38 Atherosclerotic Disease of the Proximal Aorta

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The presence of atherosclerotic plaques in the aorta is a risk factor for ischemic stroke. The proximal portion of the aorta, where the origin of blood vessels that supply the brain is located, may be the site of origin of cerebral embolism, providing an explanation for cerebral ischemic events otherwise considered of unknown etiology. This chapter reviews the principal studies on the association of aortic plaques and ischemic stroke and the related diagnostic and therapeutic issues.

Frequency of Aortic Plaques in the General Population

The atherosclerotic process in the aorta develops throughout life but becomes especially evident after the fourth decade, and the prevalence and number of atherosclerotic lesions increase continuously thereafter. In the Stroke Prevention: Assessment of Risk in a Community (SPARC) study,[1] the prevalence of "simple" (plaques <4 mm in thickness, without ulceration or mobile debris) or "complex" (plaques ≥4 mm or with complex features) atherosclerotic lesions was evaluated by transesophageal echocardiography (TEE) in 588 volunteers older than 44 years. Overall, aortic atherosclerosis of any degree and complex atherosclerosis in any segment of the aorta were present in 51.3% and 7.6% of subjects, respectively. Atherosclerosis of any degree was identified in the ascending aorta in 8.4%, the aortic arch in 31.0%, and the descending aorta in 44.9% of subjects; corresponding figures for complex atherosclerosis were 0.2%, 2.2%, and 6.0%. Atherosclerosis of any degree in any aortic segment was found to increase from approximately 17% in the group 45 to 54 years old to more than 80% in subjects older than 75 years. Complex atherosclerosis was virtually absent in the younger subgroup but was seen in more than 20% of patients older than 75 years. In a TEE study from Australia on healthy volunteers older than 59 years, the prevalence of simple plaques in the aortic arch was 22%, and that of complicated plaques (≥5 mm or with an irregular, ulcerated surface) was 4%.[2]

The prevalence of aortic atherosclerosis in the general population may depend on the characteristics, and especially the risk factor distribution, of the sample studied. In the triethnic study group of the Aortic Plaque and Risk of Ischemic Stroke (APRIS) study, TEE showed the prevalence of aortic arch atherosclerosis of any degree in 209 stroke-free volunteers older than 55 years from northern Manhattan to be 62.2%, and that of large (≥4 mm) arch plaques 23.9%.[3] These figures, which are much higher than those in the other studies, were obtained in patients with a greater burden of atherosclerotic risk factors. The APRIS study group had higher frequencies of diabetes (23.0% vs. 8.9%), hypertension (69.4% vs. 55.2%), and both past and current smoking history (60.3% vs. 39.0% and 16.1% vs. 8.2%, respectively) than the SPARC subjects.

Aortic Plaques and Ischemic Stroke

Pathology Studies

The first report of a strong association between aortic arch plaques and ischemic stroke came from a large autopsy case-control study conducted in France by Amarenco and colleagues and published in 1992.[4] The researchers showed a much greater frequency of ulcerated aortic plaques in elderly patients who had died from a stroke than in patients who had died from other neurologic diseases (26% vs. 5%; age-adjusted odds ratio [OR] 4.0; 95% confidence interval [CI], 2.1–7.8). Importantly, the highest frequency of ulcerated plaques was observed in patients with unexplained (cryptogenic) stroke (61% vs. 28%; adjusted OR 5.7; 95% CI, 2.4–3.6), thus providing a potential pathogenic mechanism for the stroke. The lack of association between ulcerated plaques and presence of significant carotid artery stenosis and atrial fibrillation, two other important sources for brain embolism, suggested an independent role of aortic plaques in the stroke risk. Among patients with ulcerated plaques, only 3% were younger than 60 years, suggesting that ulcerated plaques could be a new potential stroke risk factor exclusively in elderly subjects.

