Aortic Atherosclerotic Disease and Stroke

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In the 1940s, most strokes were attributed to cerebral vasoconstriction, a mechanism that is not given a great deal of credence today. It was not until the early 1950s that Harvard neurologist C. Miller Fisher1 stressed the importance of carotid artery atherosclerosis as a major cause of cerebral infarction. Later that decade, the importance of atrial fibrillation as a cause of cerebral embolism began to be stressed,2 and the presence of a left atrial thrombus was first seen on angiography in 1965.3 Despite the established importance of these 2 causes of stroke, carotid disease and atrial fibrillation, nearly half of strokes were listed as “of undetermined cause” in a large stroke registry as recently as 1989.4 The 40% of 1273 cerebral infarctions in the Stroke Databank of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) were thought to be cryptogenic (from the Latin crypticus, meaning secret or mysterious). The clinical syndrome in those patients, as well as the angiographic and computed tomographic (CT) findings, could be reclassified as embolic; however, because no source of embolus could be identified, the authors kept these strokes in the undetermined cause category.

In 1990, a third leading cause of embolic stroke was identified on transesophageal echocardiography (TEE), namely severe atherosclerotic plaques in the aortic arch.5 The 3 patients described in that initial report were a 68-year-old woman with dysarthria and an embolus to the foot, a 77-year-old woman with a cerebellar infarction after cardiac catheterization, and a 70-year-old man with staggering, diplopia, and a visual field cut. All 3 had severe plaque in the aortic arch on TEE. In addition, freely mobile projections were seen superimposed on the plaques, making it seem likely that these findings were the reason for the patients’ embolic events. That atherosclerosis of the aorta and arterial emboli are related is not a new concept. In fact, since 1862, pathologists have suggested that “eroded atherosclerotic plaque” may result in embolic arterial occlusions.5–7 However, it required sophisticated imaging technology such as TEE (Figure 1) and later CT and magnetic resonance imaging (MRI) to view these lesions in vivo.

The subject of the risk of aortic arch plaque as seen on TEE has been reviewed several times in the last 15 years.8–10 More recently, the ability to image aortic plaque and its contents has improved significantly through the use of different imaging modalities, and our understanding of the associated clinical syndromes has increased. Although most investiga-

tors feel that aortic atherosclerosis is a leading cause of embolic disease, doubts have been raised.11 All of these issues are discussed in this review.

Definitions

Aortic atherosclerotic lesions have been referred to in several different ways in the medical literature. These include atheromas, protruding atheromas, atherosclerotic debris, and plaque. For the purposes of this review, we define these lesions as plaques. The mobile components to these plaques have been called mobile debris, mobile plaque, and superimposed thrombi. These mobile lesions are most often thrombi. Clinical data show that the plaques with high risk for embolization are those that are ≥4 mm thick. We refer to these lesions as severe plaques. Finally, the term complex plaque has been used in the literature to refer to those plaques that are ≥4 mm thick (called severe here), contain mobile elements (most often thrombi), or both.

Prevalence of Aortic Atherosclerosis

Most studies of aortic plaque include patients who were symptomatic and referred for diagnostic studies. However, the Stroke Prevention: Assessment of Risk in a Community (SPARC) study enrolled patients at random and therefore was not subject to referral bias.11 Of 588 patients having TEE as part of the study (average age, 66.9 years), aortic plaque in any location was present in 43.7%, of which complex plaque (defined as ≥4 mm or mobile) was present in 7.6% of patients. Aortic plaques were present in the ascending aorta in 8.4%, but complex plaques were noted in the ascending aorta in only 0.2%. Plaques were present in the aortic arch in 31%, but complex arch plaques were present in only 2.2%. Finally, descending aortic plaques were seen in 44.9%, and complex plaques in the descending aorta were present in 6.0%. Thus, the number with any or complex aortic plaque on TEE increased from the ascending aorta distally.

It should be noted that this information is true for a relatively elderly population that is homogeneous (white). Half of the patients were male. The prevalence of aortic plaque in other groups not subject to referral bias is not known.

Aortic Atherosclerotic Plaque and the Risk of Stroke

It is important to realize that the prevalence of severe aortic plaque in stroke patients (14% to 21%) is on the same order

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63
of magnitude as that of the other 2 important causes of embolic stroke, carotid artery disease (10% to 13%) and atrial fibrillation (18% to 30%), which were documented in 2 large series of consecutive stroke patients.12,13 Early investigators looked for a risk of embolization in patients with the largest aortic plaques as measured with TEE.8 In this study, patients with aortic plaque thickness ≥5 mm had a significantly higher risk of stroke and peripheral embolization.

The French Aortic Plaque in Stroke (FAPS) group evaluated a large number of patients with varying plaque thickness and found not only that increasing plaque thickness imparted increasing risk but also that the odds ratio (OR) was significantly greater in those with a plaque thickness ≥4 mm.12 The OR for stroke in patients with plaques <1 mm was 1.0 (no increased risk); for 1- to 3.9-mm plaques, it was 3.9; and for plaques ≥4 mm, it was a good deal higher, 13.8. This study also supports causality with respect to arch atheromas and stroke rather than mere association (for which these plaques would just be a marker for generalized atherosclerosis and stroke risk), because the OR for stroke in patients with plaques in the descending aorta (which would not be likely to embolize upstream to the head) was only 1.5 for the largest plaques ≥4 mm (versus an OR of 13.8 for those in the arch).

