Pulse Pressure Is an Age-Independent Predictor of Stroke Development After Cardiac Surgery

Alexandre Benjo, Richard E. Thompson, Derek Fine, Charles W. Hogue, Diane Alejo, Anita Kaw, Gary Gerstenblith, Ashish Shah, Dan E. Berkowitz, Daniel Nyhan

Abstract—Chronologic age is a strong predictor of adverse outcomes after cardiac surgery. The variability in age-related cardiovascular changes suggests that age may not be the most accurate predictor of adverse perioperative outcomes. Vascular stiffness has emerged as an important surrogate of vascular aging. In a retrospective review, we investigated the value of vascular stiffness, as assessed by brachial pulse pressure (PP) measurements, in predicting stroke in 703 patients (63.4% men and 36.6% women). Patients were followed for 348±215 days after cardiac surgery. We used a multivariable logistic model and unadjusted and adjusted Cox proportional-hazard models to assess the probability of stroke and the hazards of stroke over time. Stroke patients had a significantly higher PP (81.2 mm Hg versus 64.5 mm Hg; P=0.0006). In the logistic regression model, PP was an independent predictor of stroke development (unadjusted odds ratio: 1.35; 95% CI: 1.13 to 1.62, for every 10-mm Hg increase in PP; P=0.001). In the unadjusted and adjusted Cox models, PP again predicted stroke (hazard ratio: 1.32; 95% CI: 1.12 to 1.57; hazard ratio: 2.62; 95% CI: 1.49 to 4.60, respectively; P=0.001 for both) for every 10 mm Hg increase in PP. Age, gender, and diabetes were not independent predictors of stroke. Ejection fraction was inversely related to stroke in the adjusted model. Kaplan–Meier estimates and corresponding log-rank test indicated that the probability of stroke-free survival function was significantly lower (P=0.0067) in patients with PP ≥72 mm Hg versus <72 mm Hg. This analysis suggests that indices of vascular stiffness could be important predictors of neurologic complications. (Hypertension. 2007;50:630-635.)

Key Words: clinical science ■ cardiac surgery ■ pulse pressures ■ stroke ■ hypertension

Cardiac surgical procedures are increasingly undertaken in elderly patients who often have multiple comorbid conditions, including hypertension (HTN) and diabetes mellitus. This observation is notable, because patient age has consistently been identified as an important predictor of adverse outcomes after cardiac surgery. In the general population, age, even in the absence of established risk factors, is the most important predictor of cardiovascular disease. It is increasingly recognized, however, that advancing age is associated with potentially modifiable and reversible morphological and functional changes in the vasculature which impart risk for adverse cardiovascular events. The rates at which age-related vascular changes develop exhibit considerable heterogeneity across individuals, especially in the elderly, and the predictive value of conventional risk factors decreases with age. Together these observations have led to the emerging concept that chronologic age may not in fact be the best predictor of cardiovascular events, but rather that “vascular” age should be viewed as a more precise predictor of adverse cardiovascular events.

Age-related vascular changes are manifest as increased vascular stiffness, a variable that has emerged as a critical feature of vascular aging and an independent risk factor for cardiovascular disease.7–9 Central vascular stiffness is a function of the aorta and its main branches, which are embryologically and structurally distinguishable from distal arteries and arterioles. Physiologically, central vessels function not only to cushion and dampen the pressure oscillations produced by ventricular ejection but also to transfer energy and mechanical signals along the vasculature. The latter consists of propagated waves that are reflected at points of structural or functional discontinuity in the arterial tree. Antegrade/incident and retrograde/reflected waves contribute to the actual arterial pressure waveform. In a compliant, nonstiff, usually young vasculature, the reflected wave returns to the central circulation during diastole, augmenting diastolic myocardial perfusion. In contrast, in a stiff, usually elderly vasculature, the reflected wave returns to the central circulation during systole, amplifying systolic aortic and ventricular pressures. These hemodynamic developments result in increased ventricular loading conditions and in compromised vital organ perfusion. Vascular stiffness is, thus, manifest as increased systemic blood pressure, increased
Table 1. Demographic Data of Patients