In a 1996 necropsy study, Khatibzadeh and coworkers[5] found evidence of arterial embolization in 40 of 120 unselected patients (33%). Complicated aortic arch plaques were significantly associated with arterial embolism (OR, 5.8; 95% CI, 1.1–31.7), independent of and with a similar strength to the associations of severe ipsilateral carotid artery disease and atrial fibrillation with arterial embolism.

In Vivo Studies—Transesophageal Echocardiography

TEE, the most sensitive and most widely used technique for examining the proximal portion of the aorta, has allowed the study of the association between aortic plaques and

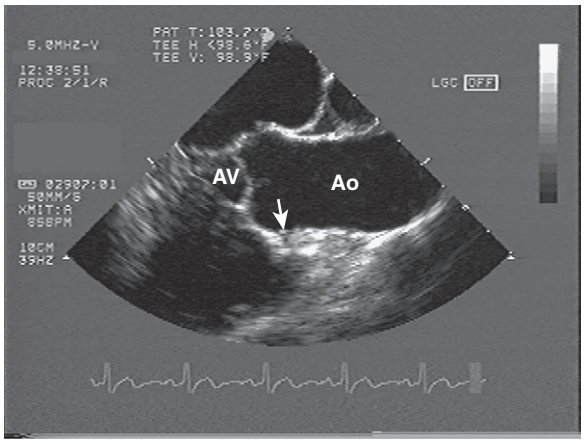

Figure 38-1 Longitudinal view of the ascending aorta (Ao) by transesophageal echocardiography. The entire ascending aorta is visualized from the aortic valve (AV) to the initial curvature of the aortic arch. The takeoff of the right coronary artery is visible *(arrow)*.

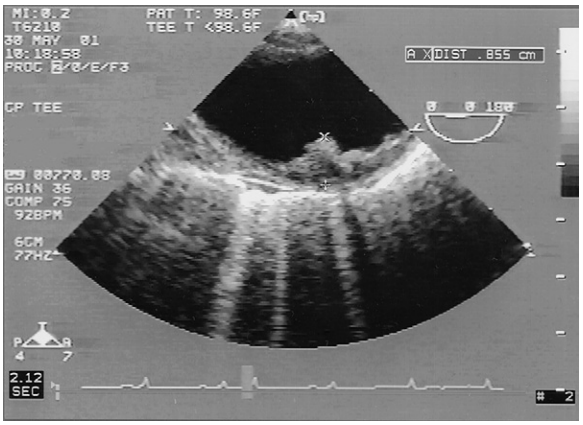

Figure 38-3 Protruding atherosclerotic plaque in the distal aortic arch. Measurement of plaque thickness, perpendicular to the major axis of the aortic lumen, is shown. Plaque thickness (0.855 cm) is displayed in the upper right corner.

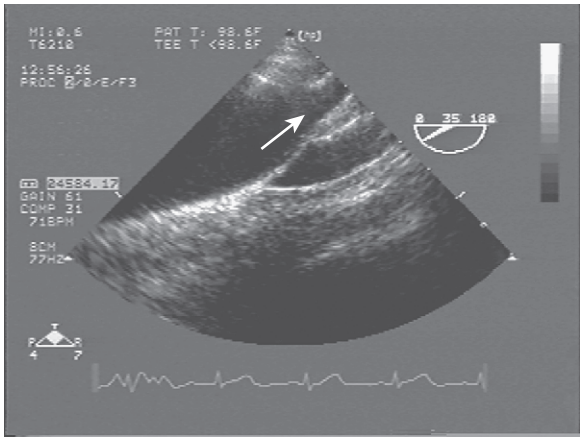

Figure 38-2 Transesophageal echocardiography visualization of the midportion to distal portion of the aortic arch. The takeoff of the left subclavian artery is visible *(arrow)*.