The risk of stroke in 1 year for patients with severe plaque in the aortic arch on TEE is high: 10% to 12%. This risk was found in 3 independent studies14–17 (Table 1). The risk of all vascular events is even higher, with stroke or peripheral emboli seen in 33% in 1 year in a prospective study.14 This study included patients with previous events (which is also a risk factor for emboli) and those without previous events.

Between 1988 and 2000, a study looked at 1111 patients with severe thoracic aortic plaque on TEE.17 Severe plaque, defined as intimal thickness ≥4 mm, was found in the aortic arch (350 patients, 31%), descending aorta (also 350 patients, 31%), or both (396 patients, 36%). Severe plaques were rarely seen in the ascending aorta (only 10 patients, 1%). All patients were referred for TEE on the basis of clinical indications, and the time of follow-up in this retrospective study averaged 34 months. There were embolic events in 111 patients, which was 21% of the 519 patients for whom follow-up information was available.

### Aortic Plaque and Atherosclerotic Risk Factors

Aortic plaque is an expression of generalized atherosclerosis. As such, it is most often seen in the elderly (the average age of those with ≥4-mm plaque on TEE is 70 years).14 It also is more common in patients with hypertension and hypercholesterolemia and in those who smoke.18 Plaque in the aorta is associated not only with these traditional atherosclerotic risk factors but also with elevated levels of homocysteine,19,20 markers of a thrombotic diatheses (prothrombin and activated protein C resistance),21 and inflammatory markers such as elevated white blood cell count22 and C-reactive protein.23 It also is found to a greater degree in patients with left ventricular hypertrophy.24

Investigating the association between race and aortic plaque, one group found that whites had a significantly higher prevalence of aortic plaque than blacks, even though they had a lower prevalence of hypertension and diabetes (OR, 1.37).25 This unexplained phenomenon was confirmed by a second group.26

### Atherosclerosis in Other Vascular Beds

#### Carotid Artery Disease

Although aortic plaques are independent risk factors for stroke and peripheral emboli, it is not surprising that patients with significant carotid atherosclerosis also have a higher prevalence of aortic arch atherosclerosis than do those without carotid disease and therefore have >1 potential source of embolization to the brain.8,13,27 One retrospective study28 found aortic arch plaques in significantly more stroke and transient ischemic attack patients with carotid stenosis (38%) than in those without carotid stenosis (17%). That study also found that mobile thrombi superimposed on the aortic arch plaques were exclusively found in patients whose carotid stenosis was >80%. Thus, patients with the highest-risk

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**Table 1. Stroke Risk in Patients With Severe Aortic Arch Plaque**

<table>
<thead>
<tr>
<th>Reference Events</th>
<th>Study Type</th>
<th>Follow-Up</th>
<th>Severe Aortic Plaque, n</th>
<th>Brain, %</th>
</tr>
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<tbody>
<tr>
<td>1994 Tunick et al14</td>
<td>Prospective, single center</td>
<td>14 mo</td>
<td>42</td>
<td>12</td>
</tr>
<tr>
<td>1996 FAPS15</td>
<td>Prospective, multicenter</td>
<td>2.4 y</td>
<td>331</td>
<td>24</td>
</tr>
<tr>
<td>1998 SPAF16</td>
<td>Prospective, multicenter, high-risk NVAF</td>
<td>14 mo</td>
<td>134</td>
<td>10</td>
</tr>
<tr>
<td>2002 Tunick et al17</td>
<td>Retrospective, single center</td>
<td>36 mo</td>
<td>519</td>
<td>18</td>
</tr>
</tbody>
</table>

NVAF indicates nonvalvular atrial fibrillation.
carotid lesions also had the highest-risk aortic plaques. Therefore, when one sees a patient with stroke and severe carotid stenosis, it is important to always consider the possibility that the embolic event may have originated in the aortic arch. When the stroke or transient ischemic attack is contralateral to the carotid stenosis or is associated with peripheral emboli, the aorta should always be evaluated. This evaluation should also take place in patients who have neurological events after recovery from a technically successful carotid operation.

**Coronary Artery Disease**

The Framingham study found an association between aortic calcification seen on chest x-ray and the development of coronary artery disease. Aortic plaque seen on TEE has been correlated with a higher prevalence of coronary artery disease and the presence of significant angiographic coronary artery stenosis. In addition, the lack of aortic plaque on TEE has also shown to predict the absence of coronary artery disease. The sensitivity and specificity of the presence of aortic plaque for the prediction of significant coronary stenosis were both 90%. The positive predictive value of plaque detected by TEE was 95%; the negative predictive value was 82%. In addition, CT has shown that the presence of aortic plaque was predictive of obstructive coronary artery disease independently of coronary artery calcification. The sensitivity of aortic plaque for predicting the presence of obstructive coronary artery disease was 89%, and the specificity was 63%. Because a patient without aortic plaque on TEE is less likely to have obstructive coronary artery disease, younger patients without a clinical suspicion of coronary disease who are undergoing open heart surgery to repair congenital defects or acquired valve disease may not need coronary angiography if the TEE does not show aortic plaque. TEE may be very important for an additional reason in patients who are slated to have coronary bypass (or other) heart surgery: Aortic plaque identified by TEE may have a big impact on the outcome of heart surgery. The implications of identifying aortic plaque for heart surgery are discussed below.

