Relationship Between the Ambulatory Arterial Stiffness Index and the Lower Limit of Cerebral Autoregulation During Cardiac Surgery

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Background—Pulse pressure, the ambulatory arterial stiffness index (AASI), and the symmetric AASI are established predictors of adverse cardiovascular outcomes. However, little is known about their relationship to cerebral autoregulation. This study evaluated whether these markers of vascular properties relate to the lower limit of cerebral autoregulation (LLA).

Methods and Results—The LLA was determined during cardiac surgery with transcranial Doppler ultrasonography in 181 patients. All other variables were calculated from continuous intraoperative readings obtained before cardiopulmonary bypass. The LLA varied directly with the AASI ($\beta=3.12$ per 0.1 change in AASI, $P<0.001$) and to a lesser extent the symmetric AASI ($\beta=2.02$ per 0.1 change in symmetric AASI, $P=0.022$), while peripheral pulse pressure was not significantly related ($\beta=0.0, P=0.99$). Logistic regression revealed that the likelihood of LLA being $>65$ mm Hg increased by 50% (95% confidence interval, 11%-102%, $P=0.008$) for every 0.1 increase in the AASI. The AASI was able to predict a LLA above certain thresholds (area under the curve receiver operating characteristic for AASI predicting an LLA $>65$ mm Hg: 0.60; 95% confidence interval, 0.51%-0.68%, $P=0.043$). Incorporating additional variables improved the model’s predictive ability (area under the curve for AASI predicting a LLA $>65$ mm Hg: 0.75; 95% confidence interval, 0.68–0.82, $P=0.036$).

Conclusions—These data indicate that the LLA is related to the mechanical properties of the vasculature as represented by the AASI. The AASI can be used to predict LLA threshold levels during cardiac surgery. It is now possible to link elevations in the LLA with an increased AASI as determined from readily accessible intraoperative variables. (J Am Heart Assoc. 2018;7:e007816. DOI: 10.1161/JAHA.117.007816.)

Key Words: ambulatory arterial stiffness index • cardiac surgery • cerebral autoregulation • lower limit of cerebral autoregulation • pulse pressure

Preserved cerebral autoregulation and maintenance of systemic blood pressure within the cerebral autoregulatory range are key principles underlying the perioperative care of patients presenting for cardiac surgery and other procedures. In the perioperative setting, a substantial number of strokes result from tissue ischemia caused by inadequate cerebral perfusion throughout the perioperative period. Similarly, it has been shown that the incidence of adverse neurologic outcomes is increased when cerebral perfusion pressure is not maintained above the lower limit of cerebral autoregulation (LLA). The LLA is defined as the pressure below which blood flow in the brain becomes pressure dependent, and is often assumed to be a mean arterial blood pressure (MAP) of 50 mm Hg. However, previous studies by our group have questioned this assumption and demonstrated that during surgery and anesthesia, the range for the LLA varies considerably between 40 and 90 mm Hg. Moreover, despite the commonly held presumption of such a relationship, no association has been established between preoperative MAPs and the LLA. To date, there are no reliable and widely used predictors of the LLA that can be derived from routine perioperative data, nor are there any commercially available methods to determine this limit in the clinical setting.

Both hypertension and arterial stiffness are risk factors for stroke. Furthermore, systolic hypertension and arterial stiffness are highly interdependent, and both are associated with increased pulse pressure (PP). We have shown previously that increased preoperative brachial PP is an age-independent predictor of stroke development after cardiac surgery.
Clinical Perspective

What Is New?

- This study investigates the relationship between the lower limit of cerebral autoregulation and vascular properties as quantified separately by the intraoperative ambulatory arterial stiffness index (AASI), the symmetric AASI, and peripheral pulse pressure in patients undergoing cardiac surgery.
- The AASI predicts the lower limit of cerebral autoregulation with a greater ability than the symmetric AASI; pulse pressure has no predictive ability.
- The lower limit of cerebral autoregulation is related to the mechanical properties of the vasculature as represented by the AASI.

What Are the Clinical Implications?

- It is now possible to link elevations in the lower limit of cerebral autoregulation with an increased AASI as determined from readily accessible intraoperative variables.
- Determination of vascular properties might be used not only to predict postoperative outcomes, but also to change perioperative management strategies in regard to ensuring adequate cerebral perfusion.