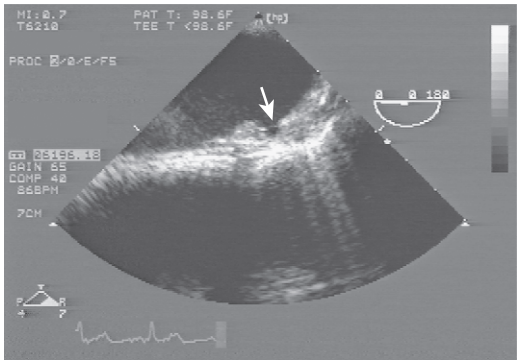

Figure 38-4 Complex plaque in the distal aortic arch. A large ulceration *(arrow)* is visible.

ischemic stroke in vivo.The proximity of the esophagus to the aorta and the absence of interposed structures allow the use of high-frequency ultrasound transducers, providing high-resolution images of the vessel. In the search for aortic plaques as the potential cause of ischemic stroke, the portion of aorta proximal to the takeoff of the left subclavian artery is the focus of the examination. Although the existence of retrograde diastolic flow has been demonstrated in the aorta,[6,7] its occurrence is probably an infrequent mechanism for embolization to the brain.Therefore, plaques that are located more distally in the aorta are an unlikely cause of stroke. The initial portion of the aorta can be accurately visualized by TEE from the aortic valve level to the initial curvature of the arch (Fig. 38-1).The midportion and distal portions of the aortic arch are also visible in all patients (Fig. 38-2). A small portion of the vessel (proximal arch) cannot be visualized owing to the interposition of the trachea and is therefore a "blind spot" in the examination, although the introduction of multiplane transducers has allowed for a more complete visualization of the vessel in most patients. It is possible to make an accurate TEE assessment for the presence of plaques and their thickness (Fig. 38-3), as well as for the presence of ulcerations (Fig. 38-4) or superimposed thrombus (Figs. 38-5 to 38-7). TEE has been shown to be highly sensitive and specific in the detection of aortic plaques.[8,9] Its diagnostic accuracy for presence of thrombus is also high (sensitivity 91%, specificity 90%).[9] However, the sensitivity of TEE for detecting small ulcerations of the plaque surface, which may carry an additional risk for further embolic events,[2,10,11] has been described as less than optimal (approximately 75%).[6,7] The reproducibility of TEE measurements of aortic plaque thickness has been shown to be very good, with agreement of 84% to 88% for the diagnosis of large (≥4 mm) plaque.[12]

TEE is a safe, although semi-invasive, diagnostic test. Major complications are uncommon and due mainly to unsuspected preexisting esophageal disease. In a European series of more than 10,000 patients,[13] one death was observed. In an additional 2.7% of patients, the test could not be performed because of unsuccessful intubation (1.9%) or patient intolerance (0.8%). Similar results were obtained in a study from the Mayo Clinic involving 15,381 consecutive patients, with two deaths

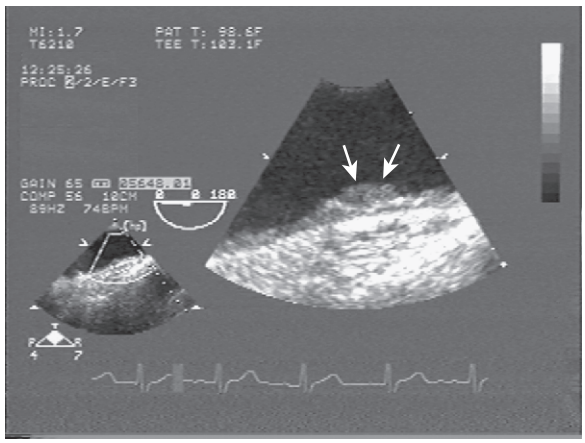

Figure 38-5 Enlarged view of a plaque in the midportion of the aortic arch. Hypoechoic material suggestive of thrombus *(arrows)* appears superimposed on the brightly echogenic plaque.