**Renal Artery Disease**

Hypertension is common in patients with aortic plaque. One of the sometimes-missed causes of hypertension is renal artery stenosis, which in older patients is yet another complication of the atherosclerotic process. One study using abdominal ultrasound to look for renal artery stenosis in patients with severe aortic plaque on TEE found it in 19% of these patients. No renal artery stenosis was detected in any control subjects (without severe aortic plaque). Therefore, renal artery stenosis should be ruled out in patients with severe aortic plaque and hypertension. In addition, TEE detection of aortic plaque may provide a clue to the cause of occult renal dysfunction in the elderly, which may occur because of recurrent renal embolization from aortic plaque.

**Abdominal Aortic Aneurysm**

Severe thoracic aortic plaque was found in twice as many patients with abdominal aortic aneurysm on abdominal ultrasound or angiography (52% in those with Taneurysm versus 25% in those without aneurysm). In addition, researchers performed abdominal ultrasound to look for aneurysms of the aorta in patients with severe thoracic aortic plaque that had been found when TEE was done for various clinical indications. Abdominal aneurysms were found in 10 times more patients with severe thoracic plaque (13.9%) than in those without such plaque (1.4%). Because an abdominal aneurysm may have a catastrophic outcome, such an aneurysm should be ruled out if severe plaque is seen in the thoracic aorta.

**Association of Aortic Plaque With Aortic Stenosis and Mitral Annular Calcification**

Several studies have reported on the association of valvular aortic stenosis and atherosclerosis. In 1 study, 92 patients who had severe aortic stenosis and underwent TEE were matched by age and sex with 91 control subjects who also underwent TEE. Severe, complex aortic plaque was noted in 47% of the patients with severe aortic stenosis compared with only 9% of the control subjects. In another study, nonobstructive aortic valve calcification (without stenosis) was also significantly associated with aortic plaque on TEE. Aortic plaque was present in 86% of those with aortic valve calcification compared with 30% of control subjects without aortic valve calcification.

Mitral annular calcification is most common in the elderly and is associated with known atherosclerosis risk factors. A different study by the same researchers found a significantly higher incidence of aortic plaque, especially complex plaque, in those with annular calcification: 74% of the patients with mitral annular calcification had complex aortic plaque versus only 22% of controls. The thickness of the mitral annular calcification was directly related to the severity of the aortic plaque. Therefore, consideration should be given to evaluation of the aorta (especially before valve replacement) in patients with severe aortic stenosis, nonstenotic aortic valve calcification, or mitral annular calcification.

**Aortic Plaque and Atrial Fibrillation**

The Stroke Prevention in Atrial Fibrillation (SPAF) study reported 382 patients with “high-risk” nonvalvular atrial fibrillation (age >75 years, hypertension, or previous stroke) who had TEE. Complex aortic plaque (mobile, ulcerated, and/or size ≥4 mm) on TEE was present in 35% of the atrial fibrillation patients. Those with plaque had a stroke risk in 1 year of 12% to 20%. The risk was dramatically lower, only 1.2%, in the high-risk nonvalvular atrial fibrillation patients who did not have significant aortic plaque. Therefore, if a stroke occurs in the setting of high-risk nonvalvular atrial fibrillation and an “upstream” severe aortic plaque is present, the atrial fibrillation may not be the only possible cause of the embolus.

The SPARC study, also, found an association of aortic plaque and atrial fibrillation using a community-based approach. However, the association was no longer significant after an adjustment was made for age.

**Atherosclerosis of the Aorta: Risk Factor or Innocent Bystander?**

To avoid the referral bias inherent in many of the TEE studies of aortic plaque, the SPARC investigators selected 585 patients randomly from the community for evaluation with
TEE and follow-up for 5 years. Simple aortic plaques, seen in 253 persons, were not found to be associated with cardiac or cerebral events. Complex plaques, present in 44 patients, were marginally associated, but this association was no longer present after adjustment for additional clinical risk factors. Why do these results conflict with the data mentioned above in this review, which support the malignant nature of severe aortic plaque seen on TEE? The answer lies in the distribution of complex plaques that were found in these randomly selected, community-based patients. Only a small number of complex plaques were found in an area that could embolize to the brain. Complex aortic plaque was seen in the ascending aorta in only 1 patient (0.2% of their patients). Complex plaque was also seen in the aortic arch in only 2.2%. Most of the complex plaques found in this study were in the descending aorta (6%, 35 patients). Such plaques in the descending aorta are very unlikely to embolize backward in the circulation to the brain (except in the unusual coincident case of severe aortic insufficiency). In fact, in the FAPS study, the OR for stroke in patients with severe plaque in the descending aorta was only 1.5 (versus 13.8 for plaques of the same size in the ascending aorta or arch). Thus, although the community-based study described above is an important contribution and avoids the referral bias inherent in the other studies of aortic plaque, it does not appear to be powered to detect the association of aortic plaque and stroke because it does not contain enough patients with high-risk plaque in the proximal aorta.