However, while easy to determine clinically, is not a robust measure of vascular stiffness and, by definition, depends directly on blood pressure. To minimize some of these shortcomings, the ambulatory arterial stiffness index (AASI) was introduced in 2006 as a noninvasive marker of arterial stiffness that is less blood pressure dependent.9 The AASI is defined as 1 minus the average slope of diastolic on systolic blood pressure (BP) derived from multiple BP readings that are generally obtained over 24 hours in an ambulatory setting. Moreover, the AASI accounts for variability in the relationship between the systolic and diastolic BP.10 The hypothesis is that for a given increase in diastolic BP, an increase in systolic BP is disproportionally greater in stiff arteries than in compliant ones. Therefore, a higher AASI represents a stiffer artery. Though the AASI is generally used as a marker for arterial stiffness, it is only a surrogate marker. It is not highly specific of arterial stiffness but rather of central PP.11–13 Studies suggest that the close univariate association between the AASI and aortic pulse wave velocity does not necessarily imply a single mechanistic link.14 In fact, it has been suggested that the AASI is influenced by peripheral vascular resistance and heart rate.12 Moreover, a narrow range of diastolic BP values tends to flatten the regression slope and artificially increase the AASI.11 This fact has led to a modified version of the AASI that derives from a symmetric regression rather than a standard regression, the symmetric AASI (s-AASI).9,15 Despite its limitations, a number of studies have shown that the AASI is a reliable and independent predictor of adverse cardiovascular events in multiple populations and that it is more sensitive than PP for predicting cardiovascular events.10,16,17 However, the association between either the AASI or s-AASI and the pathophysiology of neurologic outcomes remains to be fully established.18 Our goal in this study was to determine the extent to which the AASI, s-AASI, or PP are associated with shifts in the LLA in patients undergoing cardiac surgery.

Methods

The data, analytic methods, and study materials will not be made available on request to other researchers for purposes of reproducing the results or replicating the procedure. This retrospective cohort study utilized data derived from patients enrolled in a previous prospective study that determined the limits of cerebral autoregulation during cardiac surgery with cardiopulmonary bypass (CPB).2,4,19 The protocol was approved by the Johns Hopkins Medicine Institutional Review Board (IRB00070516). Informed consent was obtained from all participants. Patients undergoing cardiac surgery with CPB were eligible for the study. We reviewed the electronic medical records between October 2009 and February 2016.

Measurements of AASI, s-AASI, and PP

We calculated the AASI, s-AASI, and peripheral PP from intraoperative continuous BP readings measured directly from the radial artery, all of which were obtained before the initiation of CPB, and recorded every 1 minute. The AASI was defined as 1 minus the regression slope of diastolic over systolic BP.9 If the computed AASI was outside the 0 to 1 range or $R^2$ of the fit was $<0.2$, the AASI was not retained for further analysis. For the s-AASI, we plotted systolic BP values against diastolic BP values and assessed a linear relationship between the 2 using a symmetric regression procedure that treats both variables in a symmetric way. The resulting symmetric slope was used for the calculation of the s-AASI.9 The s-AASI was defined as 1 minus the symmetric regression slope as suggested by Gavish et al.9 PP was defined as the mean of the difference between systolic and diastolic BP.

Patient Care

All patients received routine intraoperative care, including invasive continuous radial artery pressure monitoring. Midazolam, fentanyl, and isoflurane were used for anesthesia, and vecuronium was used for muscle relaxation. Nonpulsatile flow with a target flow rate of 2.0 to 2.4 L/min per m$^2$ was used.

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for CPB. Alpha-stat pH management was performed, and oxygenation and normocapnia were ensured by continuous inline arterial blood gas monitoring with hourly calibration. The attending anesthesiologist and surgeon, who were unaware of results from LLA determination, chose the target MAP empirically based on institutional standard of care.

Limits of Cerebral Autoregulation Measurements
For each patient, bilateral middle cerebral arteries (MCAs) were monitored by transcranial Doppler ultrasonography via 2- to 2.5-MHz transducers fitted on a headband (Doppler Box, DWL; Compumedics, Charlotte, NC). Cerebral blood flow (CBF) velocity was sampled during CPB with an analog-to-digital converter at 60 Hz and then processed with ICM+ software Version 6.1 (University of Cambridge, Cambridge, UK). The signal acquisition and analysis methods have been described previously. The mean velocity index was obtained as the moving Pearson correlation coefficient between MAP and CBF velocity. Mean velocity index values were placed in 5 mm Hg MAP bins. The LLA was defined as the MAP at which the mean velocity index incrementally increased from <0.4 to ≥0.4. If the mean velocity index was ≥0.4 for all MAPs, an impaired autoregulation pattern, the LLA was defined as the MAP at which mean velocity was the lowest. The LLA was measured separately for the left and right side of the head, and the higher value was chosen for the analysis.

