PM, Mathew JP; Alzheimer's Disease Neuroimaging Initiative (ADNI) Study Group; Neurologic Outcomes Research Group (NORG): ^{18}F-florbetapir positron emission tomography-determined cerebral β-amyloid deposition and neurocognitive performance after cardiac surgery. Anesthesiology 2018; 128:728–44

2. Landau SM, Fero A, Baker SL, Koeppe R, Mintun M, Chen K, Reiman EM, Jagust WJ: Measurement of longitudinal β-amyloid change with 18F-florbetapir PET and standardized uptake value ratios. J Nucl Med 2015; 56:567–74
3. Jagust WJ, Landau SM, Koeppe RA, Reiman EM, Chen K, Mathis CA, Price JC, Foster NL, Wang AY: The Alzheimer's Disease Neuroimaging Initiative 2 PET Core: 2015. Alzheimers Dement 2015; 11:757–71

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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.

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References

1. Sun LY, Chung AM, Farkouh ME, van Diepen S, Weinberger J, Bourke M, Ruel M: Defining an intraoperative hypotension threshold in association with stroke in cardiac surgery. Anesthesiology 2018; 129:440–7
2. Sun X, Lindsay J, Monsein LH, Hill PC, Corso PJ: Silent brain injury after cardiac surgery: A review: Cognitive dysfunction and magnetic resonance imaging diffusion-weighted imaging findings. J Am Coll Cardiol 2012; 60:791–7
3. Hori D, Nomura Y, Ono M, Joshi B, Mandal K, Cameron D, Kocherginsky M, Hogue CW: Optimal blood pressure during cardiopulmonary bypass defined by cerebral autoregulation monitoring. J Thorac Cardiovasc Surg 2017; 154:1590–8.e2
4. Holmgaard F, Vedel AG, Lange T, Nilsson JC, Ravn HB: Impact of 2 distinct levels of mean arterial pressure on near-infrared spectroscopy during cardiac surgery: Secondary outcome from a randomized clinical trial. Anesth Analg 2019; 128:1081–8
5. Sperna Weiland NH, Brevoord D, Jöbsis DA, de Beaumont EM, Evers V, Preckel B, Hollmann MW, van Dieren S, de Mol BA, Immink RV: Cerebral oxygenation during changes in vascular resistance and flow in patients on cardiopulmonary bypass - A physiological proof of concept study. Anaesthesia 2017; 72:49–56

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Hypotension and Stroke in Cardiac Surgery: Comment

To the Editor:

I have long been concerned that anesthesiologists, at least occasionally, are unwittingly accepting intraoperative mean arterial pressures (MAPs) that may bring the central nervous system very close to the thresholds for ischemic injury.[1] The recent report by Sun *et al.* offered a caution about intraoperative hypotension and was therefore a result that I was inclined to welcome.[2] They reported, on the basis of a retrospective examination of a large electronic database, an association between MAPs less than 65 mmHg before, during, or after cardiopulmonary bypass (CPB) and the occurrence of postoperative stroke. However, in spite of my biases, I found myself with some uncertainties about the strength of their observations. I am concerned about unmeasured (or merely unreported) covariates. In part, the prompt for that concern was the nearly simultaneous publication of an investigation by Vedel *et al.* (about which Sun *et al.* inevitably had no opportunity to comment).[3] Vedel *et al.* assigned cardiac surgery patients to MAPs of either 40 to 50 or 70 to 80 mmHg on CPB. The investigation was randomized and prospective. The CPB parameters, which were reported in detail, were common to the two groups, with the exception of pressors and inotropes in the latter group. The primary endpoint was the volume of new diffusion weighted imaging lesions in the postoperative period. There were no differences between the groups in that endpoint or in several secondary endpoints. While relatively small numbers (98 and 99 patients per group) might be suspected of having resulted in type II statistical errors, every trend (diffusion weighted imaging lesion volume, stroke, cognitive dysfunction at the time of discharge, mortality) was in favor of the low pressure group.

I write to seek the opinions of Sun *et al.* as to possible explanations for the apparently contradictory results of the two studies. Their retrospective trial reports a stroke association with MAP less than 65 mmHg while the prospective, randomized trial reports no disadvantage to a MAP of 40 to 50 mmHg. That prompted my concern about covariates. I have several questions. First, why was there so much MAP variation, especially during CPB, within one cardiac surgery group? Were the lower MAPs in some patients a function of the perceived fragility of the aorta? The references cited by Sun *et al.* confirm the importance of aortic atherosclerosis as a conspicuous stroke risk factor.[4,5] Was an assessment of the severity of atherosclerotic disease of the aortic arch performed and recorded in their patients? Sun *et al.* provide little information about CPB technique and/or its variation among practitioners and over time. Were differences in the practices of individual surgeons, anesthesiologists, and perfusionists contributors to outcome differences among patients? More specifically, were the CPB techniques the same for all patients? As a reflection of the possible influence of variations in CPB technique, was the stroke rate constant over the 6-yr study period? I hope that this letter will present Sun *et al.* an opportunity to strengthen their work by providing information about potential covariates.

As a minor additional concern, to which I seek no response, I think that there are some references to the literature that are misrepresentations of the cited papers, or at a minimum will be misunderstood. An assertion offered in the Introduction is one such: "Optimal blood pressure thresholds for stroke