In several case reports, there is direct evidence that severe aortic plaque does in fact cause embolization. In a TEE performed for a patient during diffuse embolization (which resulted in multiple organ failure and death), particulate matter was seen detaching from an aorta filled with severe plaque and traveling distally in the circulation. In another patient who underwent aortic cannulation during open heart surgery, a mobile component of an aortic arch plaque, presumably thrombus, was actually struck and detached from the plaque during cannulation of the aorta under TEE visualization. The patient awoke from surgery with a stroke. Furthermore, patients with aortic arch plaque have far more emboli to the left brain and periphery than they do to the right brain. This is true because the innominate artery (which supplies the right brain) is proximal to aortic arch plaque in most cases. Finally, pathological specimens have shown that the mobile components to aortic plaques are most often thrombi, which can detach and embolize (Figure 2).

Figure 2. A, TEE showing junction of aortic arch and descending aorta. Atherosclerotic plaque is shown on top with 2 superimposed mobile thrombi (T; arrows). B, Gross pathological specimen of 2 thrombi attached to atherosclerotic plaque (P) surgically removed from aorta (shown on TEE in A). C, Microscopic pathological specimen of the same lesion. D, Gross pathological specimen of thrombus surgically removed from femoral artery of the same patient.
Pathological Correlations

In 1992, a landmark autopsy study evaluated 500 patients with stroke and other neurological diseases. The authors showed that ulcerated plaques were present in the aortic arch in 26% of 239 patients with cerebrovascular disease but in only 5% of 261 patients with other neurological diseases. In addition, the prevalence of ulcerated plaques in the aortic arch was much higher (61%) in 28 patients with “cryptogenic stroke” than in the 155 patients with stroke and carotid disease or another known cause of stroke, in whom the prevalence was only 22%.

Since the first reports, investigators have found that a significant number (25% to 50%) of severe aortic plaques seen on TEE have a mobile component. These plaques may be found in patients with both a large and a small atherosclerotic burden. They range in size from 1 mm to several centimeters. Case reports of 2 such patients who underwent surgery documented that these mobile lesions were in fact thrombi superimposed on atherosclerotic plaque. In one of these patients, red thrombi were seen both superimposed on the aortic plaque and in the specimen removed from the femoral artery where it had embolized (Figure 2).

The presence of thrombi on aortic plaques was further documented on autopsy in a more recent study, which found aortic thrombi in 17 of 120 cases, as well as a significant association of complex plaque with previous emboli. In addition, mobile lesions in the aorta seen on TEE in 6 patients were seen to be thrombi on surgical pathology. A TEE study showed changes in morphology when TEE was repeated in the same patients over a period of time. New mobile lesions were seen on plaques that initially had none, and some of the presumed thrombi had disappeared (dissolved or embolized) by the time that the repeat study was performed.

In the coronary arteries, thrombosis has been shown to occur when the arterial wall contains a large lipid core, which predisposes to plaque rupture. A similar situation probably exists in the aorta. One group found that aortic plaques that contain a preponderance of lipid are likely to have undergone thrombosis. Calcified aortic plaques (which are less lipid laden) have a lower risk of plaque rupture, thrombus formation, and embolization (see Table 2).

Cholesterol Crystal Embolization (the Atheroemboli or “Blue Toe” Syndrome)

The syndrome of stroke and peripheral embolization described above is most often the result of thromboembolism to medium- and larger arteries from unstable aortic plaques. Much less common is the “classic” syndrome of diffuse cholesterol crystal embolization, the atheroemboli or “blue toe” syndrome. In the latter entity, there is a diffuse showering of cholesterol crystals from unstable aortic (or other arterial) plaques. This showering may occur spontaneously or may be precipitated by disruption of plaques during trauma, interventional procedures such as angiography or cardiac catheterization, or vascular surgery. Patients with this syndrome suffer from cerebral dysfunction, renal failure, intestinal infarction, and limb ischemia that is usually diffuse, distal, and bilateral. There is a very high mortality rate. This syndrome is a much rarer complication of aortic atherosclerosis than is the syndrome of thromboembolism. Thromboembolism occurs in up to 33% of patients with severe aortic plaque on TEE in 1 year. In contrast, atheroembolism was reported in 0.7% of patients with severe aortic plaque on TEE.

Imaging Modalities

Contrast Angiography

Historically, imaging of the aorta was done first (in vivo) with contrast angiography. This technique can define major aortic abnormalities; however, it is invasive and requires the use of contrast and radiation. In addition, angiography may miss important aortic plaques viewable by TEE. Therefore, angiography should not be used to evaluate aortic plaque.