Statistical Analysis
We first performed univariate linear and logistic regression analysis to assess the association between the LLA and perioperative variables, including the AASI, s-AASI, and PP. For logistic regression, the dependent variable was being a member of the population with a LLA above the median value of the LLA. Multivariate linear regression and logistic regression were then performed using a forward stepwise approach beginning with the AASI to assess the relationship between the LLA and its predictor variables. Variables from the univariate analysis that were not included in the final multivariate model were then incorporated into the model 1 at a time and the resulting model was compared with the reference multivariate model using a likelihood ratio test. The potential contribution of nonlinearity and interaction of model variables was assessed. A total sample size of 157 patients was required for the multiple linear regression to satisfy a significance level of 0.05 with power of 0.80, assuming an effect size $f^2$ of 0.15 (Cohen’s standard medium effect size), and the number of predictors of 20 (G-power software 3.1.9.2; Faul et al, University of Kiel, Kiel, Germany).

The predicted LLA was calculated by using the variable from the multivariate model. Receiver-operating characteristic curves were created to determine values of the predicted LLA and the AASI or s-AASI. Outcomes of statistical tests were considered significant at $P<0.05$, and all tests were 2-sided. Analysis was performed with Stata (Version 14, Stata Corp, College Station, TX) and Mathematica (Version 11.0, Wolfram Research Inc, Champaign, IL).

Results
LLA estimates were available from 191 subjects. However, extraction of the AASI was not possible in 10 subjects using the criteria given above. Hence, a total of 181 patients were included in the analysis. The patients’ demographics and pre- and intraoperative characteristics are shown in Table 1. Of the 181 patients included, 101 (55.8%) were 70 years of age or older and 27 (14.9%) were 80 years of age or older. The transcranial Doppler-based LLA ranged from 35 mm Hg to 95 mm Hg, with a mean (SD) of 64 (13) mm Hg (Figures 1A and 1C). The LLA was >50 mm Hg in 150 (82.9%) patients. The mean (SD) of the AASI was 0.57 (0.11) and that of the s-AASI was 0.49 (0.10). The duration of intraoperative BP readings and BP variation for the determination of the s-AASI are shown in Table 2.

Both the AASI and the s-AASI were related to the LLA, with the linear fit for the AASI being superior to the one for the s-AASI ($\beta$=3.12 mm Hg, $P<0.001$ versus $\beta$=2.02 mm Hg, $P<0.022$ for each 0.1 increase; Figure 1A). Each 0.1 increment in the AASI led to a 50% increase in the odds of the LLA being above the median LLA of 65 mm Hg ($P=0.008$, Table 3). The odds of the LLA being above the median LLA of 65 mm Hg increased by only 26% for each 0.1 increment of the s-AASI, but this relationship was not significant ($P=0.11$, Table 3). As expected, the s-AASI was almost always lower than the AASI (Figure 1B). PP was not significantly related to the LLA, as depicted in Figure 1C ($\beta$=0.00, $P>0.99$).

Details on the univariate relationship between the LLA and perioperative variables are given in Table 3. The LLA was significantly associated with the AASI, parameters related to body weight, preoperative estimated glomerular filtration rate, and mean MAP throughout CPB. Neither intraoperative PP nor MAP was significantly associated with the LLA (Table 3).

The multivariate model to determine independent predictors of the LLA is presented in Table 4 ($R^2$=0.31). The AASI, mean MAP during CPB, and lowest body temperature were significantly associated with the LLA ($\beta$=27.6, $P<0.001$; $\beta$=6.2, $P<0.001$; $\beta$=9.5, $P=0.002$, respectively). Body mass index and preoperative creatinine reached statistical significance ($P=0.01$ and 0.046, respectively). Preoperative PP did not improve the model for LLA ($P=0.44$). Age, sex, height, weight, prior smoking history, prior cerebrovascular accident,
Table 1. Demographics and Perioperative Characteristics

