Determination of Etiologic Mechanisms of Strokes Secondary to Coronary Artery Bypass Graft Surgery

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Background and Purpose—Current research focused on stroke in the setting of coronary artery bypass graft (CABG) surgery has missed important opportunities for additional understanding by failing to consider the range of different stroke mechanisms. We developed and implemented a classification system to identify the distribution and timing of stroke subtypes.

Methods—We conducted a regional study of 388 patients with the diagnosis of stroke after isolated CABG surgery in northern New England from 1992 to 2000. Data were collected on patient and disease characteristics, intraoperative and postoperative care, and outcomes. Stroke etiology was classified into 1 of the following: hemorrhage, thromboembolic (embolic, thrombotic, lacunar), hypoperfusion, other (subtype not listed above), multiple ($\geq$2 competing mechanisms), or unclassified (unknown mechanism). The reliability of the classification system was determined by percent agreement and κ statistics.

Results—Embolic strokes accounted for 62.1% of strokes, followed by multiple etiologies (10.1%), hypoperfusion (8.8%), lacunar (3.1%), thrombotic (1.0%), and hemorrhage (1.0%). There were 54 strokes with unknown etiology (13.9%). There were no strokes classified as "other." Nearly 45% (105/235) of the embolic and 56% (18/32) of hypoperfusion strokes occurred within the first postoperative day.

Conclusions—We used a locally developed classification system to determine the etiologic mechanism of 388 strokes secondary to CABG surgery. The principal etiologic mechanism was embolic, followed by stroke having multiple mechanisms and hypoperfusion. Regardless of mechanism, strokes predominantly occurred within the first postoperative day. **(*Stroke*. 2003;34:2830-2834.)**

Key Words: cerebral infarction ■ coronary artery bypass ■ embolism

Stroke is a devastating complication of coronary artery bypass graft (CABG) surgery, with a reported incidence ranging from 1.3% to 4.3%.[1–7] Research focused on reducing the incidence of stroke has largely centered on identifying preoperative risk factors, with stroke as the outcome of interest. While contributing useful insights, this work has missed important opportunities for additional understanding by failing to consider different stroke mechanisms.

There are 2 principal etiologic mechanisms for strokes. Ischemic strokes are caused by inadequate perfusion of a vascular bed, leading to ischemia and cell death. There are 3 different mechanisms of ischemia: embolism from the heart, aorta, or proximal arteries; thrombosis of large or small extracranial or intracranial arteries; and systemic hypoperfusion. Hemorrhagic strokes originate either from primary hematomas most often related to uncontrolled hypertension or from the reperfusion of a previously infarcted area.[8] The different types of stroke presumably reflect different risk factors. While research efforts have focused principally on identifying preoperative risk factors, not much work has focused on identifying and understanding etiology. Without this information, researchers are unable to understand how best to reduce the incidence of stroke in this population. A classification system based on etiologic mechanism and an understanding of pathophysiology would help to accomplish this objective.

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We conducted a regional medical record review of all patients diagnosed with stroke after undergoing isolated CABG surgery in northern New England. We developed and implemented an etiologic stroke classification system to identify the distribution and timing of stroke subtypes.

Methods

Setting

This study takes advantage of the work conducted by the Northern New England Cardiovascular Disease Study Group (NNECDSG), a voluntary research consortium composed of clinicians, research scientists, and hospital administrators at the 7 regional institutions that are sole providers of coronary revascularization in northern New England and 1 Massachusetts-based institution. Since its inception in 1987, the NNECDSG has maintained prospective registries on all patients undergoing CABG, heart valve replacement, and percutaneous coronary interventions. The group fosters continuous improvement in the quality of care for patients undergoing these procedures through the pooling of process and outcomes data and the timely feedback of these data back to clinicians through group meetings and regional, center, and surgeon-specific reports.[9]

Study Design

This is a regional retrospective study of 388 patients with the diagnosis of stroke secondary to isolated CABG surgery at 5 NNECDSG medical centers between April 1992 and June 2000.

Classification System

The NNECDSG classification system divided stroke into 2 principal mechanisms: hemorrhage and ischemia. Definitions for each stroke mechanism were developed by consensus and based on pathophysiology (Appendix).

In a hemorrhagic stroke, blood accumulates outside the vasculature, leading to increases in cerebral pressure and ultimately cellular death.