Transesophageal Echocardiography

Transesophageal echocardiography (TEE) frequently visualizes the aortic root and proximal ascending aorta. In some patients, the aortic arch can be seen from the suprasternal notch and the descending aorta from that window and on apical views. Aortic plaque may be visualized with TEE B-mode imaging. Harmonic imaging may add to the accuracy of this technique.

Transequaphageal Echocardiography

Most echocardiographers feel that TEE is more accurate than TTE for the critical measurement of plaque thickness (Figure 3 and Table 2) and for the diagnosis of mobile thrombi. The TEE probe is closer to the aorta and can be used at a higher frequency, thus allowing for higher resolution than on TTE. TEE is safe, can be brought to the bedside for critically ill patients, and allows the evaluation of other possible reasons for stroke. An accurate and detailed evaluation of the aorta, including the origin of the great vessels, is possible, and there is excellent interobserver and intraobserver variability.

Plaque composition may be evaluated with TEE, including plaque calcification. The latter feature is important because the embolic risk is lower if aortic plaques are calcified. The reason for this decrease in risk may be that lipid-laden (noncalcified) plaques, which appear hypoechoic on TEE, are more prone to rupture and thrombosis, and these superimposed thrombi embolize to cause stroke and other organ damage.

The ability to record the amount of plaque at different levels in the aorta on TEE allows estimation of the total plaque burden. This is useful for assessing risk and the response to therapy. Newer TEE technology allows

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TABLE 2. Plaque Characteristics and Stroke Risk

<table>
<thead>
<tr>
<th>Findings associated with high stroke risk</th>
<th>1</th>
<th>1–1.9</th>
<th>2–3.9</th>
<th>≥4</th>
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</thead>
<tbody>
<tr>
<td>Thrombus (mobile or not)</td>
<td>1</td>
<td>3.3</td>
<td>4.1</td>
<td>13.8</td>
</tr>
<tr>
<td>Ulceration</td>
<td></td>
<td>4.1</td>
<td>13.8</td>
<td></td>
</tr>
<tr>
<td>Large lipid core (hypoechoic)</td>
<td></td>
<td>4.1</td>
<td>13.8</td>
<td></td>
</tr>
<tr>
<td>Finding associated with lower stroke risk</td>
<td>Data derived from Amarenco et al.</td>
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**Kronzon and Tunick Aortic Atherosclerotic Disease and Stroke**
3-dimensional reconstruction of the aorta, which may improve the localization and quantification of atherosclerotic plaque burden and risk.

The limitations of TEE include occasional discomfort for the patient (gagging), the frequent use of conscious sedation, and the rare risk of oropharyngeal and esophageal damage. In addition, the small portion of the ascending aorta that is masked by the tracheal air column near the origin of the innominate artery may not be seen on TEE; thus ~2% of plaques may be missed.

Epiaortic Ultrasound Imaging
Epiaortic imaging, yet another way to evaluate the aorta, is accomplished by placing a transducer directly on the aorta when the chest is open. The application of ultrasound is discussed later, in the section describing cardiac and aortic surgery in patients with atherosclerosis.

Magnetic Resonance Imaging
In 1983, MRI was first used to image aortic atherosclerosis. More recently, MRI was compared with TEE for the evaluation of aortic plaque. In this study, MR angiography underestimated plaque thickness in the aortic arch, probably because of difficulties in defining the aortic wall on the contrast-enhanced MR angiograms.

One important advantage of MRIs is that they reveal contrast between different tissue types and can thus identify morphological components of the atherosclerotic plaque such as calcification, fibrocellular tissue, lipid, and thrombus. Plaque stability depends on the size of the lipid core (Figure 4), the thickness of the fibrous cap, and inflammation within the cap. All of these parameters can be evaluated with MRI.

In addition, MRI can be used to monitor the progression and regression of atherosclerotic plaques. To improve the signal-to-noise ratio of MRI, a radiofrequency receiver probe may be placed in the esophagus. One study used a transesophageal probe to obtain images that correlated well with those obtained by TEE and provided important information about plaque composition.

MR angiography (Figure 5) is a valuable technique because it may supply 3-dimensional images of the entire vascular tree, including the small area masked by the tracheal air column on TEE.
Although MRI images supply important information about aortic plaque, MRI requires expensive and cumbersome equipment and cannot be done at the bedside or on patients in intensive care. This equipment also cannot be used on patients with ferromagnetic implants, particles, pacemakers, or defibrillators. In addition, claustrophobia in some patients may be a limiting factor. Finally, MRI is difficult to use for assessing mobile thrombi, which are an important factor in the development of embolization from unstable plaques. For these reasons, MRI is not routinely by most cardiologists to evaluate atherosclerosis in patients with stroke or other embolic syndromes.

Computerized Tomography
CT scanning is yet another modality frequently used to evaluate the aorta and its branches (Figure 6). Unenhanced dual-helical CT with thin sections has been reported to be successful in detecting protruding aortic plaque, especially in areas not visualized by TEE (94% of plaques detected by TEE were seen with CT). Additional benefits over the contrast-enhanced CT technique have been reported using spiral computerized dual-helical CT scanning. In this study, the plaques were identified in 95% of cases as compared with TEE, and plaque thickness could be assessed accurately.