<table>
<thead>
<tr>
<th>Patients (N=703)</th>
<th>Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n (%)</td>
<td>455 (63.4)</td>
</tr>
<tr>
<td>Whites, n (%)</td>
<td>652 (80)</td>
</tr>
<tr>
<td>Mean age, mean±SD, y</td>
<td>64.9±11.4</td>
</tr>
<tr>
<td>Age &gt;65 y, n (%)</td>
<td>414 (52.4)</td>
</tr>
<tr>
<td>Postoperative length of stay, mean±SD, d</td>
<td>11.1±11.8</td>
</tr>
<tr>
<td>CABG, n</td>
<td>790</td>
</tr>
<tr>
<td>CABG+valve surgery, n (%)</td>
<td>297 (37.6)</td>
</tr>
<tr>
<td>Follow-up, n (%), d</td>
<td>348±215</td>
</tr>
<tr>
<td>Presurgical renal dysfunction, n (%)</td>
<td>46 (5.8)</td>
</tr>
<tr>
<td>New renal dysfunction (doubling of preoperative creatinine to ≥2 mg/dL or need for dialysis), n (%)</td>
<td>91 (11.5)</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>42 (6.0)</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass graft surgery.

pulse pressure (PP), or increased pulse wave velocity,7–9,15–17 each of which has been used in studies of vascular stiffness.6,8,15 Peripheral pressures, eg, brachial PP, are not the same as central pressures and are greater than central PP in a young compliant vasculature, but central PP increases and may equalize peripheral PPs in a stiff vasculature. The influence of vascular stiffness on outcome after cardiac surgery has not been investigated previously. In this retrospective review, we used peripheral (brachial) PP as an index of vascular stiffness and determined its influence on stroke development.

Methods

All patients undergoing coronary artery bypass graft surgery with or without cardiac valve surgery between January 1, 2004, and November 30, 2005, were evaluated in this retrospective analysis. The study was approved by the Johns Hopkins Institutional Review Board. Data included that collected as part of the Institutional Cardiac Surgical Database and other data obtained by query of the patient’s electronic medical chart. Information from the surgical database was collected by research personnel specifically trained in data extraction using predesigned data forms and validated data entry methods. We collected the following variables: age, gender, type of surgery, race, body mass index, history of diabetes mellitus, and preoperative renal dysfunction (defined as a creatinine ≥2 mg/dL or need for dialysis). Precatheterization peripheral systolic, diastolic, and PP (defined as the difference between systolic and diastolic pressure) were also collected. These pressures were obtained using oscillometry over the brachial artery before the catheterization procedure. Hemodynamic data obtained at the time of cardiac catheterization (left ventricular end diastolic pressure, ejection fraction, and central aortic pressures) were available in 339 patients. An interval of ≥1 day existed between catheterization and the patient’s subsequent cardiac surgery. Stroke was defined as a new, nonreversible focal neurologic deficit, diagnosed clinically by a neurologist with or without confirmation by brain imaging.

Statistical Analysis

In initial confirmatory analyses, group differences were statistically assessed by the Student’s 2-sample t test for continuous measures and the χ² goodness-of-fit test for categorical data. Logistic models were used to calculate both the unadjusted and adjusted odds ratio of stroke for the independent predictors. “Stroke-free” survival curves were constructed using the method of Kaplan–Meier, whereas the unadjusted and adjusted hazards ratios of stroke were calculated using the Cox proportional-hazards regression model. Differences in

Figure 1. Illustrates the relationship between pulse pressure (x axis) and the predicted probability of developing stroke (y axis in percent) in patients who had cardiac surgery. An increase in PP was significantly associated with an increased probability of developing stroke.

Results

Clinical data were available from 703 patients (63.4% men and 36.6% women) who underwent cardiac surgery at the Johns Hopkins Medical Institutions from January 2004 through November 2005. The average age of these patients was 64.9 years. (Table 1). PP was higher in women than men (70.6±24.9 mm Hg versus 62.4±20.1 mm Hg; P=0.0001). The proportion of women in the upper quartile of PP (79 to 134 mm Hg) for this cohort was higher than the proportion of men (56.7% versus men, 44.9%; P=0.016).

Forty-two patients (6%) had a postoperative stroke, all of which occurred within 30 days of surgery. Of the stroke patients, 7 (16.7%) died compared with 54 deaths (8.2%) among the nonstroke patients (P=0.058). Stroke occurred in 8.8% of women compared with a stroke incidence of 4.7% for men (P=0.034). Importantly, stroke patients were not significantly (P=0.481) older than patients who did not have strokes.

Stroke patients had a higher mean PP than those without stroke (81.2 mm Hg versus 64.5 mm Hg; P=0.0006). Based on the logistic regression analysis model, PP was an independent predictor of stroke (unadjusted odds ratio: 1.35; 95% CI: 1.13 to 1.62 for every 10 mm Hg increase in PP; P=0.001; Figure 1).

