Pathogenesis and Risk Factors for Cerebral Infarct After Surgical Aortic Valve Replacement

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Background and Purpose—Stroke is a potentially devastating complication of cardiac surgery. Identifying predictors of radiographic infarct may lead to improved stroke prevention for surgical patients.

Methods—We reviewed 129 postoperative brain magnetic resonance imagings from a prospective study of patients undergoing surgical aortic valve replacement. Acute infarcts were classified as watershed or embolic using prespecified criteria.

Results—Acute infarct on magnetic resonance imaging was seen in 79 of 129 patients (61%), and interrater reliability for stroke pathogenesis was high ($\kappa=0.93$). Embolic infarcts only were identified in 60 patients (46%), watershed only in 2 (2%), and both in 17 (13%). In multivariable logistic regression, embolic infarct was associated with aortic arch atheroma (odds ratio [OR], 3.4; 95% confidence interval [CI], 1.0–12.0; $P=0.055$), old subcortical infarcts (OR, 5.5; 95% CI, 1.1–26.6; $P=0.04$), no history of percutaneous transluminal coronary angioplasty or coronary artery bypass graft (OR, 4.0; 95% CI, 1.2–13.7; $P=0.03$), and higher aortic valve gradient (OR, 1.3 per 5 mm Hg; 95% CI, 1.09–1.6; $P=0.004$). Watershed infarct was associated with internal carotid artery stenosis $\geq 70\%$ (OR, 11.7; 95% CI, 1.8–76.8; $P=0.01$) and increased left ventricular ejection fraction (OR, 1.6 per 5% increase; 95% CI, 1.08–2.4; $P=0.02$).

Conclusions—The principal mechanism of acute cerebral infarction after aortic valve replacement is embolism. There are distinct factors associated with watershed and embolic infarct, some of which may be modifiable. (Stroke. 2016;47:2130-2132. DOI: 10.1161/STROKEAHA.116.013970.)

Key Words: brain ■ carotid stenosis ■ cerebral infarction ■ embolism ■ magnetic resonance imaging

Stroke complicating cardiac surgery is associated with prolonged length of stay, higher cost, and increased morbidity and mortality.1,2 Periprocedural radiographic infarcts are much more common than clinical events, and a greater understanding of the mechanisms of injury could lead to improved stroke prevention.

Previous attempts to determine the pathogeneses of infarcts after cardiac surgery have been limited by retrospective review of radiology reports, and imaging consisting of a mixture of head computed tomography or magnetic resonance imagings (MRIs) at nonstandardized time points. We investigated pathogenic mechanisms of periprocedural radiographic infarct from a prospective study of patients undergoing aortic valve replacement for calcific aortic stenosis with standardized MRI assessments.

Study Design
Retrospective review of a prospective observational cohort study of subjects aged $\geq 65$ years undergoing open surgical aortic valve replacement for calcific moderate-to-severe aortic stenosis. The study protocol was described in a previous publication.2 MRI with diffusion-weighted imaging was obtained in 129 of 196 patients (66%) on median postoperative day 6 (interquartile range, 5–8).

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Infarct Classification System
Two blinded neurologists independently reviewed MRIs for stroke location and type (embolic versus watershed). Acute infarct was defined as increased signal on diffusion-weighted imaging sequence with an appropriate apparent diffusion coefficient correlate. Watershed infarcts were subcategorized into cortical border zone and internal border zone. Strokes were categorized as embolic if there were ≥1 diffusion-weighted imaging lesions in a nonwatershed territory or an isolated single small lesion (<1.5 cm) in a possible watershed territory (Figure). Fluid-attenuated inversion recovery sequencing was reviewed for evidence of old infarction. Areas of disagreement were resolved independently by a third blinded neurologist.

Statistical Analysis
Inter-rater reliability of the pathogenic classifications was measured with κ statistics. Demographic, clinical, and operative factors were tested for association with watershed and embolic stroke using t test, Fisher exact test, χ² test, or Wilcoxon ranked-sum test, as appropriate. Factors in univariate analysis with P < 0.1 were evaluated in a multivariable logistic regression model. Statistical analysis was performed using STATA 13.0 (College Station, TX).

Results
Acute infarct was seen in 79 of 129 patients (61%; mean age, 75±6 years; male, 66%; and nonwhite, 7%). Embolic strokes only were identified in 60 patients (46%), watershed only in 2 (2%), both in 17 (13%), and no infarct in 50 (39%). There was an excellent interrater agreement on assessment of the presence of each of the infarct type (κ=0.93). Table I in the online-only Data Supplement presents the demographic, clinical, and surgical characteristics, and univariable testing for each stroke type.

