Carbon Dioxide, Blood Pressure, and Stroke: Comment

To the Editor:

In their article, Vlisides *et al.*[1] present retrospective associations between hypotension, hypocarbia, and hypercarbia and clinically apparent postoperative strokes, with 122 used in the analysis. (Covert strokes are nearly 10 times as common,[2] but were not considered.) They conclude that there are strong associations between mean arterial pressure (MAP) less than 55 mmHg and end-tidal pressure of carbon dioxide exceeding 45 mmHg. Both outcomes are biologically plausible and might guide clinical care, assuming that the relationships are proven causal in trials. However, some clarification about certain aspects of this report would be helpful, especially given previous analyses with 120 and 1,553 strokes that showed no association between hypotension and stroke.[3,4]

Case-control studies depend critically on correctly identifying case and control populations (avoiding selection bias). Curiously, patients with strokes in a limited population were matched to a much broader population from which there was a less rigorous attempt to identify strokes: "as stroke cases were initially screened and identified before control cases, when there were fewer cases overall in the Multicenter Perioperative Outcomes Group Database." This is a highly unorthodox approach that leaves the broader population contaminated by an unknown number of unidentified strokes. More seriously, the broader population might differ in important but unidentified ways from the population from which strokes were extracted. A confirmatory sensitivity analysis restricted to the patients from whom strokes were drawn would be reassuring.

The size of the population from which strokes were identified remains unclear, but apparently was about 600,000 patients. The incidence of overt postoperative stroke is reported to be roughly 0.4 to 0.6% in various noncardiac populations.[4,5] Vlisides *et al.* identified 126 strokes, corresponding to an incidence of 0.02% (assuming 600,000 patients) which is about a factor of 25 less than expected. Consequently, there is substantial potential for selection bias because the identified stroke patients may poorly represent the full population who suffer postoperative strokes. To the extent that the analysis was based on a possibly nonrepresentative sample, the presented associations may be inaccurate.

Table 4 indicates that only 8% of the observed strokes were detected on the day of surgery, and less than 60% within 3 days. There is no plausible biologic mechanism to explain why intraoperative hypotension or hypercarbia would provoke strokes days after surgery. Furthermore, half the strokes were embolic. Again, there is no obvious reason why intraoperative hypotension or hypercarbia would provoke embolic strokes. Residual confounding is the most likely explanation for such biologically implausible associations.

Specifically, there are many factors such as cardiovascular disease that provoke both hypotension and stroke, thereby generating confounded noncausal relationships between one and the other. Vlisides *et al.* naturally adjusted for observed confounding, but there is always unobserved confounding. Furthermore, even known confounders are often poorly characterized such as only being known dichotomously (*e.g.*, history of cardiovascular disease or not), which precludes sophisticated adjustment based on severity. As an example, the authors note that they had sparse data about β-blocker use—although acute β-blocker use is known to cause perioperative strokes.[6] Adequacy of confounding adjustment is key to any observational analysis. Observational analyses differ with respect to confounding risk; the risk in this case seems especially high.

There were no significant bivariable associations for amounts of hypotension below a range of thresholds (table 2). For example, area less than 60 mmHg was 15 mmHg-min in stroke patients and 14 mmHg-min in reference patients. The analogous areas were 35 and 33 mmHg-min for area less than 65 mmHg. Consequently, all reported significance is consequent to statistical adjustment. Normally univariable associations are strong, and then adjusted downward in multivariable analyses. It is unusual for statistical significance to result entirely from multivariable adjustments. A corollary is that modest differences in statistical modeling, especially confounder adjustment, might substantially alter the results rather than simply fine-tuning obviously meaningful differences in the underlying data.

The risks of hypotension (and presumably pressure of carbon dioxide) accrue at the extremes. A consequence is that the most interesting conclusions are often based on limited data. For example, in this case, investigators are looking for the "cross" between serious hypotension and strokes, although few patients will have both—especially with only 122 analyzable strokes. Along those lines, it would be helpful to provide a histogram showing the distribution of blood pressures as a guide to the range of reliable risk estimates.