CT scanning has been used in conjunction with positron-emission tomography (PET). This combination can localize fluorodeoxyglucose uptake by atherosclerotic plaque in the aortic wall. This combined technique has the potential to identify active atherosclerosis and unstable plaque. However, its current clinical utility is still not clear.

Although CT scanners are now available in most institutions and information can now be obtained rapidly, the studies are limited by the size and price of the equipment, the frequent need for contrast injection, and exposure of the patient to radiation. In addition, in 1 study, CT scanning proved to be inferior to epiaortic ultrasound for diagnosing atherosclerosis of the ascending aorta. Nevertheless, CT scanning is probably the current technique of choice for evaluating vascular calcification. As is the case with MRI, most cardiologists do not routinely refer patients with stroke for CT scanning to image aortic plaques.

Iatrogenic Embolization From Aortic Plaque
Cardiac Catheterization and Angiography
Although the risk is low, thromboembolism or atheroembolism may occur during cardiac catheterization, balloon pump placement, or angiographic instrumentation of the aorta. However, everyone active in catheterization can remember a dramatic instance of stroke or peripheral emboli (or both) occurring during or shortly after one of these procedures. The actual risk reported in a large series was 0.5%. Most patients with embolic complication after catheterization have severe plaque on TEE. One mechanism that has been suggested for causing these complications is the scraping of atherosclerotic debris by coronary guiding catheters. In 1 study that evaluated this mechanism, debris was collected in the backflow from catheters in 50% of catheterizations involving patients with atherosclerotic coronary artery disease.

It is possible that the right brachial or right radial artery approach might avoid these complications by avoiding negotiation of the descending aorta and aortic arch, which is inherent in the femoral approach. As noted earlier, plaques are relatively uncommon in the ascending aorta compared with the arch and descending aorta. To date, however, no study has confirmed the relative safety of this approach.

Epiaortic Ultrasound
During cardiac surgery, the aorta is usually imaged with TEE. High-quality images of the aorta may also be obtained by placing an ultrasound transducer directly on the aorta when the chest is open (epiaortic ultrasound). Aortic plaque identified with the epiaortic technique has been shown to predict early and late complications of heart surgery, including stroke and renal insufficiency. One advantage of epiaortic ultrasound is its ability to image the entire ascending aorta (the distal part of which is masked by the tracheal air column on TEE). One disadvantage of epiaortic ultrasound is that images can be obtained only when the chest is open. Another disadvantage is that one cannot always image the
entire aortic arch (the major site of plaque formation that is responsible for stroke). Finally, epiaortic ultrasound cannot be used easily during minimally invasive heart surgery, which is becoming much more common.

**Cardiac Surgery**

Stroke and peripheral emboli may complicate surgery that uses cardiopulmonary bypass, with an increased risk in the elderly. These complications occur in 2% to 7% of patients reported.\(^{82,83}\) Embolic complications have been attributed to air emboli, manipulation of the aorta during graft anastomosis, cross-clamping, palpation, and the “sandblasting” effect from the cannula jet of high-velocity flow (Figure 7). In 1 series, patients with severe aortic arch plaque had a higher incidence of intraoperative stroke than did those without severe plaque.\(^{84}\) One of the patients in this study had an intraoperative stroke after the cannula was observed going through an aortic arch plaque with a superimposed mobile thrombus. The thrombus was no longer seen after cannulation. In a later study, intraoperative stroke was directly related to aortic plaque burden.\(^{85}\) When analyzed by autopsy, embolic complications were a major cause of death during heart surgery. Emboli were found in 31% of postmortem examinations.\(^{86}\)

In a study of 268 patients with severe aortic arch plaque on TEE, the plaque was a highly significant risk factor for stroke that occurred during heart surgery.\(^{87}\) Strokes occurred in 11.6% of patients with severe arch plaque (6 times higher than the general intraoperative stroke risk at that institution). The in-hospital mortality in those with intraoperative stroke was 39%, and many of the survivors were severely disabled. The patients with intraoperative stroke spent nearly 4 times the number of days intubated than did other patients and had a 3-times-higher incidence of prolonged awakening from anesthesia. As a result, their length of stay in the recovery room and intensive care unit was significantly longer. In addition, the total hospital length of stay was very long for patients with severe aortic arch plaque (6 weeks) both with and without stroke (Comorbiditly other than stroke was high in these patients as well). Finally, the in-hospital mortality for the entire group of 268 patients with severe aortic arch plaque was high, 14.9%. Another study showed that patients with plaques that have a lower ultrasonic density have a higher incidence of stroke during cardiopulmonary bypass, perhaps because lower-density plaques may be higher in lipid content than high-density plaques.

