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Cerebral Amyloid and Cognition after Surgery: Reply

In Reply:

We thank Meng *et al.* for their letter to the editor regarding our study exploring cerebral β-amyloid deposition and cognition after cardiac surgery.[1] The authors have pointed out several important limitations of our study, which we have already acknowledged in the original publication.

Certainly, postoperative cognitive dysfunction has a complex pathophysiologic basis without a clear etiology in current understanding. Our study was designed to explore one potential mechanism contributing to cognitive decline after cardiac surgery, while adjusting for other well-established predictors. However, as we acknowledged, our sample size was limited and only designed to explore the relationship between global cortical amyloid deposition, using the novel positron emission tomography β-amyloid tracer ^{18}F-florbetapir, and cognitive change after cardiac surgery. We do not draw any definitive conclusions from our results, but rather present them to add to the discussion in the field of postoperative cognitive decline research and to potentially generate hypotheses and offer methodologies for future investigations. Limiting analyses to subjects with normal amyloid burden, as suggested by Meng *et al.*, also seems pointless, as the effect of abnormal amyloid deposition could not then be assessed.

With regard to the timepoints selected for imaging, we agree with Meng *et al.* that baseline imaging would have been optimal, but this was unfeasible given funding constraints for this explorative study. As clearly acknowledged in our publication, we were not assessing change in amyloid deposition from presurgery to postsurgery, given that amyloid deposition takes place over a significantly longer time period (see our reference to the article by Landau *et al.*[2]). Again, as we already noted in our discussion, despite the evidence in the literature for a longer time course for amyloid deposition, we cannot exclude the possibility of a change in amyloid deposition from preoperatively to 6 weeks postoperatively.

Finally, Meng *et al.* note additional limitations of our study, including the failure to address the association of preoperative amyloid status in patients with persistent (long-term postoperative cognitive decline), the impact of major surgery and anesthesia on amyloid burden, and the association of amyloid deposition in cerebral nuclei with cognitive impairment. To address the first two points: again, our study was explorative in nature and not powered to answer questions related to the influence of baseline amyloid burden on long-term postoperative cognitive decline or how surgery and anesthesia may alter cerebral amyloid burden. Comparing our cohort's 6-week and 1-yr postsurgical amyloid data did reveal an interesting suggestion of accelerated amyloid deposition compared to known longitudinal amyloid deposition rates in nonsurgical patients (from the Alzheimer Disease Neuroimaging Initiative cohort data[3]); however, once again, our sample size is underpowered to definitively answer these and similar questions, as we have already acknowledged. Finally, with respect to the histologic evaluation of amyloid deposition and its correlation with cognitive impairment, this is difficult to perform in living postsurgical patients, which is why we elected to use noninvasive positron emission tomography imaging with a well-studied amyloid tracer.

We look forward to future investigations to help answer these many important questions related to the potential role of cerebral amyloid deposition in cognitive impairment and postoperative cognitive decline.

Competing Interests

The authors declare no competing interests.

Rebecca Y. Klinger, M.D., M.S., Joseph P. Mathew, M.D., M.H.Sc., M.B.A. Duke University, Durham, North Carolina (R.Y.K.). kling004@mc.duke.edu

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Hypotension and Stroke in Cardiac Surgery: Comment

To the Editor:

We read with great interest the paper by Sun *et al.*[1] and support their aim to reduce the occurrence of cerebral injury after cardiac surgery, since this is a feared and devastating complication. Overt stroke rate has been reported to occur in 1 to 2% of cases after cardiac surgery, whereas the frequency of covert injury detected by diffusion weighted magnetic resonance imaging has been reported to be more than 50%.[2] In agreement with previous observations, Sun *et al.* report age, type of surgical procedure, preoperative hypertension, time on cardiopulmonary bypass (CPB), emergent operation, and occurrence of atrial fibrillation postoperatively as risk factors for stroke.[1] The main result from their study is the observation that hypotension during surgery was a significant risk factor of stroke, in this setting the only modifiable risk factor. However, in the multivariable analysis, the risk of a low mean arterial pressure (MAP) was only statistically significantly associated during CPB. This clearly emphasizes the importance of the intraoperative phase and suggests that a low blood pressure should be treated, although a potential benefit can only be assessed in interventional trials and not based on retrospective data. Regarding the choice of intervention, there are two principally different approaches: one approach is to increase MAP by using vasoconstrictors and thereby increase the organ perfusion pressure, and an alternative approach is to increase pump flow during CPB. To better understand the contribution from each of these approaches, the study lacks information on the actual pump flow delivered during CPB, which we believe is a major shortcoming. Can the authors provide data on average flow during CPB in patients with and without stroke? Are there any associations between duration of low flow and the occurrence of stroke?

Even though CPB has been around for more than 60 yr, there is still no consensus on limits for cerebral autoregulation during CPB. Hori *et al.* published a study in 2017 using a combination of integrated MAP and transcranial ultrasound demonstrating very variable limits for cerebral autoregulation between patients. In this respect, there was no safe lower MAP level, but the product of duration and magnitude of MAP below lower individual limits of cerebral autoregulation was associated with an increased risk of stroke.[3] This technique is not yet available on a commercial basis. However, what is worth noticing is the fact that whenever a patient was below the lower limit of cerebral autoregulation, they increased MAP by increasing flow on CPB, making the interpretation of a "sufficiently high" MAP more complex.

Cerebral monitoring has gained widespread interest, and one widely used technique is near infrared spectroscopy to monitor cerebral tissue oxygenation as a surrogate for cerebral blood flow. In a randomized study, patients were allocated either to a higher MAP target (70 to 80 mmHg) or a low MAP target (40 to 50 mmHg) during CPB with a fixed pump-flow of 2.7 (SD 0.1) l per min/m^2. The high target MAP was achieved with vasopressors, mainly norepinephrine infusion. The high-target group had significantly lower mean cerebral tissue oxygenation levels and a higher accumulated desaturation load less than 10% from baseline.[4] These data support a previous proof-of-concept study demonstrating that cerebral tissue oxygenation does not improve by a vasoconstrictor-induced increase in MAP; instead, vasoconstrictors led to a cerebral tissue oxygenation decrease. Only by increasing flow on CPB by 0.5 l · min · m^2 could cerebral tissue oxygenation be increased in parallel with an increase in MAP.[5] In conclusion, focusing exclusively on MAP as a single parameter without considering the concomitant flow delivery will only tell us half of the story.

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Competing Interests

The authors declare no competing interests.