| Variable                  | Results (n=181) |
|---------------------------|-----------------|
| **Preoperative data**     |                 |
| Age, y                    | 71±8 (58–84)    |
| Male, n (%)               | 123 (68.0)      |
| PP, mm Hg                 | 65±16 (41–98)   |
| MAP, mm Hg                | 94±13 (74–115)  |
| HR, bpm                   | 65±15 (49–87)   |
| Height, cm                | 171±10 (155–186) |
| Weight, kg                | 87±18 (60–120)  |
| BSA, m²                   | 2.01±0.24 (1.62–2.42) |
| BMI, kg/m²                | 29.6±6.1 (21.4–40.4) |
| Creatinine, mg/dL         | 1.06±0.33 (0.70–1.60) |
| Estimated GFR, mL/min per 1.73 m² | 72±22 (41–103) |
| Hb, g/dL                  | 12.4±2.1 (8.8–15.6) |
| LVEF, %                   | 52±12 (25–65)   |
| **Medical history**       |                 |
| CVA, n (%)                | 19 (10.5)       |
| COPD, n (%)               | 26 (14.4)       |
| Smoking history, n (%)    | 103 (56.9)      |
| PVD, n (%)                | 33 (18.2)       |
| Hypertension, n (%)       | 161 (89.0)      |
| CHF, n (%)                | 28 (15.5)       |
| Preoperative afib, n (%)  | 25 (13.8)       |
| Diabetes mellitus, n (%)  | 86 (47.5)       |
| Previous cardiac surgery, n (%) | 15 (8.3) |
| **Type of surgery**       |                 |
| CABG, n (%)               | 97 (53.6)       |
| CABG-valve, n (%)         | 78 (43.1)       |
| Valve, n (%)              | 6 (3.3)         |
| **Intraoperative data**   |                 |
| AASI                       | 0.57±0.11 (0.39–0.75) |
| s-AASI                     | 0.49±0.10 (0.29–0.64) |
| PP (pre-bypass mean), mm Hg | 60±10 (46–77)  |
| MAP (pre-bypass mean), mm Hg | 79±8 (67–94)   |
| HR (pre-bypass mean), bpm  | 65±15 (49–87)  |
| CPB duration, min         | 110±47 (51–176) |
| Aortic cross-clamp duration, min | 69±29 (32–118) |
| MAP during CPB, mm Hg     | 75±8 (64–87)    |
| r SO₂ mean, NIRS, %*      | 54±9 (39–67)    |
| Lowest body temperature, °C | 31.4±2.8 (27.0–34.7) |
| Highest body temperature, °C | 36.4±0.9 (35.0–37.6) |
| LLA, mm Hg, n (%)         | 64±13 (45–85)   |

The results are expressed as mean±SD (95% confidence interval) or as n (%). AASI indicates ambulatory arterial stiffness index; afib, atrial fibrillation; BMI, body mass index; bpm, beats per minute; BSA, body surface area; CABG, coronary artery bypass grafting; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; CVA, cerebrovascular accident; GFR, glomerular filtration rate; Hb, hemoglobin; HR, heart rate; LLA, lower limit of cerebral autoregulation; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; NIRS, near-infrared spectroscopy; PP, pulse pressure; PVD, peripheral vascular disease; rSO₂, regional oxygen saturation; s-AASI, symmetric ambulatory arterial stiffness index. *Average of left- and right-sided mean rSO₂.

In this study of patients undergoing cardiac surgery, we investigated the relationship between the LLA and previously reported predictors of cardiovascular outcomes as quantified separately by the AASI, the s-AASI, and PP. The LLA varied...
directly with the AASI and to a lesser extent the s-AASI, but neither PP nor MAP showed an association. These data indicate that the LLA is related to the mechanical properties of the vasculature as best represented by the AASI. Furthermore, the AASI can be used to predict threshold levels for the LLA during cardiac surgery. It is now possible to link elevations in the LLA with an increased AASI as determined from readily accessible intraoperative variables.