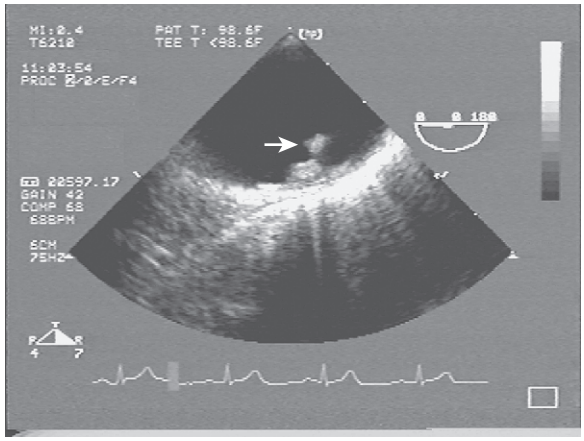

Figure 38-6 Complex plaque in the midportion of the aortic arch. A large pedunculated portion can be seen *(arrow)*, which was highly mobile in real-time imaging.

(0.01%) and a 1.7% overall incidence of complications.[14] In another series of 901 patients, intubation was unsuccessful in 1.2% of cases, there were no deaths, and a low incidence (0.6%) of major complications was observed.[15] Our experience in patients with stroke has shown no higher frequency of patient discomfort, unsuccessful intubation, or significant complications.[16] Moreover, the test can be safely performed even in patients of very advanced age.[17]

Case-Control Studies

Tunick and colleagues[18] first reported a higher frequency of aortic plaques 5 mm or thicker in 122 patients referred for TEE with a history of arterial embolism than in 122 age- and sex-matched patients with other cardiologic diagnoses (27% vs. 9%; OR, 3.2; 95% CI, 1.6–6.5).This retrospective study, in which data were not adjusted for other potential embolic sources, was followed by other case-control studies that focused on the risk of ischemic stroke associated with TEE-detected aortic arch plaques. The principal studies in this category are summarized in Table 38-1. Amarenco and colleagues[19] studied 250 patients

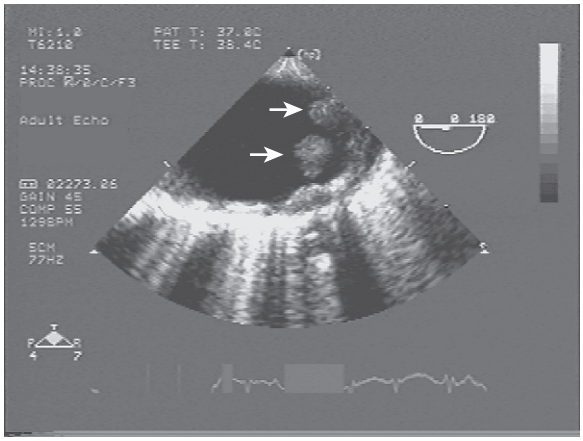

Figure 38-7 Complex atherosclerotic plaque of the distal aortic arch. Two large thrombi *(arrows)* are visible.

with acute ischemic stroke older than 60 years and 250 controls. They found that arch plaques between 1 and 3.9 mm in thickness were associated with stroke after adjustment for conventional stroke risk factors (adjusted OR, 4.4) but that a sharp increase in risk was present for plaques 4 mm or thicker (adjusted OR, 9.1; 95% CI, 3.3–25.2). Also, only the stroke risk associated with plaques 4 mm or thicker was independent of the presence of carotid stenosis and atrial fibrillation.[19] The investigators speculated that the sharp increase in risk observed for larger plaques might depend on the more frequent presence of superimposed thrombus, which would be included in the measurement of plaque thickness, and to a more frequent presence of mobile components, a circumstance also observed in other studies.[20] In this study, plaques 4 mm or thicker were also significantly more frequent in patients with cryptogenic stroke than in patients with stroke of determined origin (28.2% vs. 8.1%; OR, 4.7; 95% CI, 2.2–10.1).

