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EDITORIAL COMMENT

Post-Coronary Artery Bypass Grafting Stroke

Where Is It Coming From?*

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In this issue of the *Journal*, Lee et al. (1) report findings from 1,367 consecutive cases of coronary artery bypass grafting (CABG) performed between 2004 and 2007 at the Asan Medical Center in Seoul, South Korea, all of whom underwent pre-operative magnetic resonance angiography (MRA) of the carotid and cerebral arteries as part of a research protocol. A total of 33 post-operative strokes were detected, of which 15, or approximately one-half, were detected in the first 24 h. Of the 33 strokes, 15 were considered to be from atherosclerosis in the cerebral and/or carotid circulation; the other 18 strokes were classified as originating from other sources. Lee et al. (1) categorized the findings on the pre-operative MRA studies as showing significant (≥50% stenosis) in: 1) the extracranial carotid circulation; 2) the extracranial cerebral circulation; 3) the intracranial cerebral circulation; or 4) either the extracranial or intracranial cerebral circulation or both. The main conclusion reached by these authors is that atherosclerosis in the cerebral circulation, not extracranial carotid atherosclerosis, was the most frequent culprit for

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the post-CABG strokes in this series. Two ways of examining the data support this conclusion. First, the authors compared the proportions of those found pre-operatively to have significant atherosclerosis in each of these areas of the circulation who had post-operative strokes (Table 3 in Lee et al. [1]) versus those who did not. There was no significant difference in this proportion for extracranial carotid disease, whereas there were significant differences for the other 3 categories of MRA-detected atherosclerosis, namely, in the cerebral circulation. Second, it is possible to see from examination of the Online Tables in Lee et al. (1) that of the 15 stroke patients with atherosclerotic sources detected on MRA, most had significant disease in >1 of the categories. Of the 15 patients, 7 had significant extracranial carotid atherosclerosis, but all had either significant extracranial or significant intracranial cerebral atherosclerosis, and all but 1 had significant intracranial cerebral atherosclerosis. None of these 15 patients had significant extracranial carotid atherosclerosis alone. Based on correlation with post-stroke brain imaging, the authors believe that only 3 of these 15 atherosclerotic strokes could be accounted for by extracranial carotid disease alone. Comparison of this paper with 2 earlier reports of large case series of post-CABG stroke indicate areas where the paper by Lee et al. (1) is both consistent with previous observations and adds to what is known.

In 2003, Likosky et al. (2) reported a case series of 388 patients from the New England Cardiovascular Disease Study Group with a diagnosis of stroke after isolated CABG surgery. These investigators used data from neurological examinations and brain imaging studies to characterize the strokes, and they concluded that the sources were predominantly embolic. Consistent with the report by Lee et al. (1), nearly one-half (41.7%) occurred on the first post-operative day. Pre-operative cardiac and vascular imaging data were not systematically obtained or reported. Thus, the sources of the embolic stroke were not classified.

In 2009, Li et al. (3) reported a case series of 4,335 patients undergoing isolated CABG surgery, aortic valve replacement, or both, over a 5-year period in the Lehigh Valley Hospital and Health Network in Pennsylvania. Patients undergoing urgent surgery were excluded from the study. Post-operative stroke was detected in 76 patients (1.8%). Most (90.9%) underwent pre-operative carotid ultrasound imaging, and those with clinically-diagnosed stroke underwent post-operative brain imaging. Of the 76 patients with stroke, all had pre-operative carotid ultrasound imaging performed. Of these, 18 patients (23.7%) had significant carotid stenosis, but in 14 of these 18, the authors found that the stroke occurred outside the territory of the diseased carotid artery. These authors concluded that a very small number of embolic strokes originated in significant pre-operatively detected ipsilateral carotid atherosclerosis. The conclusions reached by an editorialist were that prophylactic carotid stenting or endarterectomy in asymptomatic patients who have significant carotid atherosclerosis is likely to put the patient at risk without much prospect of benefit, that pre-CABG carotid imaging of asymptomatic patients is unlikely to be beneficial, and that meticulous perioperative attention to known embolic sources, in particular the aorta and the heart, is likely to have the greatest prospect of reducing stroke risk in this setting (4).

No previous large case series obtained pre-operative MRA imaging of the extracranial carotid arteries and the extracranial and intracranial arteries in patients before they

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underwent CABG. The report by Lee et al. (1) is, therefore, the first to be able to correlate these MRA findings with the brain imaging distribution of infarcts in post-CABG stroke patients. The findings of Lee et al. (1) are consistent with those of these previous reports in that the rate of post-CABG stroke is in the same range (33 strokes in 1,367 patients, 2.4%) and that approximately one-half of the strokes occurred in the first 24 h. The underlying level of risk for stroke was not identical in these papers. For example, it is not stated in the paper by Lee et al. (1) how many of the CABG procedures were urgent/emergent versus elective and how many involved valve replacement as well as CABG. Both nonelective status and combined cardiac procedures are associated with higher stroke risk (5).