We further divided ischemic strokes into 2 subcategories: thromboembolism (embolic or in situ clot) and hypoperfusion. Patients were likewise classified into 1 of 3 types of thromboembolism (embolic, lacunar, or thrombotic). Embolic thromboembolism is hereafter called embolic. There are 2 predominant causes of embolic strokes, namely, cardiac and noncardiac. Cardiac emboli may originate either from the atrium, in cases of atrial fibrillation, or from the ventricle, in cases of recent myocardial infarction or left ventricular aneurysm. Noncardiac emboli may originate from atherosclerotic plaque from the bifurcation of the common carotid artery, the aortic arch, and/or the ascending aorta.[10–14] Embolic strokes characteristically cause multiple infarcts in multiple territories and predominantly occur in the distribution of the middle cerebral artery.

Lacunar thromboembolism (hereafter called lacunar) was defined as ischemic stroke caused by hypertension-induced arteriosclerosis and stenosis of the penetrating arteries in the deep cerebral white matter.

Thromboembolic thrombotic (hereafter called thrombotic) strokes may have 1 of several mechanisms, relating either to stenosis of vessels or plaque rupture. First, patients may have a thrombotic event due to atherosclerosis or narrowing of blood vessels secondary to cholesterol buildup, smoking, or chronic high blood pressure. Second, patients with a variety of hematologic abnormalities, such as elevated red blood cell or platelet counts, have an increased risk of developing a thrombotic stroke. Thrombotic plaques may lyse and become sources of emboli. Surgery causes an activation of acute-phase reactants and enhances the development of thrombi engrafted on stenotic arteries.

Hypoperfusion (also called watershed) strokes, either unilateral or bilateral, arise from a combination of extracranial stenoses and systemic hypotension. Research suggests that unilateral watershed strokes are caused primarily by emboli, whereas the bilateral type is usually due to systemic hypotension.[15] On CT or MRI, watershed strokes appear as an area of hypodensity between the middle and anterior cerebral artery or the middle and posterior cerebral artery.

Strokes caused by ≥2 competing mechanisms were classified as having multiple mechanisms. Strokes secondary to an unknown mechanism (eg, insufficient information in the medical record) were categorized as unclassified. Strokes caused by an identified mechanism not listed above (eg, intravascular abnormality such as coagulopathy) were classified as "other."

Abstraction Process

Institutional review board approval was achieved at each participating medical center.

Nurse abstractors collected information regarding preoperative, intraoperative, and postoperative care and course not previously collected through our regional registries. Abstractors photocopied the discharge summary, operative note, neurology consultation reports, radiology reports, death certificates, and autopsy records when applicable or available. The abstraction form together with these reports and medical record information will hereafter be referred to as the abstraction tools. All patient, clinician, and hospital identifiers were removed to comply with privacy requirements and to eliminate potential biases in the classification process.

Classification Process

The etiologic mechanism was determined through a 2-stage process. If the neurologist and radiologist agreed on the principal mechanism, the stroke was classified accordingly. In those cases in which either (1) there was only a neurological consultation or radiological report or (2) the neurologist's and radiologist's opinions were discordant, the patient's abstraction tools were submitted to 1 of 3 endpoint committees.

There were 3 endpoint committees, each consisting of 4 individuals. Two of these 4 were cardiothoracic surgeons, while the other 2 were neurologists, anesthesiologists, or neuroradiologists. Strokes were randomized to 1 of the 3 committees. Respective abstraction tools were submitted to each committee member 1 week in advance of all conference calls. Each week, 1 member of each committee was appointed as the primary reviewer on at least 1 case, while other members were appointed as secondary reviewers. Classification of the stroke was determined and disagreements were resolved through consensus.

Interrater Reliability

We tested the reliability of the classification system through the random resubmission of 72 abstraction tools (19%) to a second endpoint committee that was unaware of the first committee's findings. If the second committee agreed with the classification of the first committee, the stroke was classified accordingly. However, if the second committee disagreed with the first committee's findings, the stroke was classified as "unclassified."

Statistical Analysis

The interrater reliability of the classification process was measured with the use of κ statistics.[16] The κ statistic, a measure of agreement between ≥2 reviewers, is sensitive to values of 0 in cells, and therefore the classification system was collapsed into 2 categories (embolic and nonembolic) because of the dominance of the embolic etiology. The distribution and timing of symptom onset (from the day of surgery) was determined.

Results

The κ statistic was 0.43, suggesting moderate agreement between committee classifications.[16,17]

Figure 1 summarizes the distribution of stroke mechanism. Embolism accounted for 62.1% of the strokes. Of the embolic strokes, 19.9% were classified as having an unknown source of embolus. There were no strokes classified as "other."

