Clinically Silent Cerebral Ischemic Events After Cardiac Surgery: Their Incidence, Regional Vascular Occurrence, and Procedural Dependence

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Background. **The reported frequency of stroke after coronary artery bypass grafting varies between 1.5% and 6%, approaches 10% after aortic valve replacement, and may occur in between 40 to 70% in high-risk groups. Clinically silent infarction may be far more frequent and could contribute to long-term cognitive dysfunction in patients after cardiac procedures. Using diffusion-weighted magnetic resonance imaging we document the occurrence, vascular distribution, and procedural dependence of silent infarction after cardiac surgery with cardiopulmonary bypass. We also document the association of preexisting white matter lesions with new postoperative ischemic lesions.**

Methods. **Thirty-four patients underwent T2-weighted fluid attenuated inversion recovery and diffusion-weighted magnetic resonance imaging before and after cardiac surgery with cardiopulmonary bypass for coronary artery bypass grafting, aortic valve replacement, and mitral valve repair or replacement surgery. Images were evaluated by experienced neuroradiologists for number, size, and vascular distribution of lesions.**

Results. **Mean age of participants was 67 ± 15 years. Imaging occurred before and 6 ± 2 days after surgery. New cerebral infarctions were evident in 6 of 34 patients (18%), were often multiple, and in 67% of patients were clinically silent. The occurrence of new infarctions by surgical procedure was as follows: aortic valve replacement (2 of 6), coronary artery bypass grafting and aortic valve replacement (3 of 8), aortic valve replacement with root replacement (1 of 1), coronary artery bypass grafting and mitral valve repair or replacement (0 of 4), mitral valve repair or replacement (0 of 2), and isolated coronary artery bypass grafting (0 of 13). New infarction occurred in 6 of 15 (40%) of all procedures involving aortic valve replacement. The severity of preexisting white matter lesions trended toward predicting the occurrence of new lesions ($p = 0.055$).**

Conclusions. **Diffusion-weighted imaging reveals new cerebral infarctions in nearly 40% of patients after aortic valve replacement.**

(Ann Thorac Surg 2006;81:2160–6)

Stroke is the third leading cause of death in the developed world and the leading cause of long-term disability [1]. Stroke occurs in 1.5% to 6% of all patients presenting for coronary artery bypass grafting (CABG) [2–4], although patients undergoing aortic valve replacement appear to be at higher risk, suffering stroke in approximately 10% of cases in several studies [5, 6]. Advanced age and previous stroke markedly increase risk [4]. Stroke after cardiac surgery doubles the duration and cost of hospitalization, portends a 5- to 10-fold increase in early mortality, and 69% of survivors suffer severe disability [7]. The cause of stroke is believed to be primarily embolic, whereas the role of hypotension and inadequate flow is thought to be considerably less important [8], and hemorrhagic stroke is infrequent.

Embolic processes are at the top of the list of suspected culprits leading to postoperative cognitive dysfunction (POCD), although this is far from certain. There is general agreement that the incidence of POCD early after cardiac surgery is high, but that cognitive performance returns nearly to baseline in 6 to 12 weeks for most patients [9, 10]. Although most recover, Newman and colleagues [10] suggest that early POCD may herald further long-term cognitive decline. The association of long-term POCD with cardiopulmonary bypass has recently been disputed [11]. There may nonetheless be a subpopulation in which long-term cognitive deterioration [10], and even dementia [12], may be accelerated, such as in those suffering from perioperative stroke or

Accepted for publication Jan 13, 2006.

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Published by Elsevier Inc

0003-4975/06/$32.00
doi:10.1016/j.athoracsur.2006.01.080

Table 1. Univariate Analysis of Risk Factors

Variable	(+)New Ischemic Lesion (n = 6)	(−)New Ischemic Lesion (n = 28)	*p* Value
Age (y)	68 ± 14	64 ± 18	0.63
Hypertension	6/6 (100%)	21/28 (75%)	0.22
Diabetes mellitus	0/6 (0%)	6/28 (21%)	1.0
Smoking	3/6 (50%)	12/28 (43%)	.55
Peripheral vascular disease	0/6 (0%)	5/28 (18%)	1.0
Previous TIA/stroke	3/6 (50%)	5/28 (18%)	0.13
Atrial fibrillation	1/6 (17%)	8/28 (29%)	0.87
CPB duration (min)	122 ± 33	125 ± 15	0.84
WML			.055
None	2/6 (33%)	5/28 (18%)	
Mild	0 (0%)	14/28 (50%)	
Moderate	2/6 (33%)	6/28 (21%)	
Severe	2/6 (33%)	3/28 (11%)	

CPB = cardiopulmonary bypass; TIA = transient ischemic attack; WML = white matter lesion burden.

silent ischemic events. In the nonsurgical arena, frank clinical stroke syndromes are accompanied by dementia in up to 25% to 30% of individuals [13].