Clearly, patients with severe aortic arch plaque represent a high-risk group for heart surgery that uses cardiopulmonary bypass (with cannulation of the aortic arch), and this must be factored into the risk-benefit analysis for these patients. Furthermore, aortic arch endarterectomy is not an effective way to prevent embolization during surgery in these patients. In fact, it has been shown to increase the risk of serious embolization dramatically. In a subgroup of 43 patients evaluated retrospectively, aortic arch endarterectomy was performed for the purpose of preventing intraoperative stroke. The stroke occurrence was nearly 3 times higher (34.9%) if an endarterectomy was done just before the heart operation (coronary bypass or valve) than if an endarterectomy was not

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**Figure 6.** A, Contrast-enhanced helical CT showing severe ascending and descending aortic plaques (arrows). B, Contrast-enhanced helical CT showing a large aortic arch lesion, probably a thrombus (arrow). C, Contrast-enhanced helical CT showing ulcerated ascending (straight arrow) and descending (curved arrow) aortic plaque. All panels reproduced from Tunick et al\(^{106}\) with permission from the American Journal of Roentgenology.

**Figure 7.** Intraoperative TEE of the aortic arch. Doppler flow jet emanates from the aortic cannula. Note the severe plaque narrowly missed by the cannula and jet (arrow).
done (12%). One possible mechanism for this increase in stroke rate was disruption of the intimal surface, leading to new thrombus formation, or perhaps embolization of a thrombus and debris during the manipulation itself. The strokes that occurred in all of the patients with severe arch plaque (with and without endarterectomy) were major neurological events, with a high mortality (39%) and morbidity.

Other techniques have been used in an effort to prevent intraoperative stroke. It has been shown that TEE-guided aortic cannulation reduced perioperative stroke and death during on-pump cardiac surgery.90 Others have suggested using axillary artery cannulation for patients with extensive aortic plaque.91 Finally, ascending aortic replacement has been performed successfully in patients with severe ascending aortic plaque, with no strokes in 27 patients with moderate to severe plaque in the ascending aorta.92

Because the cause of stroke during heart surgery is most often embolization from the aorta during cannulation, off-pump techniques without aortic manipulation have been used to prevent stroke during coronary bypass operations (the “no-touch” technique).92 In a case-control study, off-pump coronary artery bypass surgery had a lower risk of death, stroke, and embolic complications.93 In addition, off-pump coronary artery bypass surgery recently was compared with conventional on-pump coronary bypass surgery, and significantly fewer retinal and cerebral microemboli were found.94

Because patients with coronary artery disease are at risk for having severe aortic arch plaque, strong consideration should be given to screening these patients with TEE before deciding on their operative management.

Cognitive Dysfunction After Coronary Artery Bypass Surgery

Although stroke is a major and devastating complication of heart surgery, interest has increased recently in quantifying more subtle neuropsychological changes resulting from these operations. Cognitive dysfunction has been defined as impaired verbal or visual memory and language comprehension, impaired abstraction and spatial orientation, and decreased attention and psychomotor processing speed. Such impairment was found after coronary bypass surgery in 53% of patients at discharge. Moreover, although the figure decreased to 24% of patients at 6 months, cognitive dysfunction increased again to 42% of patients at 5 years. Patients with a decline at 5 years were more likely to have had dysfunction at hospital discharge.95 This late decline in cognitive function may be due to an additional accrual of cerebral damage related to the patients’ aortic atherosclerosis, putting them at risk for further cerebral embolization. Another research group related the increase in the confusion level after conventional coronary bypass surgery to mild to moderate aortic disease (intimal-medial thickness ≥2 mm).96 Although severe aortic plaque is associated with intraoperative stroke, it does not follow that mild to moderate plaque is benign. However, in another study,97 the authors felt that the burden of aortic plaque did not correlate directly with a decline in cognitive function after coronary bypass surgery. They concluded that neurocognitive dysfunction is likely to be multifactorial and related to age, education, and baseline cognitive index.

Further investigations are necessary to fully evaluate the role of aortic plaque in causing these lesser degrees of cerebral dysfunction after surgery that are not life-threatening but may certainly affect quality of life.

Treatment

Anticoagulation and Antiplatelet Drugs

Because severe aortic plaque is associated with intravascular embolization of thrombus, the first attempts to prevent embolization in patients with severe aortic plaque involved treatment with anticoagulation. Three reports dealt with the issue of whether warfarin is beneficial in patients with aortic plaque. The first described 31 patients with mobile thrombi in the aorta on TEE.98 Warfarin reduced the incidence of vascular events in these patients. Strokes occurred in 3 of 11 patients not treated with warfarin and in none of those on warfarin. A second group reported an observational study of 129 patients with severe aortic plaque on TEE.99 Treatment with oral anticoagulation, aspirin, or ticlopidine was not randomized. In this study, there was a reduction in the number of embolic events in patients with plaques ≤4 mm who received oral anticoagulants. For patients with mobile thrombi, there was a significant reduction in mortality on anticoagulants, although the trend toward fewer embolic events did not reach statistical significance in this group. Both studies were small, observational, and retrospective.