Figure 2 displays the timing from CABG surgery to the presentation of stroke. Most strokes presented on the first postoperative day (41.7%); an additional 20.4% occurred on the second postoperative day.

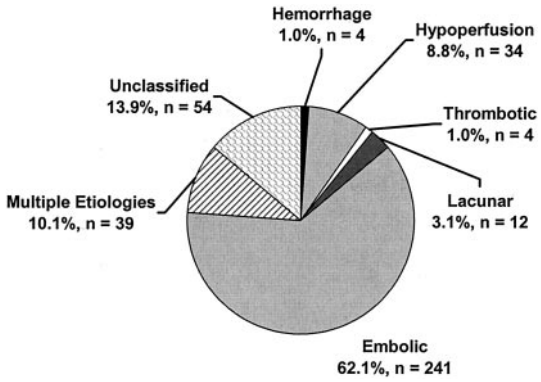

Figure 1. Classification of stroke mechanism.

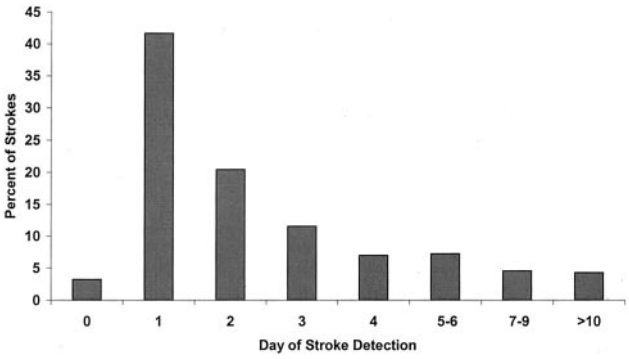

Figure 2. Days from CABG surgery to stroke detection.

We had information concerning timing of stroke onset for 95.9% of patients (372/388). Day of stroke detection did not differ appreciably by stroke subtype ($P=0.15$) (Figure 3). Stroke mechanism was grouped into 3 categories because of insufficient sample size in some categories: embolic, hypoperfusion, and other etiologies (hemorrhage, lacunar, thrombotic, unclassified, and multiple etiologies). There were both early (44.7%) and late (37.9%) incidences of embolic strokes, but this did not reach statistical significance.

Discussion

We used a locally developed classification system to determine the etiologic mechanism of 388 strokes secondary to CABG surgery. The classification system performed moderately well, as determined by its reliability across endpoint committees. By using information regarding the patient experience as identified in the medical record, we were able to classify >75% of the 388 strokes occurring in the northern New England region from 1992 to 2000 into an etiologic category. Our distribution of stroke subtypes is similar to other published studies, namely, the predominance of the embolic mechanism followed by hypoperfusion. Most strokes in our study regardless of mechanism were detected on the first postoperative day.

This study reflects our experience over 8 years tracking major neurological deficits. The dataset, although large, was collected from 5 medical centers in a single region of the United States. It is likely that our findings are representative of the experience at other medical centers around the country, as the NNECDSG definition for stroke is quite similar to the one used by the Society for Thoracic Surgeons in their national registry.[18] We found that a minority (21/409; 5.1%) of those patients originally classified as having a stroke did not meet our registry definition, either because of nonfocal symptoms (5/21) or apparent data entry errors (7/21). These patients were not included in our analysis. We believe that any such misclassification would be randomly distributed across all patients and would thus sway any effect toward the null hypothesis. The same argument may be applied to the potential misclassification of etiologic mechanism, although we were pleased with the results of the interrater reliability test.

We encountered 5 limitations in the data collected for this study, which reflect both record keeping by clinicians as well as the current state of the medical record system. These limitations were not unique to 1 surgeon or medical center. First, many operative notes lacked details concerning the extent and location of aortic and carotid artery disease. Transesophageal echocardiography and epiaortic scanning were not routinely performed and recorded in our region, likely resulting in an underestimation of the true contribution of emboli to the overall classification system. Second, pa-