Improved methods for identifying subpopulations at risk for both stroke and POCD may allow protective measures to be taken. Echocardiographic studies suggest that the occurrence of stroke [14], silent cerebral ischemic events [15], and cognitive dysfunction [14] may be associated with the degree of atheromatous disease in the ascending aorta. White matter lesions (WMLs) occurring in the brain and identified with magnetic resonance imaging (MRI) are thought to be the result of hypertensive small vessel disease [16], yet may also have other causes. White matter lesions have also been associated with an increased risk of stroke [17] and with dementia [18] in the general population. Goto and associates [19] have suggested that the frequency of preexisting brain WMLs is predictive of post-CABG stroke and neurocognitive dysfunction.

The present investigation was undertaken to measure the procedure-related frequency and regional distribution of both silent and frank strokes in cardiovascular surgery patients. Secondarily, this study was undertaken to test the predictive value of the severity of preexisting WMLs on new ischemic events after cardiac surgery.

Patients and Methods

After approval from the institutional review board at the University of Pennsylvania in 2000, informed written consent was obtained from all participants. Between 2000 and 2005, 34 unselected patients, who had been entered into two noninvasive MRI cerebral blood flow studies designed to measure the impact of cardiopulmonary bypass and age on perioperative cerebral hemodynamics, completed all aspects of a multi-modal MRI imaging analysis to include T2-weighted fluid-attenuated inversion recovery and diffusion-weighted MRI (DWI) imaging, before and after surgery. These patients underwent CABG, mitral valve repair or replacement, or aortic valve replacement (AVR), all with cardiopulmonary bypass.

Magnetic resonance imaging pulse sequences were supplied by the magnet manufacturers of 1.5-T General Electric (Milwaukee, WS) or 3.0-T Siemens MRI systems (Siemens Medical Solutions USA, Inc, Malvern, PA). Potential risk factors for stroke examined included age older than 65 years, previous stroke or transient ischemic attack, hypertension, diabetes mellitus, atrial fibrillation, smoking, and peripheral vascular disease. Medical records were reviewed for discharge diagnosis of stroke, surgical procedure performed, and duration of cardiopulmonary bypass.

Assessment of preexisting brain WML severity used the fluid-attenuated inversion recovery MRI images. The extent of WMLs was graded as none, mild, moderate, and severe using a simplification of the method published by Liao and coworkers [16], in which the intraclass correlation coefficients for interreader and intrareader reliability were 0.68 and 0.71. Mild was defined as a thin rim of fluid-attenuated inversion recovery hyperintensity in the periventricular region with scattered subcortical white matter disease; moderate was defined as a thick periventricular rim and multiple subcortical lesions; and severe was defined as the presence of WMLs too numerous to count, as well as more confluent periventricular, deep, and subcortical disease.

Assessment of postoperative cerebral ischemic events on MRI used DWI studies. These images were evaluated for number, size, and vascular distribution of lesions. Comparison between preoperative and postoperative DWI image series allowed for confirmation of the new ischemic lesion.

All images were examined by two experienced neuroradiologists, blinded to the operative procedure performed.

Intraoperative transesophageal echocardiography videotape and digital records were available for review in 21 of 34 patients, and studies were reviewed by three

Table 2. Procedural Dependence of Ischemic Lesions

Procedure	No. of Procedures	New Lesion Frequency
AVR	6 (18%)	2/6 (33%)
AVR/root	1 (3%)	1/1 (100%)
AVR/CABG	8 (24%)	3/8 (38%)
AVR summary	15 (44%)	6/15 (40%)
CABG	13 (38%)	0/13 (0%)
MVR	2 (6%)	0/2 (0%)
MVR/CABG	4 (12%)	0/4 (0%)
Totals	34	6/34 (18%)