Vlisides *et al.* present their associations in terms of "an approximately 10 to 17% increased relative risk of stroke per 10 units (mmHg-min)" with MAP 55 mmHg or less. In our experience, across many hospitals, MAPs less than 55

mmHg are uncommon and short-lived because they inevitably treated. It would be helpful to know what fraction of the patients had 10 min with MAP less than 55 mmHg, and how many of them experienced a stroke. The authors also note the adjusted odds of stroke are 2.0 for patients who sustained "10 minutes with a MAP of 50 mmHg and $ETCO_2$ of 28 mmHg." Again, it would be helpful to know what fraction of patients met this stringent criterion. Assuming the reported control incidence, along with a factor-of-2 risk increase in patients who experienced substantial and sustained hypotension and hypocapnia, the number needed to treat would be 5,000—which does not seem to support the authors' conclusion that these "risk factors can be modified to reduce the incidence of postoperative stroke."

Competing Interests

Dr. Sessler serves on advisory boards and has equity interests in Perceptive Medical (Newport Beach, California). He is a consultant for Edwards Lifesciences, a company that funds research conducted in the Department of Outcomes Research.

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Carbon Dioxide, Blood Pressure, and Stroke: Reply

In Reply:

We thank Dr. Sessler[1] for his interest in our article.[2] Stroke is a devastating complication for surgical patients and a challenging outcome to study. Dr. Sessler raises important points, and we welcome the opportunity to engage in constructive dialogue to raise clinical and scientific awareness of this important topic.

We think it is important to first describe for readers the context surrounding perioperative stroke research. First, the majority of postoperative strokes evade clinical detection (*i.e.*, covert stroke, as mentioned by Dr. Sessler).[3] As such, these strokes will not be recorded in routinely collected data (electronic health record, clinical registry, or billing databases) and, thus, they are unavailable for analysis. Second, intraoperative physiologic contributions to postoperative stroke remain incompletely understood. This is because cerebral perfusion is a complex process regulated by multiple physiologic variables (*e.g.*, blood pressure, metabolic demand, autoregulation, chemoregulation). This physiologic complexity might explain, in part, why intraoperative hypotension is inconsistently identified as a risk factor. We do point out, however, that other studies not discussed in Dr. Sessler's letter have described an association between intraoperative hypotension and stroke.[4,5] Third, commonly used modeling techniques (*e.g.*, logistic or binomial regression)[6,7] cannot disambiguate the relationship between physiologically related variables and stroke; more sophisticated approaches such as the seemingly unrelated regression technique used in the current analysis may be more appropriate.[8] Thus, all researchers in this field face a complex picture,

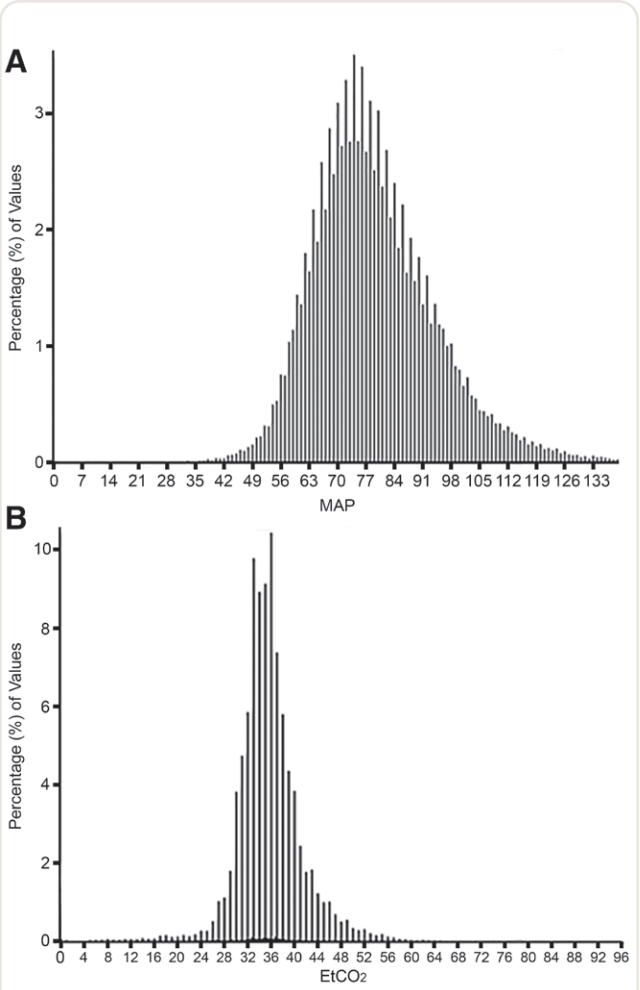

Fig. 1. Histogram of all available (*A*) mean arterial pressure (MAP) and (*B*) end-tidal carbon dioxide ($ETCO_2$) values throughout all stroke (n = 122) and control (n = 497) cases.

including physiologic knowledge gaps that might account for inconsistent findings across studies.