Cerebral arterioles match CBF and cerebral metabolic requirements by vasodilation and constriction despite changes in cerebral perfusion pressure. This action is referred to as cerebral pressure autoregulation. Cerebral autoregulation relies on robust cerebrovascular reactivity that leads to vasodilation when cerebral perfusion pressure decreases and vasoconstriction when it increases. The cerebrovascular endothelium, perivascular nerves, and

Figure 1. Continued

Table 2. Intraoperative Continuous Pre-CPB BP Measurement for the Determination of the AASI

| Variable            | Median | IQR       |
|---------------------|--------|-----------|
| Maximum SBP, mm Hg  | 176    | 160–200   |
| Median SBP, mm Hg   | 114    | 108–122   |
| Minimum SBP, mm Hg  | 74     | 66–80     |
| Range of SBP, mm Hg | 100    | 86–124    |
| Maximum DBP, mm Hg  | 92     | 80–104    |
| Median DBP, mm Hg   | 56     | 50–60     |
| Minimum DBP, mm Hg  | 38     | 32–42     |
| Range of DBP, mm Hg | 52     | 44–64     |
| Duration of BP measurement, min | 140 | 114–168 |

AASI indicates ambulatory arterial stiffness index; BP indicates blood pressure; CPB, cardiopulmonary bypass; DBP, diastolic blood pressure; IQR, interquartile range; SBP, systolic blood pressure.
vascular smooth muscle cells play distinct roles in the regulation of CBF.\textsuperscript{25} It is well known that an acute drop in arterial BP induces a decrease in cerebral vascular tone,\textsuperscript{27} whereas increased cerebral flow velocity induces cerebral vasoconstriction.\textsuperscript{25} From a physiological point of view, the LLA represents the point of maximal cerebrovascular dilation.

### Table 3. Univariate Analysis of the Relationship Between the LLA and Perioperative Variables for Both Linear (β) and Logistic (OR for LLA >65 mm Hg) Regression

| Variable                  | β (95% CI)       | P Value | OR (95% CI)       | P Value |
|---------------------------|------------------|---------|-------------------|---------|
| **Preoperative data**     |                  |         |                   |         |
| Age                       | −0.04 (−0.20 to 0.21) | 0.75    | 1.00 (0.96–1.04)  | 0.95    |
| Male                      | 0.14 (−4.07 to 4.34) | 0.95    | 0.69 (0.36–1.29)  | 0.24    |
| PP                        | 0.00 (−0.08 to 0.23) | <0.99   | 1.00 (0.98–1.02)  | 0.92    |
| MAP                       | 0.07 (−0.08 to 0.23) | 0.35    | 1.01 (0.98–1.03)  | 0.49    |
| HR                        | −0.06 (−0.19 to 0.08) | 0.40    | 0.98 (0.96–1.00)  | 0.11    |
| Height                    | 0.08 (−0.11 to 0.27) | 0.42    | 1.00 (0.97–1.03)  | 0.92    |
| Weight                    | −0.15 (−0.26 to −0.05) | 0.005*  | 0.98 (0.97–1.00)  | 0.041*  |
| BSA                       | −10.7 (−18.7 to −2.7) | 0.009*  | 0.26 (0.072–0.93) | 0.038*  |
| BMI                       | −0.59 (−0.90 to −0.27) | <0.001* | 0.94 (0.89–0.99)  | 0.020*  |
| Prior CVA                 | 1.5 (−4.9 to 7.9)   | 0.48    | 1.09 (0.41–2.84)  | 0.87    |
| Hypertension              | 3.3 (−3.0 to 9.5)   | 0.31    | 1.29 (0.49–3.41)  | 0.61    |
| PVD                       | 1.8 (−3.1 to 7.1)   | 0.77    | 1.29 (0.60–2.77)  | 0.51    |
| Diabetes mellitus         | 0.1 (−3.9 to 4.0)   | 0.97    | 1.03 (0.57–1.87)  | 0.92    |
| CHF                       | −1.7 (−7.2 to 3.7)  | 0.53    | 0.79 (0.34–1.83)  | 0.59    |
| COPD                      | 0.3 (−5.3 to 5.9)   | 0.91    | 1.10 (0.47–2.55)  | 0.82    |
| Smoking history           | −0.3 (−4.2 to 3.7)  | 0.90    | 0.95 (0.52–1.73)  | 0.87    |
| Afib                      | 0.03 (−5.4 to 6.0)  | 0.92    | 1.19 (0.51–2.79)  | 0.69    |
| Creatinine                | −4.4 (−10.4 to 1.6) | 0.15    | 0.68 (0.26–1.75)  | 0.43    |
| GFR                       | 0.098 (0.009 to 0.188) | 0.032*  | 1.01 (0.99, 1.02) | 0.28    |
| Hb                        | −0.01 (−0.96 to 0.94) | 0.98    | 1.02 (0.88–1.18)  | 0.78    |
| LVEF                      | −0.02 (−0.18 to 0.14) | 0.82    | 1.00 (0.98–1.03)  | 0.77    |
| **Intraoperative data**   |                  |         |                   |         |
| AASI                      | 3.12 (1.43–4.82)\textsuperscript{T} | <0.001* | 1.50 (1.11–2.02)\textsuperscript{T} | 0.008*  |
| s-AASI                    | 2.02 (2.90–3.74)\textsuperscript{T} | 0.022*  | 1.26 (0.95–1.67)\textsuperscript{T} | 0.11    |
| Pre-bypass PP, mm Hg      | 0.09 (−0.10 to 0.29) | 0.35    | 1.01 (0.98–1.04)  | 0.52    |
| Pre-bypass MAP, mm Hg     | −0.16 (−0.40 to 0.08) | 0.19    | 0.99 (0.95–1.02)  | 0.42    |
| Pre-bypass HR, bpm        | −0.06 (−0.19 to 0.08) | 0.39    | 0.98 (0.96–1.00)  | 0.11    |
| CPB duration              | −0.05 (−0.09 to −0.00) | 0.033*  | 0.99 (0.99–1.00)  | 0.12    |
| Aortic cross-clamp duration | −0.06 (−0.12 to 0.01) | 0.10    | 0.99 (0.98–1.01)  | 0.32    |
| MAP during CPB            | 0.73 (0.50–0.97)   | <0.001* | 1.12 (1.06–1.17)  | <0.001* |
| rSO\textsubscript{2} mean | 0.01 (−0.20 to 0.22) | 0.93    | 1.01 (0.98–1.04)  | 0.54    |
| Lowest body temperature   | 0.65 (−0.06 to 1.34) | 0.07    | 1.09 (0.98–1.22)  | 0.12    |
| Highest body temperature  | −0.22 (−2.4 to 1.96) | 0.84    | 0.90 (0.65–1.25)  | 0.53    |