AVR = aortic valve replacement; CABG = coronary artery bypass grafting; MVR = mitral valve replacement or repair.

cardiologists who were blinded to neurologic outcome and brain imaging data. These studies were evaluated for aortic atheroma lesion grade (thickness), mobility, and ulceration. Up to four segments in each patient were studied: (1) aortic root—segment terminating at sinotubular junction, (2) ascending aorta—segment visualized in mid-esophageal long-axis view, (3) proximal aortic arch—the straight segment visible in the transverse plane in the high esophagus, and (4) distal aortic arch—portion of the arch immediately proximal to the left subclavian artery ostium,. In some patients the proximal or distal transverse arch was not adequately visualized to allow assessment. The most severe lesion was recorded for each segment. Atheroma were graded using the technique described by Hartman and associates [20]: grade I—no or minimal intimal thickening; grade II—extensive intimal thickening; grade III—sessile atheroma less than 5 mm; grade IV—sessile atheroma 5 mm or greater; and grade V—if there was any mobile component. An ulceration was defined as a discrete indentation of the luminal surface of the atheroma with base width and maximum depth of at least 2 mm each. Calcification of the mitral annulus and the aortic valves was graded as none, mild, moderate, and severe based on subjective visual assessment of extent of involvement. The presence of a patent foramen ovale and left ventricular ejection fraction were also recorded.

Cardiopulmonary bypass was conducted with clear priming solution, cooling to 28° to 32°C and using a membrane oxygenator. Proximal coronary anastomoses were achieved with variable side clamping or single aortic cross-clamping approaches, depending on surgeon's preference and patient's anatomy. Air removal maneuvers are routinely used after intracardiac work and include Trendelenburg positioning, air aspiration, and venting from the proximal aorta with or without echocardiographic guidance.

Differences in continuous variables between groups experiencing and not experiencing stroke were tested for significance using one-way analysis of variance and Student's t test. Significance of categorical variables was tested using Fisher's exact test. In all cases the specific p values are stated.

Results

The mean age of the 34 patients studied was 67 ± 15 years and included 6 women and 28 men. Subjects were imaged in the week before and at 6 ± 2 days after surgery, imaging being delayed because of medical instability, presence of pacemaker or temporary pacing wires, and magnet availability. New cerebral ischemic lesions were evident on DWI in 6 of 34 patients (18%). New lesions were clinically "silent" in 4 of 6 or 67% of these patients. In a single patient, clinical evidence of stroke occurred in the absence of a lesion on DWI or fluid-attenuated inversion recovery images.

Table 1 demonstrates the relative frequencies and significance levels of the tested variables. Even in this limited study, WML severity trended toward predicting new postoperative ischemic lesions ($p = 0.055$).

The occurrence of new ischemic lesions by surgical procedure is shown in Table 2. New ischemic lesions occurred only in procedures that included replacement of the aortic valve, with none after CABG alone or after any procedure involving mitral valve repair or replacement. The primary diagnosis in 5 of 6 of these patients experiencing new ischemic lesions was severe calcific aortic stenosis within a three-cusp valve. In a single

Table 3. Ischemic Lesions—Preoperative and Postoperative Lesion Characterization

Patient No.	Procedure	WML Grade	No. of Postoperative Lesions	Lesion Sizes (mm) and Location	Clinical Stroke
1	AVR/Root	3	2	8, 3 [R. corona radiata]	yes
2	AVR	4	1	2 [R. precentral gyrus]	no
3	AVR/CABG	4	4	35 [L. occipital], 4 [R. cerebellum], 4 [R. centrum semiovale], 4 [R. caudate]	yes
4	AVR	3	8	9 [L. corona radiata], 4 [R. frontal], 4 [L. frontal], 4 [L. caudate], 4 [R. centrum semiovale]	no
5	AVR/CABG	1	2	12 [L. centrum semiovale], 4 [R. medial parasaggital parietal lobe]	no
6	AVR/CABG	1	1	2 [L. cerebellum]	no

AVR = aortic valve replacement; CABG = coronary artery bypass grafting; WML Grade = preoperative small vessel ischemic disease, 1—none, 2—mild, 3— moderate, 4—severe.