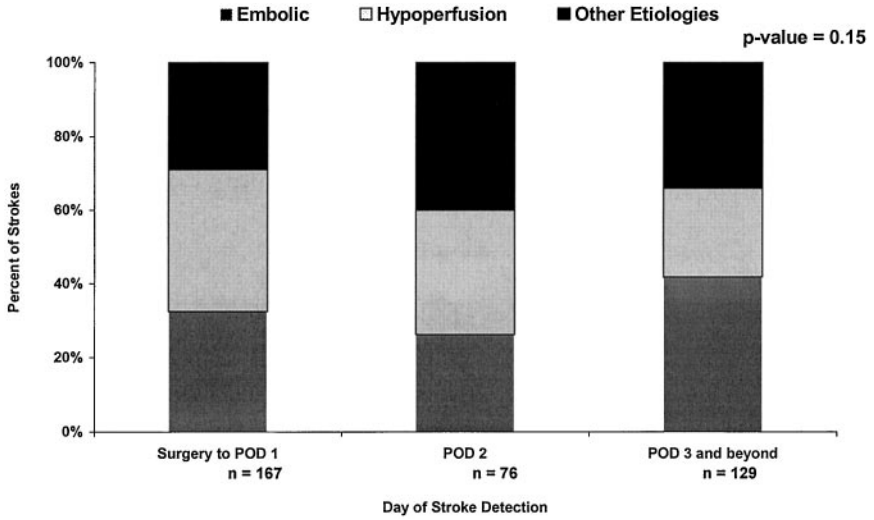

Figure 3. Day of stroke detection by stroke mechanism. POD indicates postoperative day.

tients often did not have a detailed neurological evaluation, which might have provided further understanding of both the mechanism and extent of nervous system involvement. Third, radiological reports often did not describe in sufficient detail the involved cerebral circulation, which might account for a portion of the unclassified strokes. Fourth, patients presenting with neurological symptoms often received a CT scan to rule out a hemorrhage. However, work done by Bamford and colleagues[19] has shown that CT scans in the acute phase show abnormalities in only 50% of cases. Fifth, while most patients usually received a postoperative brain imaging study (often negative as a result of the timing of the study in relation to the presentation of symptoms or its insensitivity in detecting ischemia), referring physicians often ordered or suggested that a patient receive a follow-up study, which was often not completed. Unfortunately, without a second CT study, one cannot know whether the patient's symptoms correlate with a lesion or whether the clinical presentation is due to delirium or the effects of anesthesia.

Despite these limitations, we are confident that our findings are in agreement with the peer-reviewed literature. We have no reason to believe that these limitations are unique to our region of the country or that they severely hampered our ability to determine the etiologic mechanism.

Evidence regarding the source, extent, and effects of embolic load during and after surgery comes from several sources. Clinicians use a variety of diagnostic tools to measure embolic load: transcranial Doppler ultrasonography, echocardiography, and radiography.[20] The number of detectable emboli is attributed in part to the type and timing of the imaging technique used because emboli come from various sources and in a multitude of sizes and shapes.[21] Barbut and Caplan[21] reported that the number of emboli was unevenly distributed among the different stages of surgery. Clamping and unclamping of the aortic cross clamp has accounted for >60% of the total number of emboli in some studies, while flurries have been detected during aortic cannulation and during inception and termination of cardiopulmonary bypass. Since the number of emboli detected at the onset and release of clamping has been correlated with age and transesophageal echocardiography–determined atheroma severity, one may infer that the majority of the emboli are atheromatous in nature. Baker found that the highest embolic load, using transcranial Doppler, occurred during the onset of the cross clamp and that the rate of emboli was highest at the initiation of cardiopulmonary bypass.[22] In recent years, the use of off-pump revascularization procedures, which do not utilize aortic cross clamps or extracorporeal circulation, has been promoted as a mechanism to reduce the risk of embolic strokes.[23] We have previously reported results from our regional experience with off-pump revascularization procedures that revealed a nonsignificant protective effect for the procedure versus traditional CABG with regard to stroke risk (1.3% versus 1.8%; $P=0.221$). In the present study 3.6% of patients with strokes had an off-pump revascularization procedure. As such, we were not powered to detect differences in etiologic mechanism for patients undergoing on- versus off-pump procedures.

Regional cerebral hypoperfusion may occur in patients with chronic hypertension, diabetes, or senile atherosclerotic disease. Chronic hypertension may result in narrowing of penetrating arteries (leading to susceptibility to lacunar stroke in the setting of cerebral hypoperfusion), decreased collateral flow, or reduction in ischemic tolerance through alterations in cerebral autoregulation.[20] Controversy surrounds appropriate levels of mean arterial pressure during and after surgery. Gold et al,[24] in a randomized study of 248 elective CABG patients, found that patients maintained at higher levels of mean arterial pressure (80 to 100 mm Hg) during cardiopulmonary bypass had lower incidence of neurological deficits. Barbut and Caplan,[21] in a series of 100 patients continuously monitored by transcranial Doppler, found a 17% reduction in perfusion from baseline in patients free from neurological deficit compared with 43% for patients with strokes. The number of emboli was lower in those without neurological deficits.