AASI indicates ambulatory arterial stiffness index; Afib, atrial fibrillation; BMI, body mass index; bpm, beats per minute; BSA, body surface area; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; CVA, cerebrovascular accident; GFR, glomerular filtration rate; Hb, hemoglobin; HR, heart rate; LLA, lower limit of cerebral autoregulation; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; OR, odds ratio; PP, pulse pressure; PVD, peripheral vascular disease; rSO\textsubscript{2}, regional oxygen saturation; s-AASI, symmetric ambulatory arterial stiffness index.

\textsuperscript{T}For both linear and logistic regression, the AASI and s-AASI were multiplied by 10 so that β and the OR represent the increase per 0.1 U of either.

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It has been reported that a direct relationship exists between the AASI and central PP. A close relationship between aortic vascular stiffness, pressure pulsatility, cerebral microvascular function, and brain damage has also been suggested. Moreover, microvascular structure and function are altered in the presence of excessive pressure pulsatility resulting from increased large artery stiffness. Therefore, when the heart contracts, the forward pressure

### Table 4. Multivariate Linear and Logistic Regression to Determine Independent Predictors of the LLA*

| Variable                        | \( \beta \) (95% CI) | \( P \) Value | OR (95% CI) | \( P \) Value |
|---------------------------------|----------------------|---------------|-------------|---------------|
| Intercept                       | -23.0 (-52.7 to 6.6) | 0.127         | 0.000 (0.000-0.00) | <0.001†      |
| AASI                            | 2.76 (1.26-4.26)†    | <0.001†       | 1.52 (1.09-2.12) | 0.013‡       |
| MAP (mean during bypass)        | 0.62 (0.40-0.85)     | <0.001† 〈<0.001 | 1.12 (1.06-1.18) | <0.001† 〈<0.001 |
| Lowest body temperature         | 0.95 (0.35-1.56)     | 0.002‡ (0.004) | 1.15 (1.02-1.31) | 0.022‡ (0.019) |
| BMI                             | -0.38 (-0.66 to -0.09)| 0.010‡ (0.010) | 0.18         |               |
| Preoperative creatinine         | 0.079 (0.001-0.156)  | 0.046‡ (0.042) | 0.42         |               |
| Age                             |                      | 0.20         |              |               |
| Male                            |                      | 0.56         |              |               |
| Preoperative PP                 |                      | 0.44         |              |               |
| Preoperative MAP                |                      | 0.49         |              |               |
| Preoperative HR                 |                      | 0.22         |              |               |
| Height                          |                      | 0.69         |              |               |
| Weight                          |                      | 0.56         |              |               |
| BSA                             |                      | 0.91         |              |               |
| Prior CVA                       |                      | 0.52         |              |               |
| Hypertension                    |                      | 0.53         |              |               |
| PVD                             |                      | 0.52         |              |               |
| Diabetes mellitus               |                      | 0.79         |              |               |
| CHF                             |                      | 0.91         |              |               |
| COPD                            |                      | 0.95         |              |               |
| Smoking history                 |                      | 0.25         |              |               |
| Preoperative afib               |                      | 0.53         |              |               |
| Preoperative Hb                 |                      | 0.08         |              |               |
| Preoperative LVEF               |                      | 0.72         |              |               |
| Pre-bypass PP                   |                      | 0.33         |              |               |
| Pre-bypass MAP                  |                      | 0.26         |              |               |
| Pre-bypass HR                   |                      | 0.20         |              |               |
| CPB duration                    |                      | 0.56         |              |               |
| Aortic cross-clamp duration     |                      | 0.50         |              |               |
| rSO2 mean                       |                      | 0.57         |              |               |
| Highest body temperature        |                      | 0.49         |              |               |