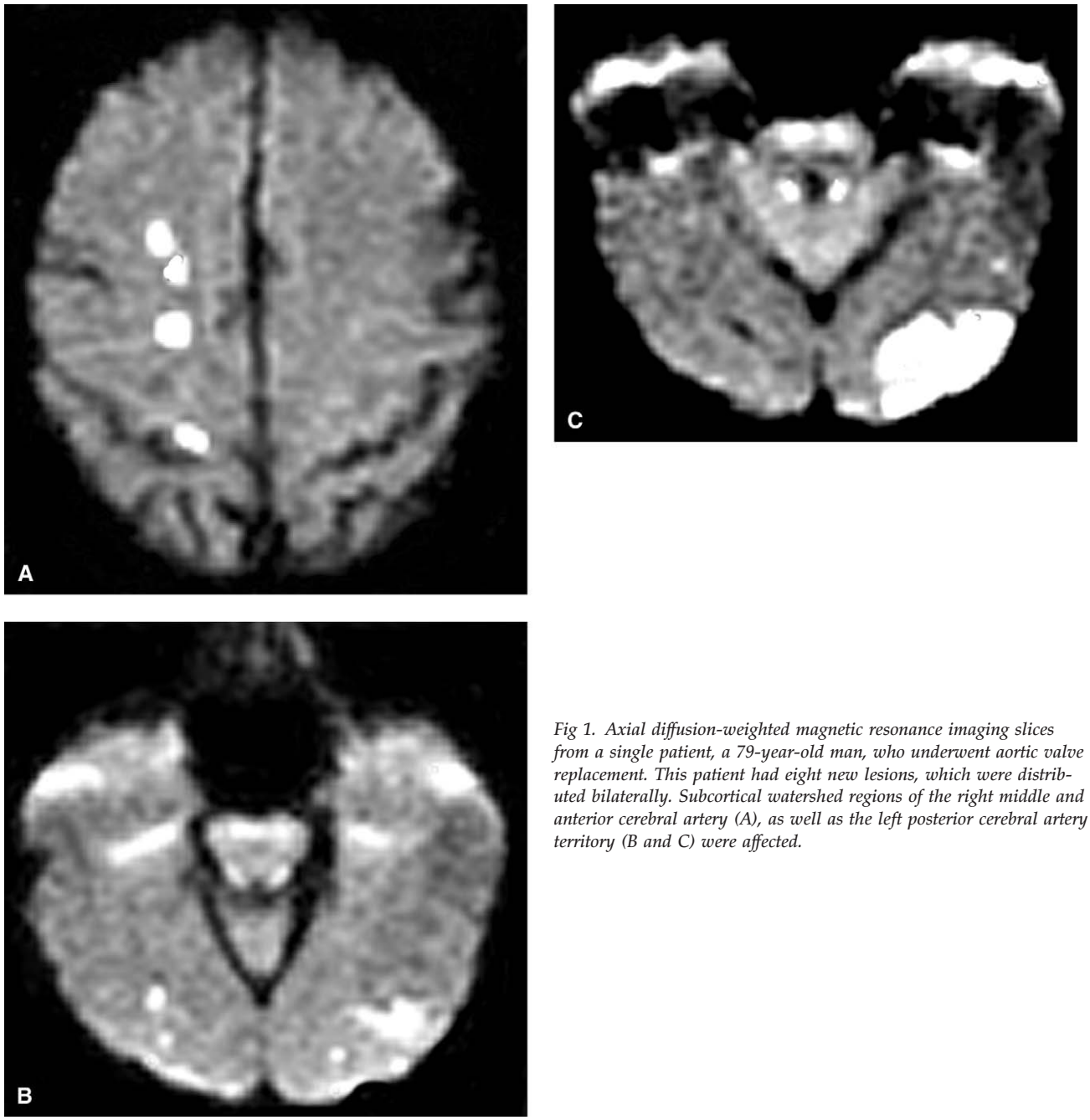

Fig 1. Axial diffusion-weighted magnetic resonance imaging slices from a single patient, a 79-year-old man, who underwent aortic valve replacement. This patient had eight new lesions, which were distributed bilaterally. Subcortical watershed regions of the right middle and anterior cerebral artery (A), as well as the left posterior cerebral artery territory (B and C) were affected.

patient the diagnosis was severe aortic insufficiency within a bicuspid aortic valve. In all cases the valve was judged by echocardiography to be severely calcified.

