

pressure undergoing abdominal surgery might be at relevant risk for renal hypoperfusion and kidney failure if a fixed MAP target of 65 mmHg was applied. The same holds true for cerebral hypoperfusion in a patient with elevated intracranial pressure.

Second, when setting a MAP target we must keep in mind that MAP is a function of blood flow (cardiac output) and vascular resistance. MAP values of 65 mmHg are not the same in (a) a surgical patient with distributive shock and hyperdynamic circulatory failure, (b) an emergency cardiac surgery patient undergoing off-pump coronary artery bypass surgery, or (c) a healthy young patient undergoing otolaryngologic surgery.

Third, some organ systems autoregulate their blood flow according to the metabolic demands and—within certain limits—maintain constant blood flow despite changes in perfusion pressure (autoregulation). In patients with arterial hypertension, the autoregulation curve (*x*-axis, perfusion pressure; *y*-axis, blood flow) is shifted to the right; this means that the lower limit of autoregulation at which blood flow almost completely depends on perfusion pressure is shifted to higher perfusion pressure (and thus MAP) values. In this context, Asfar *et al.*<sup>5</sup> demonstrated in a multicenter randomized trial evaluating low (65 to 70 mmHg) *versus* high (80 to 85 mmHg) MAP targets in patients with septic shock that patients with chronic hypertension required less renal replacement therapy in the high-pressure group compared with the low-pressure group.

Finally, there are very scarce data on the relationship between individual “normal” blood pressure (*e.g.*, from ambulatory 24-h blood pressure measurements) and perioperative blood pressure.<sup>6,7</sup> These data are needed to be able to provide individualized perioperative blood pressure management instead of a “one size fits all approach.”

From a physiologic point of view, MAP targets (and finally targets for perfusion pressure) can only be set individually considering outflow pressure of different organ systems, cardiac output, vascular resistance, and blood flow autoregulation in the context of chronic hypertension and other comorbidities. We should be very cautious with suggesting that “anesthesiologists can manage intraoperative blood pressure without reference to preoperative values.”<sup>1</sup> For the individual patient, database-derived rules applied to complex cardiovascular physiology can have deleterious effects.

### Competing Interests

Dr. Saugel collaborates with Pulsion Medical Systems SE (Feldkirchen, Germany) as a member of the medical advisory board and has received honoraria for lectures and refunds of travel expenses from Pulsion Medical Systems SE. He received institutional research grants, unrestricted research grants, and refunds of travel expenses from Tensys Medical, Inc. (San Diego, California). Dr. Saugel also received honoraria for lectures and refunds of travel expenses from CNSystems Medizintechnik AG (Graz, Austria) and research

support from Edwards Lifesciences (Irvine, California). Dr. Reuter collaborates with Pulsion Medical Systems SE as a member of the medical advisory board and received honoraria for lectures and refunds of travel expenses from Pulsion Medical Systems SE. Dr. Reuter also consulted for Masimo Corp. (Irvine, California). Mr. Reese declares no competing interests.

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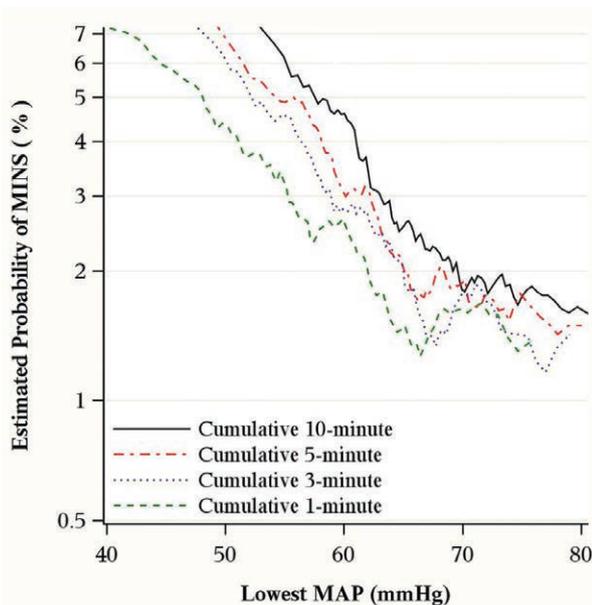
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### In Reply:

Nothing in our article<sup>1</sup> suggests that some patients cannot safely be maintained at intraoperative mean arterial pressures less than 65 mmHg. For example, some patients come to surgery with pressures at about that level and will presumably tolerate at least somewhat lower ones. Similarly, some patients may require higher pressures—presumably those with conditions that restrict organ perfusion. Importantly, the article to which Saugel and colleagues refer evaluated myocardial injury and acute kidney injury; we have previously reported associations between mean arterial

