5.6%
Death at 30 days	1.79 (1.21–2.65)	2.08 (1.34–3.24)	16%

Original model is adjusted for age, sex, comorbidities, type of surgery, emergency surgery status, estimated intraoperative blood loss, red cell transfusions, change in hemoglobin, and preoperative hemoglobin. The New model is adjusted for the original model plus ethnicity and body mass index.