Blossom et al[3] conducted a retrospective study of 3428 patients undergoing CABG. Strokes, based on CT imaging and neurological consultation, were classified as either embolic or hypoperfusion. No operational definitions for stroke subtypes were provided. Of the 46 strokes, 25 (54.3%) were embolic and 21 (45.7%) were hypoperfusion. Sixteen patients (34.8%) had an intraoperative stroke (8 embolic, 8 hypoperfusion), while the remaining 30 patients (65.2%) had a postoperative stroke (17 embolic, 13 hypoperfusion). In our own study we found that 39.4% of patients awoke with symptoms (62.9% embolic, 13.3% hypoperfusion), 46.7% had symptoms after a lucid interval (66.5% embolic, 4.5% hypoperfusion), and 13.8% had unknown time of onset. We found a bimodal distribution of the timing of embolic strokes, suggesting 2 distinct sources of embolism. Early emboli may arise from manipulation of the heart and/or aorta during cross clamping, while the latter may be attributed to postoperative atrial fibrillation.

Dashe et al[25] performed a retrospective study on 1022 consecutive CABG patients over a 2-year period to study the risk of stroke in patients with known carotid disease. Using CT imaging, Dashe et al classified strokes into 1 of 3 categories: embolism, low perfusion, and uncertain cause. Embolic strokes were diagnosed in the presence of known risk factors such as atrial fibrillation or multiple infarcts occurring within different vascular territories. Strokes due to low perfusion were diagnosed according to 3 criteria: presence of systemic hypotension, use of vasopressors or an intra-aortic balloon pump for maintaining blood pressure, or cardiopulmonary arrest before or during stroke onset. Strokes were classified as uncertain if (1) an infarct did not fulfill the criteria for either embolism or low perfusion or (2) infarcts did not have a confirmatory CT scan. If the criteria for both embolism and low perfusion were fulfilled, etiology was classified as multiple.

Dashe et al[25] classified the mechanism of 22 strokes. The distribution of stroke etiologies was as follows: 9 embolic (40.9%), 8 low perfusion (36.4%), and 4 of uncertain cause (18.2%). One stroke (4.5%) had multiple etiologies. No patient had either clinical or radiological evidence of a lacunar stroke. The higher percentage of low-perfusion strokes may be attributed to patient selection since carotid disease is a risk factor predominantly for the development of low cerebral perfusion and emboli.

We conducted a regional study aimed at understanding the etiologic mechanism of strokes secondary to CABG surgery. We used a locally developed classification system to classify 388 patients with the diagnosis of stroke after isolated CABG surgery. Embolic strokes were the predominant mechanism, followed by multiple mechanisms and hypoperfusion. Most strokes occurred on the first postoperative day. The classification system performed moderately well as measured by the κ statistic. This knowledge of the distribution and timing of different stroke mechanisms is a necessary prerequisite for any attempt to reduce its incidence.

This study represents our understanding of the etiologic mechanisms of strokes after CABG surgery based on current clinical practice. A refinement of this understanding would require more detailed and extensive information regarding the extent of aortic atherosclerosis and neurological evaluation in the medical record, widespread use of diagnostic imaging modalities, and other data. Our findings suggest that the greatest opportunity for the reduction in stroke rates may be realized through (1) identification of the association between processes of clinical care and sources of emboli and (2) redesign of clinical care to reduce and prevent their occurrence.

Appendix

Definitions of Stroke Mechanisms

Stroke
New focal neurological deficit that appears and is still at least partially evident >24 hours after its onset, occurring during or after the CABG procedure and established before discharge.

Hemorrhage
Intracranial bleeding that may be isolated or occur in other brain structures.

Thromboembolism

Embolic
Ischemic stroke with 1 of 3 likely sources of thrombus (aortic, cardiac, or carotid) identified by documented dysrhythmia, neurology, and/or imaging.

Lacunar

Ischemic stroke with classification determined by neurology and/or imaging.

Thrombotic

Ischemic stroke without evidence of embolic or lacunar origins.

Hypoperfusion
Stroke due to a mixture of extracranial stenoses and/or systemic hypotension.

Unclassified
Stroke caused by ≥2 competing mechanisms or of unknown etiology.

Other
Stroke caused by an identified mechanism not listed above.

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