In multivariable logistic regression, embolic infarct was independently associated with moderate-to-severe ascending aortic atheroma (odds ratio [OR], 3.4; 95% confidence interval [CI], 1.0–12.0; P=0.055), the presence of old subcortical infarcts (OR, 5.5; 95% CI, 1.1–26.6; P=0.04), no history of percutaneous transluminal coronary angioplasty or coronary artery bypass graft (OR, 4.0; 95% CI, 1.2–13.7; P=0.03), and higher aortic valve gradient (OR, 1.3 per 5 mm Hg; 95% CI, 1.09–1.6; P=0.004). In a separate logistic regression model, watershed infarct was independently associated with internal carotid artery stenosis ≥70% (OR, 11.7; 95% CI, 1.8–76.8; P=0.01) and increased left ventricular ejection fraction (OR, 1.6 per 5% increase; 95% CI, 1.08–2.4; P=0.02). Drop in blood pressure from baseline (obtained at preoperative clinic visit) to intraoperative nadir was not associated with watershed or embolic infarct.

Discussion
Patients undergoing MRI after surgical aortic valve replacement for calcific AS had a high rate of radiographic infarct (61%). The primary pathogenic mechanism of infarct was embolism, which is consistent with previous reports. Aortic arch atheroma is a well-documented predictor of stroke in cardiac surgery, and we identified a correlation of embolic stroke with moderate-to-severe aortic arch atheroma. Higher aortic valve gradient was also associated with embolic infarct probably reflecting greater calcification and increased atherosclerotic disease burden. Although coronary artery disease is a known risk factor for ischemic stroke, not having had previous percutaneous transluminal coronary angioplasty or coronary artery bypass graft was associated with embolic stroke in multivariate analysis possibly related to continuation of antiplatelets through the surgical period. Unfortunately, we did not have preoperative medication data to confirm or refute this hypothesis. Finally, preoperative subcortical lesions on fluid-attenuated inversion recovery were also associated with embolic infarct. Preexisting subcortical lesion burden is thought to occur in regions of hemodynamic impairment and reduced washout of small emboli.

Severe internal carotid artery stenosis was strongly associated with watershed infarction, consistent with the presumed mechanism for injury in these territories. More surprisingly, increased left ventricular ejection fraction was also associated with watershed infarct. Patients with higher ejection fraction may experience a larger drop in cerebral perfusion pressure when placed on bypass; however, overall the drop in mean arterial pressure was not associated with infarct, making this unlikely.

Strengths of our study include an aged, high-risk population, uniform imaging modality and timing, and serial clinical stroke ascertainment. Several limitations should be noted. Only 129 of 196 patients obtained MRI scans with diffusion-weighted imaging, mainly because of patient refusal and medical instability of the patient, which may have resulted in selection bias favoring milder brain injuries. Our cohort was

Figure. Magnetic resonance diffusion-weighted imaging and corresponding apparent diffusion coefficient sequences. A, Left cortical borderzone watershed infarction and right internal borderzone watershed infarction. B, Right occipital embolic infarct. C, Left embolic infarct, although in an area of possible watershed distribution the lesion is singular and <1.5 cm.
selected from 2 tertiary hospitals, representing 1 academic institution, which may limit our generalizability. Finally, there is evidence to suggest that hypoperfusion and embolism often coexist, and their radiographic patterns are linked. However, the criteria used to determine infarct type seem to be reliable and valid, and there were distinct and plausible factors associated with each infarct mechanism.

Conclusions
Radiographic ischemic infarct after open surgical aortic valve replacement for calcific aortic stenosis is common, and the principal mechanism is embolism. Risk factors for radiographic infarction were generally distinct from clinical factors and some may be modifiable.

Disclosures
This study was supported by a National Institutes of Health/National Heart Lung and Blood Institute Grant R01HL084375. Dr Messé has received significant research funding from the National Institutes of Health for this study and for participation in the Cardiothoracic (CT) Surgery Network, which is evaluating embolic protection devices in surgical aortic valve replacement. He has also received significant research funding from Glaxo Smith Kline for his role as co-PI of a neuroprotectant study for high-risk surgical aortic repair. Dr Acker has received significant research funding from Glaxo Smith Kline for his role as co-PI of a neuroprotectant study for high-risk surgical aortic repair. The other authors report no conflicts.