The logistic model evaluated whether the LLA was >65 mm Hg, its median value. AASI indicates ambulatory arterial stiffness index; afib, atrial fibrillation; BMI, body mass index; BSA, body surface area; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; CVA, cerebrovascular accident; Hb, hemoglobin; HR, heart rate; LLA, lower limit of cerebral autoregulation; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; OR, odds ratio; PP, pulse pressure; PVD, peripheral vascular disease; rSO2, regional oxygen saturation.

\*\( R^2=0.31, P<0.001. \)

\( ^† \) The 95% CI and \( P \) values for significant variables (\( \dagger \)) are given for the included variables for the multivariate model at the top. \( P \) values below these (in parentheses) indicate the significance of the model generated by the addition of the given variable without including any of those below using a likelihood ratio test. The \( P \) values for the variables listed below those deemed to be significant indicate the significance of any improvement as indicated by a likelihood ratio test between the multivariate model and one that incorporates just the additional variable. For each of the variables found to be significant in the multivariate model, the potential contribution of nonlinear terms was considered (not shown). Furthermore, the significance of interactions between the variables in the multivariate model was also considered. In no instance did the inclusion of nonlinearities or interactions contribute to the model.

\( ^‡ \) For both linear and logistic regression, the AASI was multiplied by 10 so that \( \beta \) and the OR represents the increase per 0.1 U of the AASI.
reactivity, both of which might directly influence the limit of cerebral autoregulation (LLA). Obata et al 31 reported that greater MCA pulsatility was independently associated with increased myogenic tone and impaired vasomotor reactivity, both of which might directly influence the limit of cerebral autoregulation and increase susceptibility to focal ischemia.31 Given that the amount of blood flow is greater in compliant arteries with a low pressure pulsatility,34,35 the LLA should be lower in patients with a compliant vasculature than in those with one that is more stiff. It has been postulated before and commonly assumed that the LLA is elevated in patients with hypertension.36 Although excessive pulsatility is associated with hypertension,28,37 our results indicate that the AASI is a more sensitive marker of increased LLA than peripheral PP or MAP.

Our findings are consistent with those of Joshi et al4 in that we observed no relationship between preoperative MAP and LLA. As with the previous study, we showed that LLA ranged from 35 mm Hg to 95 mm Hg in patients during cardiac surgery. In contrast to that study, however, we found relationships between the AASI and the LLA, and cerebral autoregulation. Although the s-AASI was significantly associated with the LLA, the relationship was not as strong as that between the AASI and LLA. Furthermore, the AASI appears to be a better predictor of the LLA than the s-AASI is. Our findings suggest that the LLA is dependent not only on the AASI but also on intraoperative vital signs such as MAP during CPB and the lowest body temperature. The latter relationships may be because of an epiphenomenon as both are chosen intraoperatively by the surgical team. Even though the surgical team was blinded to the LLA measurements, they could have chosen a higher MAP for patients on bypass who subjectively appeared to have an altered LLA, such as those who had hypertension that was difficult to control intraoperatively or those who appeared frail. Prior studies have shown that the duration and magnitude of BP below the LLA is associated with acute kidney injury38 and major morbidity and mortality2 after cardiac surgery. Those studies suggested that maintaining MAP within the range of cerebral autoregulation may improve postoperative outcomes. The measurement of AASI might be able to change perioperative management strategies as we predict BP targets based on the AASI to ensure that MAP remains above the LLA.