Similar results, except for the association with cryptogenic stroke, were obtained in an Australian study by Jones and coworkers,[2] who studied 215 patients with stroke and 202 healthy volunteers older than 59 years (see Table 38-1). In that study, plaques 5 mm or more in thickness or with ulcerated or mobile components were associated with a much greater stroke risk (adjusted OR, 7.1; 95% CI, 2.7–18.4) than smaller, smooth plaques (adjusted OR, 2.3; 95% CI, 1.2–4.2). However, the frequency of large or complex plaques was similar in patients with cryptogenic stroke (20%) and in patients with stroke of determined origin (23%).

In 106 patients with stroke older than 40 years and 114 age- and gender-matched controls, we found an increased risk of stroke associated with aortic plaques 5 or more mm in thickness (adjusted OR, 2.6; 95% CI, 1.1–5.9).[10] The risk was entirely due to the subgroup of patients older than 59 years, whereas the prevalence of large plaques was very low (3%) both in patients with stroke and in controls younger than that age cutoff (see Table 38-1), underscoring that large aortic plaques appear to represent a relevant clinical entity only in the elderly.

TABLE 38-1 ASSOCIATION BETWEEN PROXIMAL AORTIC PLAQUES AND ISCHEMIC STROKE: TRANSESOPHAGEAL ECHOCARDIOGRAPHIC CASE-CONTROL STUDIES

Study (Reference No.)	Cases/Controls (N)	Age (Years)	Type of Atheroma	Controls (%)	Patients with Stroke (%)	Adjusted Odds Ratio* (95% CI)
Amarenco et al[19]	250/250	≥60	1-3.9 mm	22	46	4.4 (2.8–6.8)
			≥4 mm	2	14	9.1 (3.3–25.2)
Jones et al[2]	215/202	≥60	<5 mm, smooth	22	33	2.3 (1.2–4.2)
			≥5 mm, complex	4	22	7.1 (2.7–18.4)
Di Tullio et al[10]	106/114	≥40	≥5 mm	13	26	2.6 (1.1–5.9)
	30/36	<60		3	3	1.2 (0.7–20.2)
	76/78	≥60		18	36	2.4 (1.1–5.7)
Di Tullio et al[22]	255/209	≥55	≥4 mm	24	49	2.4 (1.3–4.6)

*Adjusted for conventional stroke risk factors (also see text).
CI, confidence interval.

TABLE 38-2 RECURRENCE RATE OF EMBOLIC EVENTS AND STROKE IN PATIENTS WITH AND WITHOUT PROXIMAL AORTIC PLAQUES: TRANSESOPHAGEAL ECHOCARDIOGRAPHIC PROSPECTIVE STUDIES

Study (Reference No.)	Aortic Plaque Present/Aortic Plaque Absent (N)	Follow-up (Months)	Type of Plaque	Aortic Plaque Absent (%)	Aortic Plaque Present (%)	Adjusted* Relative Risk (95% CI)
Tunick et al[23]	42/42	14	≥4 mm	7	33	4.3 (1.2–15.0)
Mitusch et al[24]	47/136	16	≥5 mm/mobile vs. <5 mm	4.1/yr	13.7/yr	4.3 (1.5–12.0)
FAPS[25†]	331	24-48	≥4mm	2.8/yr	11.9/yr	3.8 (1.8–7.8)
				5.9/yr	26.0/yr	3.5 (2.1–5.9)
Tanaka et al[26]	42/42	14	≥4mm	7	33	4.3 (1.2–15.0)
Fujimoto et al[27]	42/42	14	≥4 mm	7	33	4.3 (1.2–15.0)

*Adjusted for conventional stroke risk factors (also see text).
†Only study conducted on patients with ischemic stroke. Data in first row refer to recurrence rate of stroke; data in second row refer to recurrence rate of all embolic events.