Table 3 summarizes the lesion characteristics for the 6 patients in whom they occurred. Among these individuals, the number of new lesions averaged 3 ± 3. Lesion size averaged less than 10 mm with a maximum diameter of 35 mm. The occurrence of clinical stroke did correlate to some extent with lesion size, as stroke was identified in patients 1 and 3, who had two of the larger lesions at 8 mm and 35 mm respectively. Patient 4 experienced the greatest number of new ischemic lesions, yet was not diagnosed with a stroke. Figure 1 depicts multiple lesions in a single individual after AVR.

The vascular distribution of new cerebral ischemic lesions is seen in Table 4. Infarctions occurred only slightly more frequently within the right hemisphere (right, 11; left, 7), with 90% occurring supratentorially, often in the watershed regions of the anterior cerebral artery and middle cerebral artery territories. Less often, infarctions occurred in defined anterior cerebral artery, middle cerebral artery, and posterior cerebral artery territories. Infarctions greater than 1 cm oc-

Table 4. Lesion Frequency by Vascular Region

	Hemisphere	
Vascular Region	Right	Left
ACA	2 (11%)	1 (6%)
MCA	1 (6%)	0 (0%)
PCA	0 (0%)	1 (6%)
Watershed	7 (39%)	4 (22%)
PICA	1 (6%)	1 (6%)
Totals	11/18 (61%)	7/18 (39%)

ACA = anterior cerebral artery; MCA = middle cerebral artery; PCA = posterior cerebral artery; PICA = posterior inferior cerebral artery.

curred only on the left side. In 50% of patients the lesions were bilateral.

Transesophageal echocardiographic data available for evaluation were limited to 21 of 34 patients, and therefore only a few generalizations can be made as to the importance of aortic atheroma in contributing to postoperative lesions. These results are summarized in Table 5. Ejection fraction was not different between those who did (60 ± 5%) and did not (55 ± 10%) exhibit new ischemic lesions. A patent foramen ovale was identified in 3 of 28 patients (11%) who did not and in 1 of 6 (17%) of those who did experience new ischemic lesions.

Comment

Diffusion-weighted magnetic resonance imaging sequences are sensitized to detect fine differences in the rate of water movement within the brain. Ischemia rapidly results in cytotoxic edema, and the decrease in the rate of water movement is identified within minutes to hours after the event with DWI techniques, resulting in better temporal sensitivity and specificity than computed tomography [21] and conventional MRI [22]. Few studies focusing on stroke after cardiac surgery have used this modality. Restrepo and colleagues [23] reported that 4 of 13 or 31% of patients presenting for CABG, most of whom were considered to be at high risk of stroke, evidenced new ischemic lesions on DWI, and in most cases the lesions were multiple. Only 1 of 13 patients diagnosed with a new ischemic lesion was diagnosed clinically with stroke. Stolz and coworkers [5] reported a series of 37 patients who underwent AVR and reported a 38% incidence of new ischemic lesion on DWI, most of which were also multiple, yet again only 20% of which were associated with clinical stroke. The imaging findings of Stolz and coworkers [5] and Knipp and colleagues [24] mirror ours in patients undergoing AVR, whereas our CABG population did not incur the frequency of new lesions as reported by Restrepo and associates (31%) [23], Vanninen and colleagues (20%) [25], or Bendszus and associates (26%) [26]. Knipp and coworkers [24] have recently published a limited report in which they reported no association between silent postoperative lesions and early or 4-month neurocognitive function.

The slight right-sided predilection for the occurrence of new lesions that we found was also reported by Restrepo and associates [23] and Knipp and colleagues [24]. Barbut and coworkers [27] have reported a high percentage of lesions occurring in the posterior circulation, yet Stolz and associates [5] reported a nearly equal distribution between the anterior and posterior circulations. Thus, there is no clear preference for vascular territory in stroke after cardiac surgery.

The frequency of the occurrence of lesions in our study in watershed regions is important. There exists considerable disagreement as to whether watershed ischemic lesions are primarily attributable to hemodynamic or embolic etiologies, or both [28]. Likosky and coworkers [8] estimate that only 10% of strokes after cardiac surgery are of hemodynamic origin. Attributing stroke to an embolic or hemodynamic process is obviously not straightforward. Although we cannot know the cause with certainty, insight from this study and several other published works is helpful in this regard. We have found in the current study that the preexisting WML burden trended toward predicting silent stroke after surgery (Table 1). Bendszus and colleagues [26] also found this relationship, and Goto and associates [19] reported that preexisting WMLs are also an important predictor of postoperative stroke.