Our investigation was not designed to establish or approximate perioperative stroke incidence, which has been estimated at 0.1% in a broad noncardiac, nonneurologic, non-major-vascular surgical population.[9] Rather, our goal was to implement a rigorous case-control matching strategy for testing physiologic hypotheses. To achieve this goal, manual identification of stroke cases was first required, which necessitated a detailed chart review across multiple study sites. During this activity, additional surgical cases were added to the Multicenter Perioperative Outcomes Group database, since data are regularly uploaded from existing and newly contributing sites. As expected, the available denominator of control cases grew during the course of the study. Because incidence estimation was not a goal of the study, the exact number of eligible control cases available at the initial time of stroke case identification was not recorded. For these reasons, the true incidence of perioperative stroke is not calculable from this study, nor should it be inferred from the flow diagram. By extension, calculating a number needed to treat or harm from this study would not be possible, given the lack of an accurate control event rate. However, given the more than 300 million surgeries performed around the globe each year,[10] we believe that identifying modifiable risk factors for perioperative stroke that are under the control of anesthesia clinicians is worth pursuing.

Dr. Sessler raises a valid point regarding selection bias given the broader population available for control case matching. To mitigate population-based selection bias, stroke cases and controls were matched to the same hospital, eligible surgeries were restricted to the same time range, and models were adjusted for time (year). We also point out that this larger pool of control cases provided more opportunities for optimal patient matching. Approximately 25% of control cases from the broader population were hand-reviewed to confirm the absence of stroke; typically, control cases are not manually reviewed in these retrospective studies.[6,7] This would require labor-intensive efforts to evaluate large volumes of cases, which is impractical and can be prohibitive for large-scale database research. Nonetheless, the control cases in our study screened negative based on billing code data, and no strokes were found in the final control cases that were manually reviewed. Overall, the results only apply to recognized stroke cases, but, as was noted, this is a problem for all researchers in this field.

We do agree that confounding is a concern with all retrospective, observational studies, including previously published work that has not identified an association between intraoperative hypotension and stroke.[6,7] This is precisely why seemingly unrelated regression modeling was used to account for the two primary (and related) exposure variables of blood pressure and carbon dioxide. In addition to adjusting for relevant comorbidities, we matched and adjusted for total body blood volume and intraoperative hemorrhage, because anemia can increase stroke risk by challenging autoregulatory mechanisms.[11] These adjustments were made in addition to the Mahalanobis distance case-control matching process described in our prespecified analysis plan.[12] Thus, while residual confounding is certainly a possibility, we used mitigation strategies targeted to both comorbid and physiologic confounding where possible.

Histograms of all available mean arterial pressure (MAP) and end-tidal ($ETCO_2$) values are presented in figure 1. Of note, 72 of 122 (59%) stroke patients experienced MAPs less than 55 mmHg for at least 10 min, and 65 of 122 (53%) experienced at least 10 min with a MAP of 50 mmHg and $ETCO_2$ of 28 mmHg. In terms of statistical approach, given adequate sample size, multivariable analysis should not be

gated by nonsignificant bivariable associations. Furthermore, seemingly unrelated regression was not used in the bivariable analyses. The choice of seemingly unrelated regression was motivated by the physiologic relationship between blood pressure and carbon dioxide; this more rigorous and sensitive approach then revealed significant associations in the multivariable analysis.

We do agree that there were likely multiple stroke etiologies, particularly for strokes occurring several days after surgery. Of note, however, delayed stroke recognition is common in hospitalized patients,[13] and the temporal relationship to surgery remains unclear in many cases. Hypotension and dyscarbia may also contribute to embolic stroke by exacerbating cerebral hypoperfusion,[14] and these physiologic disturbances may persist postoperatively, where it is generally more challenging to monitor blood pressure and ventilation. As previously stated, many physiologic knowledge gaps remain with respect to perioperative stroke.