References
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Table I. Demographic, Clinical, and Operative Characteristics by presence of watershed and embolic infarct on diffusion weighted MRI

<table>
<thead>
<tr>
<th>Clinical characteristics and demographics:</th>
<th>Overall (n=129)</th>
<th>Embolic (n=77)</th>
<th>No embolic infarct (n=52)</th>
<th>P value</th>
<th>OR (95% CI)</th>
<th>Watershed (n=19)</th>
<th>No watershed infarct (n=110)</th>
<th>P value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>75 (70-80)</td>
<td>75 (70-79)</td>
<td>76 (70-80)</td>
<td>0.84</td>
<td>1.0 (0.9-1.1)</td>
<td>77 (70-81)</td>
<td>75 (70-80)</td>
<td>0.42</td>
<td>1.0 (0.9-1.2)</td>
</tr>
<tr>
<td>Female</td>
<td>43 (33.6)</td>
<td>27 (35.1)</td>
<td>16 (31.4)</td>
<td>0.67</td>
<td>1.2 (0.6-2.5)</td>
<td>6 (31.6)</td>
<td>37 (34)</td>
<td>0.84</td>
<td>0.9 (0.1-2.6)</td>
</tr>
<tr>
<td>Non-white</td>
<td>9 (7.0)</td>
<td>4 (5.2)</td>
<td>5 (9.6)</td>
<td>0.33</td>
<td>1.3 (0.7-2.8)</td>
<td>2 (10.5)</td>
<td>7 (6.4)</td>
<td>0.51</td>
<td>0.7 (0.3-1.7)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>29 (26-32)</td>
<td>29 (27-33)</td>
<td>28 (26-33)</td>
<td>0.14</td>
<td>1.0 (0.9-1.1)</td>
<td>29 (26-32)</td>
<td>29 (26-33)</td>
<td>0.66</td>
<td>0.9 (0.9-1.1)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>4 (3.1)</td>
<td>1 (1.3)</td>
<td>3 (5.8)</td>
<td>0.15</td>
<td>0.2 (0.02-2.0)</td>
<td>1 (5.3)</td>
<td>3 (2.7)</td>
<td>0.56</td>
<td>2.0 (0.2-20)</td>
</tr>
<tr>
<td>COPD</td>
<td>11 (8.5)</td>
<td>5 (6.5)</td>
<td>6 (11.5)</td>
<td>0.31</td>
<td>0.5 (0.2-1.9)</td>
<td>0</td>
<td>11 (10)</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>110 (85.3)</td>
<td>65 (84.4)</td>
<td>45 (86.5)</td>
<td>0.74</td>
<td>0.8 (0.3-2.3)</td>
<td>17 (89.5)</td>
<td>93 (84.6)</td>
<td>0.58</td>
<td>1.6 (0.3-7.3)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>42 (32.6)</td>
<td>26 (33.8)</td>
<td>16 (30.8)</td>
<td>0.72</td>
<td>1.2 (0.5-2.4)</td>
<td>7 (36.8)</td>
<td>35 (31.8)</td>
<td>0.67</td>
<td>1.3 (0.5-3.4)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>113 (87.6)</td>
<td>66 (85.7)</td>
<td>47 (90.4)</td>
<td>0.43</td>
<td>0.64 (0.2-2.0)</td>
<td>18 (94.7)</td>
<td>95 (86.4)</td>
<td>0.31</td>
<td>2.8 (0.4-22)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>11 (8.5)</td>
<td>7 (9.1)</td>
<td>4 (7.7)</td>
<td>0.78</td>
<td>1.2 (0.3-4.3)</td>
<td>1 (5.3)</td>
<td>10 (9.1)</td>
<td>0.58</td>
<td>0.6 (0.1-4.6)</td>
</tr>
<tr>
<td>Chronic Renal Failure</td>
<td>5 (3.9)</td>
<td>3 (3.9)</td>
<td>2 (3.9)</td>
<td>0.99</td>
<td>1.0 (0.2-6.2)</td>
<td>0</td>
<td>5 (4.6)</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>43 (33.3)</td>
<td>21 (27.3)</td>
<td>22 (42.3)</td>
<td>0.08</td>
<td>0.5 (0.2-1.1)</td>
<td>7 (36.8)</td>
<td>36 (32.7)</td>
<td>0.73</td>
<td>1.2 (0.4-3.3)</td>
</tr>
<tr>
<td>Prior stroke or TIA</td>
<td>12 (9.3)</td>
<td>7 (9.1)</td>
<td>5 (9.6)</td>
<td>0.92</td>
<td>0.9 (0.3-3.1)</td>
<td>1 (5.26)</td>
<td>11 (10)</td>
<td>0.51</td>
<td>0.5 (0.6-4.1)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>83 (64)</td>
<td>48(62)</td>
<td>35(67)</td>
<td>0.6</td>
<td>0.8 (0.4-1.7)</td>
<td>11(58)</td>
<td>72 (65)</td>
<td>0.5</td>