The third study that evaluated anticoagulation was from the SPAF Investigators Committee on Echocardiography.39 This was a randomized trial of patients with high-risk nonvalvular atrial fibrillation. TEE showed severe aortic plaque in 134 patients. The risk of stroke in 1 year in patients with severe aortic plaque was reduced from 15.8% (11 events) in those treated with fixed low-dose warfarin plus aspirin (international normalized ratio, 1.2 to 1.5) to only 4% (3 events) in those treated with adjusted-dose warfarin (international normalized ratio, 2 to 3). Therefore, there was a 75% risk reduction for patients with plaque who received “therapeutic-range” warfarin. Although these were patients with atrial fibrillation who were randomized to the 2 treatment arms without regard to the presence or absence of aortic plaque, there were fewer strokes in patients with plaques who were treated with full-dose warfarin.

The data from these 3 reports suggest that warfarin is not harmful in patients with aortic plaque (there was no significant incidence of cholesterol crystal atheroemboli), and in fact there were fewer strokes in the patients who were given warfarin. It is important to note, however, that these studies were not randomized trials of treatment for patients with plaque (SPAF was randomized for treatment in atrial fibrillation patients), and the numbers were relatively small. One striking result from the SPAF study was the very low incidence of stroke (1.2%) in patients with high-risk nonvalvular atrial fibrillation if there was no aortic plaque present on TEE. Clearly, a trial with sufficient power to detect a significant treatment effect (or harm) should be conducted to evaluate the possible efficacy of anticoagulation (warfarin) and antithrombotic drugs in patients with severe thoracic aortic plaque. Such a prospective, randomized study is now
Patients With Severe Aortic Plaque (N = 519)

Figure 8. Patients remaining event free on statins, warfarin, and antiplatelet drugs. Reproduced from Tunick et al,17 with permission from Excerpta Medica, Inc.

being carried out in Europe and Australia to compare warfarin with antiplatelet therapy.

One concern in the literature is that anticoagulation has been reported in association with new or worsening atheroemboli, possibly because of bleeding into the plaques.100 However, this complication was found only rarely in the SPAF trial.39

HMG Co-A Reductase Inhibitors (Statins)

Statin drugs have been shown to reduce the stroke rate in the Cholesterol and Recurrent Events (CARE) trial.101 In this trial involving older patients with myocardial infarction and average cholesterol levels, a statin was associated with a clinically significant reduction in the risk for stroke and coronary events. To date, there has been no randomized trial of statin therapy in patients with severe aortic plaque. However, in an observational study of 519 patients17 (all of whom had severe aortic arch plaque on TEE), an embolic event occurred in 111 patients (21%). Multivariate analysis showed that statin use was independently protective against recurrent events (P = 0.0001). The absolute risk reduction was 17% (number needed to treat, 6), and the relative risk reduction was 59%. No protective effect was found for warfarin or antiplatelet drugs. The OR for embolic events in patients on statin was 0.3 (P = 0.0001). For warfarin-treated patients, the OR was 0.7 (P = NS). For patients on antiplatelet agents, the OR was 1.4 (P = NS). Patients remaining event free on different therapies are shown in Figure 8.

Aortic plaque regression during statin therapy has been reported recently through the use of combined surface and transesophageal MRI. After 6 months of therapy, there was significant aortic plaque regression and reverse remodeling that was strongly associated with LDL cholesterol reduction.102 This reduction was confirmed in 2 randomized studies of low- and higher-dose statin in patients with aortic and/or carotid plaques. There was significant regression in plaque seen on MRI during therapy that, in 1 study, was related to the level of LDL cholesterol achieved but not to the dose of statin used;103 in the other study, this regression was related to both LDL lowering and the statin dose.104

It seems likely that statin therapy decreases the risk of stroke. Mechanisms for this effect may involve multiple effects of statin drugs, including plaque regression, plaque stabilization (resulting from decreased lipid content), decreased inflammation, and inhibitory effects on the coagulation cascade at different levels. It is therefore recommended that all patients with aortic atherosclerosis be treated with statin drugs. This therapy is not necessarily dependent on the patients’ lipid levels because statin drugs may prevent strokes as a result of their pleiotropic effects.

Primary Surgical Therapy

As mentioned, prophylactic aortic arch endarterectomy before coronary bypass or valve surgery appears to be dangerous and is not indicated.87 However, there have been case reports of successful aortic endarterectomy in a few desperate cases of recurrent embolization from a large aortic thrombus superimposed on plaque.44, 45 In another case, the aortic arch was successfully replaced in a patient who had recurrent embolization and plaque-associated aortic arch thrombi.105 To date, there have been no randomized studies that evaluate these surgical approaches compared with medical therapy.

Conclusions

Proximal aortic plaque, especially in the aortic arch, has taken its place, along with atrial fibrillation and carotid atherosclerosis, as an important cause of spontaneous and iatrogenic stroke and peripheral emboli. In patients with severe aortic plaque, organ damage is most often due to thrombus embolization from unstable lesions (although cholesterol crystal atheroembolization can occur in rare cases). It is disappointing that 15 years after this syndrome was described, there is still no firm evidence-based algorithm of treatment for patients with this disorder. Although a retrospective study indicates a likely benefit from statin drugs, the results of an ongoing randomized trial of warfarin versus antiplatelet therapy are still pending.

Disclosures

None.

References


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