Lee et al. (1) found on brain imaging that approximately one-half of the infarcts were in the distribution of lesions detected on pre-operative MRA, but that only 1 corresponded to atherosclerosis in the ipsilateral external carotid artery. The infarcts were in the distribution of MRA-detected atherosclerosis in extra- and intracranial cerebral arteries. The implication is that these lesions are directly involved in the stroke mechanism. The other one-half of the strokes were presumed to be embolic from sources in the aorta and/or heart. Atrial fibrillation was present pre-operatively in 4 of these 18 patients.

Some aspects of the study by Lee et al. (1) should be interpreted with caution. Strokes occurring in the territory of a vessel with >50% stenosis were considered as secondary to it and therefore classified as atherosclerotic. This circumstance may have artifactually inflated the proportion of atherosclerotic strokes (e.g., a stroke from transient atrial fibrillation and embolization to such territories would have been considered by definition atherosclerotic instead of cardioembolic). In addition, although Lee et al. (1) mention aortic arch atherosclerosis as possibly implicated in otherwise unexplained strokes with apparent embolic features, they did not report on the presence of aortic arch atherosclerosis, a major offender in post-CABG stroke. In a multicenter study of 2,108 patients undergoing CABG, Roach et al. (6) reported that age, history of neurologic disease, and the presence of proximal aortic atherosclerosis were the strongest predictors of the most severe post-operative outcomes (fatal and nonfatal stroke) among a host of pre-operative and intraoperative variables. In that study, however, the presence of intracranial atherosclerosis was not investigated. Lee et al. (1) also did not report separate data on patients undergoing traditional CABG as opposed to off-pump CABG, a circumstance that precludes the evaluation of the effect of atherosclerosis of the cerebral arteries on the stroke risk when different levels of manipulation of the aorta are considered. In a study of 7,272 patients undergoing isolated CABG, Kapetanakis et al. (7) reported an 80% reduction in perioperative strokes with off-pump CABG compared with traditional surgical techniques that involved full aortic clamp application, as well as a 70% risk reduction when a modified (tangential) clamp application was used.

Lee et al. (1) describe an atherosclerosis index derived from the MRA findings. Not surprisingly, this index, which measures the extent of atherosclerosis, was associated with risk of stroke. However, the clinical usefulness of this index may be questioned. The authors report that for a cut point of ≥2, this score has a sensitivity of 0.82 and a specificity of 0.54; the area under the receiver-operating characteristic curve was 0.70 (Online Tables in Lee et al. [1]). These operating characteristics are reported from a derivation dataset only. Thus, the predictive validity of the index is not established. Even if it were, the clinical value of the index is not clear relative to other methods for classifying stroke risk in cardiac surgery (5).

Do the main findings of the paper by Lee et al. (1) appear valid and applicable? The sample is drawn from a single hospital in South Korea. To the extent that patients in South Korea differ in pattern or extent of atherosclerosis from other populations, there may be differences. The higher prevalence of intracranial atherosclerosis in the Asian population is well documented (8). The very high prevalence of hypercholesterolemia (Table 4 in Lee et al. [1]) suggests that the biology of atherosclerosis is not very different from Western populations. Surgical and anesthesiology technique may have differed from other settings, an intrinsic limitation of a case series from a single institution. The case series itself excluded a small number of patients (approximately 12%) who underwent carotid and cerebral MRA but did not undergo CABG, in some cases possibly because of extensive atherosclerosis demonstrated on MRA. As the authors note, this exclusion could have reduced the rate of post-CABG stroke.

In summary, this paper adds new information about an important and feared complication of CABG surgery. The authors provide suggestive evidence consistent with the hypothesis that atherosclerosis in extracranial and intracranial cerebral arteries participate in post-CABG stroke. The apparently lower stroke risk from carotid atherosclerosis in this case series may be at least in part the result of the pre-operative stenting of the 17 patients with extensive carotid atherosclerosis and/or the decision to forego CABG in some patients found to have extensive atherosclerosis on pre-operative MRA. It is also possible that the emboli causing these strokes originated in the aorta or heart and that these patients had coexistent but not causally implicated atherosclerosis on MRA in the cerebral arteries. Additional studies will be useful to confirm the findings.

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