Table 2 shows the hazard ratio (HR) and CI for the unadjusted and adjusted Cox models. The adjusted model includes those variables with a P value of ≤0.10 associated with the unadjusted HR. Because it was a variable of interest, chronological age was included in the adjusted model regardless of significance in the unadjusted case. Increases in brachial PP were associated with an increased risk of stroke development (HR: 1.32; 95% CI: 1.12 to 1.57 for each 10 mm Hg increase in PP; P<0.001, unadjusted model). This relationship remained highly significant (HR: 2.62; 95% CI:
Table 2. Association Between Clinical Variables and Stroke for Those Variables That Are or Approach Statistical Significance and Age

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted Analysis</th>
<th></th>
<th>Adjusted Analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR for Stroke (95% CI)</td>
<td>P</td>
<td>HR for Stroke (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Peripheral/brachial PP*</td>
<td>1.32 (1.12 to 1.57)</td>
<td>0.001</td>
<td>2.62 (1.49 to 4.60)</td>
<td>0.001</td>
</tr>
<tr>
<td>Postoperative renal insufficiency</td>
<td>2.85 (1.50 to 5.41)</td>
<td>0.001</td>
<td>2.41 (0.72 to 8.13)</td>
<td>0.156</td>
</tr>
<tr>
<td>Peripheral/brachial SBP*</td>
<td>1.21 (1.04 to 1.41)</td>
<td>0.014</td>
<td>0.61 (0.38 to 0.99)</td>
<td>0.044</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.93 (1.05 to 3.54)</td>
<td>0.034</td>
<td>0.86 (0.25 to 2.97)</td>
<td>0.813</td>
</tr>
<tr>
<td>Left ventricular ejection fraction†</td>
<td>0.81 (0.64 to 1.02)</td>
<td>0.073</td>
<td>0.52 (0.35 to 0.78)</td>
<td>0.002</td>
</tr>
<tr>
<td>Aortic PP*</td>
<td>1.28 (0.96 to 1.72)</td>
<td>0.098</td>
<td>0.66 (0.35 to 1.25)</td>
<td>0.204</td>
</tr>
<tr>
<td>Aortic diastolic*</td>
<td>1.45 (1.03 to 2.04)</td>
<td>0.034</td>
<td>2.59 (1.18 to 5.71)</td>
<td>0.018</td>
</tr>
<tr>
<td>Age‡</td>
<td>1.10 (0.84 to 1.45)</td>
<td>0.481</td>
<td>1.04 (0.51 to 2.12)</td>
<td>0.309</td>
</tr>
</tbody>
</table>

*HR for each 10-mm Hg increase.
†HR for each 10% increase.
‡HR for each 10-year increase.

1.49 to 4.60 for each 10 mm Hg increase in PP; \( P<0.001 \) in the adjusted model, which included age. A likelihood ratio test of the adjusted model above with and without peripheral (brachial) PP found that this variable made a highly statistically significant contribution to the hazards of stroke (\( \chi^2 = 11.54; P = 0.0007 \)). In the adjusted model, ejection fraction was inversely related to stroke (HR: 0.52; 95% CI: 0.35 to 0.78; \( P = 0.002 \)).

Figure 2 illustrates the Kaplan–Meier estimates of the stroke-free survival by days post-surgery for those with a PP of \(<72 \text{ mm Hg}\) versus \(\geq 72 \text{ mm Hg}\). The difference in stroke-free survival was significant between the low and high PP groups, as determined by the log-rank test (\( P = 0.0067 \)). This cutoff value was chosen based on the receiver operator curve analysis from the logistic regression model. The cut point of 72 mm Hg gave an optimal sensitivity and specificity of 71.4% and 66.2%, respectively, and a corresponding receiver operator curve value of 0.714.

In individuals with a compliant vasculature, peripheral PPs are greater than central PPs. With increasing central vascular stiffness, central pressures increase and can equal or sometimes exceed peripheral pressures. Figure 3 illustrates the relationship between peripheral (brachial) and central aortic PP in patients (n=339) in whom both measurements were available. These 2 values were highly correlated (\( r^2 = 0.465 \)). This suggests that peripheral PP reflects central PP in these patients and that there is a convergence of these 2 PP values.