Finally, it has been reported that the AASI, the s-AASI, and PP are independent predictors of cardiovascular mortality after adjustment for other risk factors in various populations.18,39 Moreover, some studies compared the prognostic ability of AASI with that of PP. Dolan et al10 reported that the AASI was more predictive of cardiovascular mortality and fatal stroke than PP was, especially in normotensive subjects. Muxfeldt et al17 reported that the AASI was superior to ambulatory PP as a cardiovascular risk marker in resistant hypertensive patients. Our finding of the independent relationship between the AASI and the LLA supports and complements these previous studies. One possible reason that the AASI is more predictive of the LLA is that it provides relatively more information about the structural and functional characteristics of the arteries, whereas PP is more strongly dependent on BP.10 However, in the current study we did not assess the prognostic ability of either variable; rather, we focused on the relationship between the AASI and the LLA.
The association between the 2 suggests an underlying physical basis for the LLA, with stiffer vessels requiring higher pressures to maintain cerebral perfusion, a hypothesis consistent with the mechanism of pulsatile blood flow in compliant vessels. Additional studies are necessary to assess the prognostic ability of the AASI beyond cardiac surgical patients.

An advantage of this study is that we determined the AASI from continuous intraoperative BP measurements. Even though this is not a 24-hour recording, the nature of cardiac surgery is that BPs traverse a rather large range over a relatively short interval. However, limitations of our study include the fact that the AASI is largely influenced by peripheral vascular resistance and stroke volume (decrease in peripheral vascular resistance and/or stroke volume with an increase in the AASI), which we did not assess in this study.\(^\text{12,13}\) The AASI, which was initially introduced as a marker for vascular stiffness, is now considered to be more representative of central PP and tends to overestimate the marker for vascular stiffness, is now considered to be more representative of central PP and tends to overestimate the marker for vascular stiffness.

However, in our data set, the AASI was a better predictor of the LLA than was the s-AASI. This finding could be explained by the fact that we were primarily evaluating inherent vascular properties, including, but not limited to, vascular stiffness, in a very homogeneous patient population under hemodynamically controlled circumstances. One downside of the AASI is that it does not detect nondipper hypertensive patients. We did not identify such patients in our data set because we did not perform a 24-hour evaluation, which would have included the circadian dip in BP. Many medications used during cardiac surgery (especially the anesthetics) can modulate peripheral resistance and stroke volume, and thereby increase the AASI. Thus, such medications may introduce a systemic bias for determination of the AASI. It should be noted also that blood flow velocity measurements by transcranial Doppler ultrasonography reflect volumetric blood flow only if the cross-sectional area of the MCA remains constant. Any changes in arterial diameter can introduce errors in the estimation of flow. Though Serrador et al\(^\text{40}\) demonstrated that the diameter of the MCA does not change in humans at the level of measurement during hyper/hypocapnia or during moderate hypotension, the effects of BP changes on MCA diameter have not been fully investigated.\(^\text{41}\) Finally, we did not measure central PP; rather, we measured PP from the radial artery. Therefore, we did not assess the effect of central PP on the cerebral autoregulation in this study.

**Conclusions**

We investigated the relationship between the LLA and vascular properties as quantified separately by the intraoperative AASI, the s-AASI, and PP in patients undergoing cardiac surgery. The AASI was able to predict the LLA with a greater ability than the s-AASI in such patients, but PP had no predictive ability. We found that the likelihood of a LLA >65 mm Hg increases by 50% for every 0.1 increase in the AASI. Thus, the AASI is significantly associated with changes in cerebral autoregulation. Our findings suggest an underlying physical basis for the LLA, with stiffer vessels requiring higher pressures to maintain cerebral perfusion. It is now possible to link elevations in the LLA with an increased AASI as determined from readily accessible perioperative variables and to predict the LLA from those variables. This study therefore emphasizes the importance of the AASI to intraoperative management and, together with the expanding literature on vascular stiffness and adverse outcomes, suggests that vascular stiffness should be added to our armamentarium of preoperative evaluation. Sophisticated determination of vascular function might therefore be used not only to predict postoperative outcomes, but also to change perioperative management strategies such as BP targets to ensure that patient MAP remains above the LLA.

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**Disclosures**

None.

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