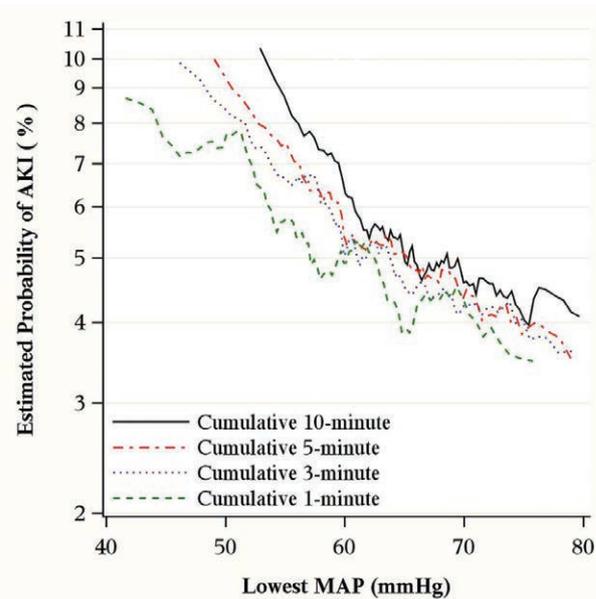


**Fig. 1.** Lowest mean arterial pressure (MAP) thresholds for myocardial injury after noncardiac surgery (MINS). Univariable relationship between MINS and absolute and relative lowest MAP thresholds. Estimated probability of MINS from the univariable moving-window with the width of 10% data. The figure shows there was a change point (*i.e.*, decreases steeply up and then flatten) around 65 mmHg. Reprinted with permission from *ANESTHESIOLOGY*.<sup>1</sup> Copyright 2017, American Society of Anesthesiologists, published by Wolters Kluwer.

pressure and 30-day all-cause mortality, and the thresholds are somewhat higher.<sup>2</sup> Harm thresholds for other organs might differ.

As Saugel and colleagues note, a strength of our analysis was inclusion of a large and diverse patient population. Furthermore, the acuity of Cleveland Clinic patients is high. The 57,300 patients we studied thus presumably included a fair number of patients who might be especially sensitive to hypotension. To the extent that some special-risk patients require higher blood pressures to perfuse key organs, we would expect that the curves relating mean arterial pressure and injury would gradually increase starting at relatively high pressures. In fact, they do not: the remarkable feature of figure 1 is that the risk of myocardial injury is essentially constant until mean arterial pressure reaches about 65 mmHg, and then increases steeply—on a logit scale no less. The curves for percentage change from baseline have a similar pattern. The relationship between mean arterial pressure and acute kidney injury looks almost the same, with risk being relatively constant until mean arterial pressure reaches 65 mmHg and then shooting up (fig. 2). Overall mortality decreases to a mean arterial pressure of 80 mmHg, and then increases sharply (fig. 3).<sup>2</sup> The threshold pressures triggering injury are thus far more notable for sharp corners than gradual increases.

Saugel and colleagues note that organ perfusion rather than blood pressure is the variable of interest, and suggest



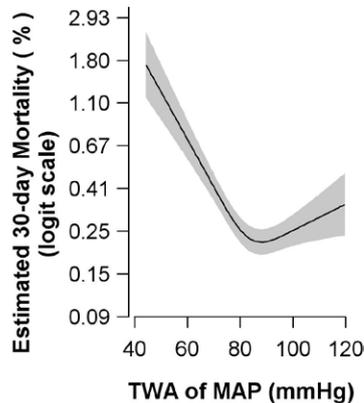
**Fig. 2.** Lowest mean arterial pressure (MAP) thresholds for acute kidney injury (AKI). Univariable relationship between AKI and absolute and relative lowest MAP thresholds. Estimated probability of AKI from the univariable moving-window with the width of 10% data. The figure shows there was a change point (*i.e.*, decreases steeply up and then flatten) around 65 mmHg. Reprinted with permission from *ANESTHESIOLOGY*.<sup>1</sup> Copyright 2017, American Society of Anesthesiologists, published by Wolters Kluwer.

that “pressure targets can only be set individually considering outflow pressure of different organ systems, cardiac output, vascular resistance, and blood flow autoregulation in the context of chronic hypertension and other comorbidities.” The trouble, of course, is that perfusion of sensitive organs including the gut, kidneys, and heart cannot be evaluated clinically. In real life, clinicians thus titrate hemodynamic management to blood pressure—which is exactly why evidence-based population thresholds are valuable.