**Discussion**

The main result of this study is that preoperative brachial PP, an index of vascular stiffness and overall vascular health, predicts the occurrence of stroke after cardiac surgery beyond that provided by currently recognized perioperative risk factors, including patient age. Vascular stiffness has emerged as an important independent predictor of adverse cardiovascular outcome in the general population.\(^7\)–\(^9\),\(^12\)–\(^18\) Vascular stiffness reflects the overall changes (central aortic dilatation, increased arterial wall thickness, elastin depletion and fragmentation, and collagen deposition) that accrue in the arterial tree with age. The influence of vascular stiffness on cardiovascular outcomes is independent of established cardiovascular risk factors. Moreover, age-related cardiovascular changes are highly variable, and indices of vascular stiffness

Kaplan-Meier survival Curve

Figure 2. Kaplan–Meier stroke-free survival for those with peripheral/brachial PP \(<72 \text{ mm Hg}\) vs those \(\geq 72 \text{ mm Hg}\) as a function of postoperative time. The 72 mm Hg differentiating pressure was chosen based on the receiver operator curve analysis from the logistic regression model.

Aortic Pulse Pressure (mm Hg)

Figure 3. Relationship between brachial and central aortic PP in patients (n=339) in whom both measurements were available. These 2 values were highly correlated (\( r^2 = 0.465 \)).
and overall vascular health have emerged as more sensitive predictors of cardiovascular outcomes than chronological age. Indeed, interventions that preferentially target central vascular stiffness have been shown to improve outcomes compared with interventions that only attenuate peripheral blood pressure.19

Because of a growing number of aged and high-risk patients, there is an increasing emphasis on perioperative complications and outcomes after cardiac surgery.1 A better understanding of risk factors might not only provide a more effective method for assessing the risks versus benefits of surgery for an individual but also foster the development of preventative strategies. Neurologic complications manifest as stroke and neurocognitive dysfunction are of particular concern, because they are associated with longer hospitalization, higher frequency of discharge to secondary care facilities, altered quality of life, and mortality.20–22 Neurologic complications were responsible for 7.2% of all deaths after cardiac surgery in the 1970s, ∼20% of deaths in the 1980s, and the number continues to increase.23,24 Previous studies and risk models investigating the relationship between risk factors and outcome after cardiac surgery have not included indices of vascular stiffness in their analysis.25–27 However, a recent meta-analysis identified increased PP as a risk factor for development of renal impairment in cardiac surgery patients.28 This is consistent with findings in nonsurgery publications.18,29,30 We used PP as an index of central vascular stiffness in this retrospective review and demonstrated for the first time an independent relationship with the development of focal neurologic deficits. Although this relationship clearly must be tested in a prospective study, the influence of vascular stiffness on outcome attains seminal importance when one considers that vascular stiffness is a modifiable risk factor amenable to intervention.5

We used focal neurologic deficits (as assessed clinically by a neurologist and a majority confirmed with brain imaging) to define stroke in this retrospective study. We did not use measures of neurocognitive decline in this analysis. The rates for stroke development in this patient population are consistent with that outlined in other studies of higher risk populations. Our findings are also consistent with those of other studies that have investigated the relationship between vascular stiffness and neurologic injury. The relationship between hypertension and the subsequent development of cognitive decline, including Alzheimer’s disease, has been extensively investigated.31–35 Many recent studies investigating the development of neurologic diseases have focused on indices of vascular stiffness and overall vascular health rather than hypertension. Qiu et al36 have demonstrated that higher PPs are associated with an increased risk of Alzheimer’s disease and dementia in adults >75 years of age. Fujiwara et al37 demonstrated that vascular stiffness as indicated by an increased pulse wave velocity was a potent risk factor for poor cognitive function in community-dwelling elderly individuals. The influence of vascular stiffness on neurologic conditions extends beyond that of cognitive decline in that indices of vascular stiffness have also been shown in a longitudinal study of individuals with no baseline cardiovascular disease or symptoms to be independent predictors of fatal stroke.38 These results in a cohort of outpatients are entirely consistent with our results obtained in the setting of cardiac surgery using cardiopulmonary bypass.