White matter lesion burden is thought by many to reflect the extent of small vessel ischemic disease [16] and occurs in regions with severe hemodynamic impairment [29]. Caplan and Hennerici [30] hypothesized that although emboli may distribute somewhat randomly, small emboli may lodge in regions with low flow, unable to wash them out.

Support for Caplan and Hennerici's hypothesis can be found in both animal and human studies. Animal studies have demonstrated that for a given embolic load, preexisting hemodynamic impairment markedly worsens the insult [31]. Conversely, in humans after cardiac surgery, Hupperts and associates [32] did not find that hemodynamic compromise regionally predicted stroke, but outside of the surgical arena, regional hemodynamic compromise, as evidenced by an increase in oxygen extraction, has proven to be a powerful predictor of future stroke [33]. Yet it is not regional hemodynamic

Table 5. Transesophageal Evaluation of Aortic Atheromatous Disease

Grade	New Ischemic Lesions (4 patients; n = 16 segments)	No New Ischemic Lesions (17 patients; n = 64 segments)
I	7/16 (44%)	30/64 (47%)
II	7/16 (44%)	23/64 (36%)
III	1/16 (6%)	6/64 (9%)
IV	0/16 (0%)	3/64 (5%)
V	1/16 (6%)	2/64 (3%)

Grade I = no or minimal intimal thickening; Grade II = extensive intimal thickening; Grade III = sessile atheroma < 5 mm; Grade IV = sessile atheroma ≥ 5 mm; and Grade V = any mobile component.

compromise alone that best predicts stroke recurrence. Malloy and Markus [34] and Markus and MacKinnon [35] have documented that it is actually the occurrence of silent emboli in patients with hemodynamic impairment that best predicts impending stroke. Thus, it is likely, as Deredyn and colleagues [36, 37] further suggest, that an important synergy exists between hemodynamic failure and embolic processes, and both may conspire to yield the multiple infarctions seen in our population.

The discrepancy between the incidence of MRI-detected ischemic lesions and the incidence of stroke reported in the current and two previous studies [5, 23] also deserves comment. Each year in the United States approximately 800,000 patients present with clinical stroke, whereas the yearly new occurrence of first-ever silent stroke (imaging evidence only) is estimated to be as high as 11 million [38]. Silent strokes therefore are far more common than clinically detected strokes in the general population, as well as in the surgical domain. In patients undergoing AVR, several reports indicate that the rate of stroke approaches 10% [5, 6], yet there are reports that the rate is as low as 1% to 2% [39]. This is a wide range, and it is possible that improved surveillance may improve sensitivity and consistency in detecting and reporting stroke.

Calcific aortic stenosis is the leading valvular disease in the United States, occurring in 2% of those older than 65 years and 4% older than 85 years of age [40]. The number of patients with this diagnosis requiring valve replacement is growing rapidly with the aging of our population. Aortic stenosis is now recognized as related to the same inflammatory processes associated with systemic atherosclerosis [41]. The surgical population requiring AVR, because of the systemic nature of atherosclerotic disease to include intracranial small vessel disease, may be at particular risk for POCD [19].

In conclusion, silent and multiple cerebral ischemic events occur frequently after AVR for calcific aortic valve degeneration, even in the absence of significant aortic disease. Preexisting WMLs trended toward predicting the occurrence of new ischemic lesions.

Diffusion-weighted MRI, because of its sensitivity in detecting ischemic cerebral embolic processes related to cardiac surgery, only a fraction of which actually lead to stroke, may be valuable as a surrogate marker of stroke [42]. Given the size of this cohort and the sensitivity of DWI in detecting ischemic events, there may be unique, cost-efficient opportunities in this subgroup of cardiac surgical patients to test neuroprotective strategies in population samples of manageable size. Lastly, the potential role of multiple infarctions after cardiac surgery in vascular cognitive impairment [43], an acceleration toward vascular dementia and Alzheimer's disease [12] in the long-term, warrants further investigation.

We wish to acknowledge the support of grants from the Society for Cardiovascular Anesthesiologists and the Foundation for Anesthesia Education and Research. We wish to also acknowledge the assistance of John Murphy, Research Coordinator, in the conduct of this project.

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