Our point is not that any particular intraoperative mean arterial pressure is safe for everyone. Clinical care should be evidence based and include reasonable extrapolations from population-based studies that are appropriate for individual patients. In some cases, optimal care will target mean arterial pressures well above 65 mmHg; occasionally it might be lower. But absent information specific to individual patients, our results suggest that mean arterial pressure should rarely be allowed to decrease below 65 mmHg. This threshold is a population-based lower limit. Optimal pressure may well be greater.

### Competing Interests

Dr. Sessler is a consultant for Edwards Lifesciences, Irvine, California. The Department of OUTCOMES RESEARCH (Anesthesiology Institute, Cleveland Clinic, Cleveland, Ohio) is funded by Edwards and Sotera, San Diego, California. Dr. Salmasi declares no competing interests.



**Fig. 3.** Estimated mortality for time weighted average (TWA) of mean arterial pressure (MAP). The figure shows that estimated mortality decreased to MAP of 80 mmHg and then increased sharply at lower pressures. Reprinted with permission from *ANESTHESIOLOGY*.<sup>2</sup> Copyright 2015, American Society of Anesthesiologists, published by Wolters Kluwer.

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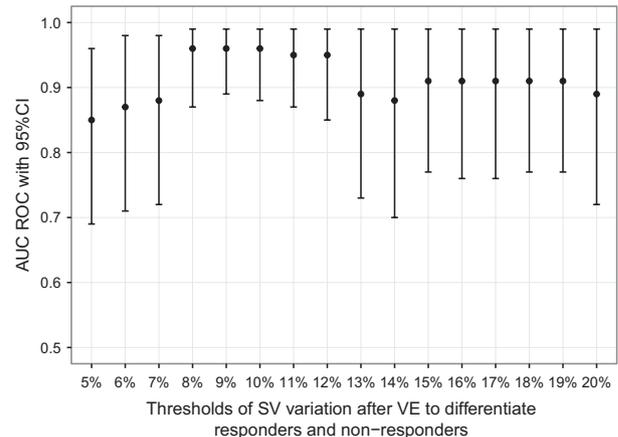
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## Diagnostic Accuracy Studies: The Methodologic Approach Matters!

*To the Editor:*

With regard to the recent *ANESTHESIOLOGY* article by Biaias *et al.*,<sup>1</sup> we acknowledge the overall quality of the report and consider the relevancy of the topic of underlying research. However, we have found several methodologic concerns that we would like to address.

First, Standards for Reporting Diagnostic Accuracy Studies have been developed as a list of items<sup>2,3</sup> that contribute to the completeness, transparency, and quality of reporting of diagnostic accuracy studies. We found that key items were lacking in the study from Biaias *et al.*<sup>1</sup> The study should have included a degree of blinding that describes whether clinical information and index test results were available to the assessors of the reference standard. A flow diagram is also required to evaluate the risk of selection bias. The reproducibility of the index test and the reference standard should also have been reported.



**Fig. 1.** Relationship between the areas under the receiver operating characteristic (AUC ROC) curves (points) with 95% CI (error bars) of the lung recruitment maneuver and the thresholds of stroke volume (SV) variation after volume expansion (VE) between 5% and 20% to differentiate between responders and nonresponders.

Moreover, the studies cited in the article that support the rationale of the reference standard and its cutoff do not to support an increase of 10% of stroke volume after volume expansion measured by proAQT (Pulsion Medical Systems, Germany) that defined fluid responders.

Second, the threshold to differentiate between responders and nonresponders should be chosen above and close to the least significant change (LSC) of the stroke volume measurement by their considered device. The LSC is defined as the minimum change that can be recognized as a significant change, not a measurement of random variation. Although LSC has been reported previously with transpulmonary thermodilution,<sup>4</sup> no data were reported using the proAQT system. Therefore, LSC for the proAQT system should have been calculated and reported by the authors. Because there was no threshold of stroke volume variation after a volume expansion to differentiate responders and nonresponders that can be supported by a solid clinical or physiologic background, another strategy would have been to provide data for several thresholds.<sup>5</sup> To address this last point, we collected data of the scatterplot given in figure 2 of the article by Biaias *et al.*<sup>1</sup> using the software ImageJ (<https://imagej.nih.gov/>; open source, National Institutes of Health, Bethesda, Maryland). This allowed us to recover raw data of variations of stroke volume after lung recruitment maneuver and after volume expansion and enabled us to perform subsequent analysis. We explored 16 thresholds between 5% and 20% using the R software and pROC package (<https://www.r-project.org/>; R-3.3.0; accessed May 3, 2016). We computed 95% CI using the bootstrap technique with thousand repetitions. In our point of view, the area under the receiver operating characteristic curve was overestimated with the chosen threshold of 10% (fig. 1). Because the threshold increases beyond the LSC of the measurement system, the area under the receiver