Cerebral Amyloid and Cognition after Surgery: Comment

To the Editor:

We read with great interest the article by Klinger *et al.* regarding the cerebral β-amyloid deposition and neurocognitive performance after cardiac surgery.[1] We congratulate them for their excellent work in exploring the etiology and pathology of postoperative cognitive dysfunction. This study demonstrated no significant correlations between β-amyloid deposition and cognitive function at several time points after cardiac surgery. However, we want to address several points regarding this study.

First, we cannot draw any definite conclusions based on this study regarding the correlation between cerebral β-amyloid deposition and neurocognitive performance after cardiac surgery. Postoperative cognitive dysfunction is a multifactorial disease with complicated etiology and pathology. An appropriate subject sample size was needed for exploring one unproved factor influencing this disease. However, this study included only seven or two samples of abnormal β-amyloid deposition burden at 6 weeks or 1 yr after cardiac surgery, respectively. Analyzing postoperative cognitive dysfunction incidence in these samples could not provide a definite conclusion. In fact, it would make more sense to analyze postoperative cognitive dysfunction incidence in subjects with normal amyloid deposition because of their larger sample size (n = 33 or 10 at 6 weeks or 1 yr, respectively).

Second, neuroimaging was mostly performed 6 weeks after surgery in this study after considering the funding constraints and benefits of patients. However, we doubt whether the choice of this time point is accurate. We prefer that neuroimaging should have been performed before surgery as a baseline neuroimaging scan. On one hand, the authors scheduled the brain imaging after 6 weeks based on Landau *et al.*'s study,[2] which showed that amyloid burden was not expected to change significantly over a 6-week time. However, Landau's study evaluated the change in cortical ^{18}F-florbetapir over a 2-yr period in several candidate cerebral regions of interest in nonsurgical participants. It did not provide any evidence about the influence of surgery on cerebral amyloid change at 6 weeks or later. On the other hand, analyzing preoperative amyloid uptake ratio with postoperative cognitive dysfunction rate could be interpreted as a potential predictive factor for postoperative cognitive dysfunction if they were correlated with each other.

Third, a recent study suggests that β-amyloid turnover rates decreased dramatically with age, which increased the likelihood of amyloid deposition,[3] and the accumulation of β-amyloid in the brain was related to long-term cognitive impairment.[4] Paradoxically, postoperative cognitive dysfunction often occurs immediately after surgery, recovers over time, and rarely persists in the longer term.[5] Thus, the underlying relationship between them could be unforeseen. Three problems that were not emphasized in this study were rather important: the association of preoperative amyloid status of patients with long-term postoperative cognitive dysfunction, the impact of major surgery and anesthesia on amyloid burden, and the association of amyloid deposition in cerebral nuclei with cognitive impairment.

In summary, this study by Klinger *et al.*[1] was a great work employing amyloid imaging to investigate the association of evolving brain amyloid burden with postoperative cognitive dysfunction in patients undergoing cardiac surgery. Although it is not convincing enough because of the sample size and study design, it supports further investigations of etiologic mechanisms underlying postoperative cognitive dysfunction because the data on this field is scarce.

Research Support

Supported by the National Natural Science Foundation of China (Beijing, China; grant No. 81571048).

Competing Interests

The authors declare no competing interests.

Xiao-Yan Meng, M.D., Xiu-Ping Zhang, M.D., Hong-Qian Wang, M.D., Wei-Feng Yu, M.D., Ph.D. Eastern Hepatobiliary Surgery Hospital, the Second Military Medical University, and Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China (W.-F.Y.). ywf808@sohu.com.

DOI: 10.1097/ALN.0000000000002783

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(Accepted for publication April 1, 2019)

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

DOI: 10.1097/ALN.0000000000002784

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