Any 1 or a combination of mechanisms could explain the relationship between vascular stiffness and end-organ damage. Stiff vessels are subject to greater cyclic load with each heart beat compared with compliant vessels, and this is known to exert a greater influence on the vascular smooth muscle cell phenotype.39 The magnitude of the PP may, thus, influence arterial remodeling characteristics in the blood vessels of vital organs.40 Moreover, the influence of stiffness changes on autoregulation in any specific patient and vascular bed are unknown, and efforts to maintain pressure within a generic “autoregulatory range” may be inherently flawed. Although vascular stiffness measurements and PP reflect central vascular properties, stiffness characteristics may also extend to arterioles and vital organs.41 The critical role of cerebral perfusion pressure and cerebral autoregulation is highlighted by the frequency with which watershed infarcts occur after cardiac surgery.42 These clinical and diffusion weighted–MRI-confirmed watershed infarcts were associated with decrements in intraoperative mean arterial pressure of >10 mm Hg and with increased mortality and the need for both short- and long-term care. These decreases in mean arterial pressure were associated with an increased frequency of bilateral watershed infarcts. Moreover, a reduction in diastolic pressure as may occur with early wave reflection will compromise diastolic blood flow augmentation to vital organs. Finally, differential input impedance in the brain and kidney compared with other organs and the exposure of small arterial vessels to high-pressure fluctuations may contribute to the observed pathophysiology in these 2 vital organs.43 Another explanation for our findings might be that vascular stiffness might identify patients with atherosclerosis of the ascending aorta, an important stroke risk factor. In a previous study, when considering the atherosclerosis of the ascending aorta detected with epiaortic ultrasound in multivariable modeling of stroke risk, we found that age was no longer a significant risk predictor of perioperative stroke.44 It should be noted, however, that atheroma burden may not be the most sensitive marker of age-related vascular changes and that even in the absence of atherosclerotic disease and established cardiovascular risk factors, structural and functional changes in the vasculature, eg, stiffness characteristics, accrue with age. These age-related vascular changes have characteristics in common with those that develop in risk factor–induced atherosclerosis, a feature that has delayed the recognition that age, per se, is a cardiovascular risk factor.3

Postmenopausal women have higher vascular stiffness than men of similar age, even after adjusting for body height, blood pressure, and cardiovascular risk.45–48 These findings might be explained in part by the absence of estrogen effects on endothelial function, smooth muscle tone and differentiation, intracellular matrix composition, and the loss of estrogen modulation of vascular inflammation.47,49–54 Our findings of higher PP in women compared with men and the link between PP and stroke are of particular interest in light of our previous findings that women are at higher risk for perioperative stroke than men and that this complication explains a
large portion of the higher operative mortality for women.\textsuperscript{20,44,55} It is possible that sex-related differences in the prevalence of vascular stiffness might contribute to the poor clinical outcomes for women with cardiovascular disease including, possibly, higher mortality and poor neurologic outcomes after cardiac surgery.

The weaknesses of this study include its retrospective nature. Our definition of “neurologic injury” included only focal deficits and did not include changes in neurocognitive indices. We contend, however, that this adds to the validity of our study in that it avoided the limitations inherent in neurocognitive assessments. In addition, all of the recorded strokes occurred within 30 days of surgery although we had longer periods of follow-up data. It is possible that some strokes were misdiagnosed or went unrecorded as the time from surgery increased. We have no reason to believe that the frequency of the later-onset strokes might be greater in patients with lower PP. Indeed, it is more likely that the converse is true, and this would further validate our conclusion. We chose to confine our outcomes to those that were readily quantifiable and about which there might be little disagreement. Moreover, our cohort of patients included those who had coronary artery bypass graft surgery only, as well as those who had coronary artery bypass graft plus valve surgery. Finally, PP is influenced by other variables that were not controlled in this study, eg, severe anemia and aortic incompetence. However, it is unlikely that patients in this setting were allowed to become anemic to a degree that would significantly modulate PP. Almost all of the valve surgeries were performed for mitral regurgitation and/or aortic stenosis, and few for aortic incompetence.

**Perspectives**

In conclusion, the major new finding of this study is that vascular stiffness, as assessed by PP, is an important age-independent predictor of stroke. Vascular stiffness is rapidly emerging as an age-independent and sensitive predictor of cardiovascular outcomes. Importantly, vascular stiffness indices reflecting central vascular characteristics have been shown to be amenable to reversal, and improvements in these indices are associated with improved cardiovascular outcomes. The results of this study should provide the background for a prospective observational study using more sophisticated measures of vascular stiffness and outcome variables as end points. Furthermore, this provides the impetus for not only incorporating PP into risk stratification, but also encompassing interventions that modify stiffness and thus risk and, as a result, outcome.

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**Disclosures**

None.

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