<td>0.7 (0.3-2.0)</td>
</tr>
<tr>
<td></td>
<td>No (%)</td>
<td>No (%)</td>
<td>No (%)</td>
<td>p-value</td>
<td>CI</td>
<td>No (%)</td>
<td>No (%)</td>
<td>p-value</td>
<td>CI</td>
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<tr>
<td>--------------------------------</td>
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</tr>
<tr>
<td>Prior PTCA or CABG</td>
<td>27 (21)</td>
<td>12 (15.6)</td>
<td>15 (28.9)</td>
<td>0.07</td>
<td>0.5 (0.2-1.1)</td>
<td>2 (11)</td>
<td>25 (23)</td>
<td>0.36</td>
<td>0.4 (0.9-1.9)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>31 (24.0)</td>
<td>15 (19.5)</td>
<td>16 (30.8)</td>
<td>0.14</td>
<td>0.5 (0.2-1.2)</td>
<td>5 (26.3)</td>
<td>26 (23.6)</td>
<td>0.8</td>
<td>1.2 (0.4-3.5)</td>
</tr>
<tr>
<td>Left ventricular ejection</td>
<td>60 (55-65)</td>
<td>60 (55-65)</td>
<td>60 (54-64)</td>
<td>0.19</td>
<td>1.0 (0.9-1.1)</td>
<td>65 (60-69)</td>
<td>60 (55-65)</td>
<td>0.02</td>
<td>1.1 (1.0-1.1)</td>
</tr>
<tr>
<td>Mean aortic valve gradient</td>
<td>44 (36-54)</td>
<td>47 (42-56)</td>
<td>40 (30-53)</td>
<td>0.005</td>
<td>1.0 (1.0-1.1)</td>
<td>49 (44-54)</td>
<td>44 (34-54)</td>
<td>0.12</td>
<td>1.0 (0.9-1.1)</td>
</tr>
<tr>
<td>Internal carotid artery stenosis &gt;70%*</td>
<td>6/98 (6.1)</td>
<td>5/98 (8.2)</td>
<td>1/98 (2.7)</td>
<td>0.27</td>
<td>3.2 (0.4-28.6)</td>
<td>3/98 (21.4)</td>
<td>3/98 (3.6)</td>
<td>0.01</td>
<td>7.3 (1.3-41)</td>
</tr>
<tr>
<td>Old infarct subcortical</td>
<td>113 (88.3)</td>
<td>73 (94.8)</td>
<td>40 (78.4)</td>
<td>0.01</td>
<td>5.0 (1.5-16)</td>
<td>17 (89.5)</td>
<td>96 (88.1)</td>
<td>0.86</td>
<td>1.2 (0.2-5.6)</td>
</tr>
<tr>
<td>Old infarct cortical</td>
<td>12 (9.4)</td>
<td>10 (13)</td>
<td>2 (3.9)</td>
<td>0.12</td>
<td>3.7 (0.8-17)</td>
<td>1 (5.3)</td>
<td>11 (10.1)</td>
<td>0.51</td>
<td>0.5 (0.6-4.1)</td>
</tr>
<tr>
<td>CPB time (minutes)</td>
<td>103 (83-136)</td>
<td>101 (80-138)</td>
<td>106 (87-131)</td>
<td>0.4</td>
<td>1.0 (0.99-1.0)</td>
<td>95 (74-144)</td>
<td>104 (84-136)</td>
<td>0.48</td>
<td>0.9 (0.9-1.0)</td>
</tr>
<tr>
<td>Concomitant MVR</td>
<td>12 (9.3)</td>
<td>5 (6.5)</td>
<td>7 (13.5)</td>
<td>0.18</td>
<td>0.4 (0.1-1.5)</td>
<td>1 (5.3)</td>
<td>11 (10)</td>
<td>0.51</td>
<td>0.5 (0.6-4.1)</td>
</tr>
<tr>
<td>Concomitant CABG</td>
<td>36 (27.9)</td>
<td>22 (28.6)</td>
<td>14 (27)</td>
<td>0.84</td>
<td>1.0 (0.5-2.4)</td>
<td>4 (21.1)</td>
<td>32 (29.1)</td>
<td>0.47</td>
<td>0.7 (0.2-2.1)</td>
</tr>
<tr>
<td>Lowest hemoglobin</td>
<td>8.1 (7.3-8.8)</td>
<td>8.2 (7.1-8.8)</td>
<td>8 (7.5-8.7)</td>
<td>0.43</td>
<td>0.9 (0.7-1.2)</td>
<td>8.1 (7.8-8.8)</td>
<td>8.2 (7.4-8.8)</td>
<td>0.42</td>
<td>0.8 (0.6-1.2)</td>
</tr>
</tbody>
</table>
All continuous variables reported as median (interquartile range) or n (%). COPD indicates chronic obstructive pulmonary disease; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; MVR, mitral valve replacement; MAP, mean arterial pressure.

All patient clinical history was defined by patient report or prior chart documentation

*Doppler ultrasound
†Intraoperative epiaortic ultrasound (moderate atherosclerosis = 3-5mm calcification, and severe atherosclerosis = >5mm calcification)
‡Baseline MAP to lowest recorded MAP during procedure