Last, it is important that we provide readers with the complete last sentence of our published article: "These physiologic perturbations may serve as risk factors that can be modified to reduce the incidence of postoperative stroke."[2] This sentence was modified and misquoted in Dr. Sessler's letter to the editor in a way that misrepresents the causal significance we ascribed to the findings. Indeed, hypotension and dyscarbia *may* serve as stroke risk factors, but confirmatory, prospective trials are ultimately required, as we originally stated in our article.

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Competing Interests

Dr. Vlisides receives support from Blue Cross Blue Shield of Michigan for research unrelated to this work. The other authors declare no competing interests.

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Tidal Volume, Positive End-expiratory Pressure, and Postoperative Hypoxemia: Comment

To the Editor:

We read the article by Turan *et al.*[1] with great interest and would like to congratulate the authors on conducting this large, important, factorial trial. The authors found that neither a "high" (8 cm H_2O) positive end-expiratory pressure (PEEP), nor a low (6 ml/kg) tidal volume strategy or a combination impacted postextubation hypoxemia or postoperative pulmonary complications. As such, the trial confirms findings of previous studies[2] that nonindividualized PEEP levels do not improve patient outcomes. It corroborates findings from a large study by Karalapillai *et al.*[3] that simply randomizing to high *versus* low tidal volumes does not seem to confer benefit for patients undergoing mechanical ventilation for general anesthesia.

We would like to add two important observations based on recent literature to the discussion of the study by Turan *et al.*[1] First, Neto *et al.*[4] and others have shown that it is not tidal volume *per se* that is the critical component of lung protection, but rather the resulting driving pressure, *i.e.,* the interaction of the applied tidal volume with the individual patient's respiratory system compliance, which is a more accurate determinant of perioperative lung injury and postoperative pulmonary complications. Our group recently corroborated these findings in a cohort of 197,474 surgical patients where higher intraoperative tidal volumes (greater than 8 ml/kg) were associated with increased risk of postoperative respiratory failure only in patients with a low compliance, and this effect was completely mediated by the resulting driving pressure.[5] In addition to lowering the applied tidal volume, modification of PEEP, which was the second factor in the trial by Turan *et al.,*[1] can reduce driving pressure through shifting tidal ventilation toward the high-compliance part of the pressure or volume loop. However, even in patients with "healthy" lungs undergoing general anesthesia, PEEP requirements are heterogeneous, and a "standard" PEEP is often inadequate.[6,7] To better understand the effect of the study intervention, it would be helpful if the driving pressure per group could be provided by Turan *et al.* to understand group differentiation regarding this crucial factor. Based on previous literature,[5,6] it may be hypothesized that the interventions in the present study[1] were effective when they resulted in a reduction in driving pressure, which might be tested in a *post hoc* analysis. In addition, it would be informative to analyze the effects of lowering tidal volume in patients with a lower respiratory system compliance.[6] It is highly likely that lung-protective ventilation in the operating room is effective only in patients with impaired compliance. A study that lumps those patients with a mass of healthy patients is bound to show a "negative" result.

Second, it is a classic phenomenon that physicians increase the respiratory rate when lowering tidal volume to maintain minute ventilation and end-tidal carbon dioxide.[8] This is relevant because it has been shown that increasing repetition of stress and strain might be equally damaging and therefore negates the effect of lowering tidal volume (and, subsequently, driving pressure).[9] Indeed, in the study by Turan *et al.*, the respiratory rate in the low tidal volume groups was more than 30% higher. Therefore, randomly assigning patients on the basis of factorial clusters with low *versus* high tidal volumes omitted the weight of impactful components like respiratory rate. Measures have been proposed to quantify this interaction of PEEP, tidal volume, and respiratory rate by estimating the intensity of ventilation. In a cohort of 230,767 surgical patients, we recently observed that an increased intraoperative ventilation intensity quantified by mechanical power was associated with higher odds of postoperative respiratory failure.[10] This was corroborated by a secondary analysis of the study by Karalapillai *et al.,*[3] who found that not tidal volume, but ventilation intensity, measured as mechanical power, incorporating the respiratory rate explained the variance in the risk of postoperative pulmonary outcomes.[11]

There is an impressive success in completing such a large trial in a 2-yr period. Based on the findings from Turan *et al.* and recent literature, we should move away from studies focusing on single, "standard" ventilator parameters, and we propose that the era of trials of mechanical ventilation in unselected patients in the operating room is over.