Using epiaortic ultrasonography instead of TEE, Davila-Roman and associates[21] studied the prevalence of aortic plaques in 1200 subjects older than 49 years undergoing cardiac surgery, 158 of whom had experienced a previous embolic event.[21] The researchers found plaques 3 mm or thicker in 26.6% of patients with a previous cerebrovascular event and in 18.1% of those without it. Aortic plaques, arterial hypertension, atrial fibrillation, and carotid artery stenosis were independently associated with neurologic events in that study.

In a later study, we reported similar results in 255 patients with stroke and in 209 age-, gender-, and race/ethnicity-matched controls from the APRIS study. Large aortic arch plaques (≥4 mm) were again found to be associated with an increased stroke risk after adjustment for other stroke risk factors (adjusted OR, 2.4; 95% CI, 1.3–4.6; see Table 38-1).[22] Complex plaque morphology and coexisting hypercoagulability increased the stroke risk, as discussed later in the chapter.

Prospective Studies

Investigators have also prospectively confirmed the role of aortic arch plaques as a risk factor for peripheral and cerebral embolization, by following up patients who had a first stroke or other embolic event and comparing the embolic recurrence rate in patients with and without proximal aortic plaques (Table 38-2). After a mean follow-up of 14 months, Tunick and colleagues[23] noted a significantly greater incidence of cerebral or peripheral embolic events in 42 patients with protruding aortic atheromas than in control subjects matched for age, gender, and hypertension status (33% vs. 7%; relative risk [RR], 4.3; 95% CI, 1.2–15.0). Similar results were reported by Mitusch and associates[24] in a group of 47 patients with large or mobile arch plaques compared with 136 patients with small or no atheroma. In that study, recurrence rate of embolic events was 13.7% per year in patients with plaques that were either 5 mm or more in thickness or mobile, and 4.1% per year in patients with plaques less than 5 mm thick (RR, 4.3; 95% CI, 1.5–12.0). In a French multicenter study of 331 patients with stroke 60 years or older,[25] arch plaques 4 mm or more in thickness were associated with an almost four-fold increase in risk of recurrent stroke, after data were adjusted for the presence of carotid stenosis, atrial fibrillation, peripheral artery disease, and other conventional risk factors (see Table 38-2). In the subgroup with large plaques, the recurrence rate was highest in patients whose index stroke was cryptogenic (16.4/100 person-years). In that study, the incidence of all vascular events was also

significantly greater in patients with large plaques (RR, 3.5; see Table 38-2). The increased risk of recurrent stroke related to large arch plaques was confirmed in two later prospective studies. In 236 patients with ischemic stroke, Tanaka and colleagues[26] observed an increased risk of recurrent stroke or myocardial infarction in patients with arch plaques ≥3.5 mm (see Table 38-2). Fujimoto and coworkers[27] followed up 283 patients with embolic stroke and no significant occlusive lesion in cerebral arteries for a mean 3.4 years. Patients who experienced a recurrent stroke (32, or 11.3%) had significantly higher prevalence of arch plaques ≥4 mm (41% vs. 22%) and of plaque extension to the cephalic branches (63% vs. 39%; see Table 38-2).

In a report from the SPARC study,[1] the importance of the association between aortic atherosclerosis and cerebrovascular events has been questioned. In 581 community-derived subjects who underwent TEE in that study, large (≥4 mm), ulcerated, or mobile plaques were associated with a history of coronary artery disease (OR, 2.35; 95% CI, 1.1–5.0) but not with a history of ischemic stroke (OR, 1.37; 95% CI, 0.44–4.3), leading the investigators of the study to question the importance of aortic plaques as a risk factor for stroke in the community. The inclusion in that study of younger subjects (45 years was the age cutoff for inclusion in the study) may have diluted the strength of the association observed between aortic plaques and stroke. Also, the prevalence of severe plaques in the proximal aorta was low (2.4%). However, we reported similar findings from the follow-up of the control group of the APRIS study (age >54 years), in which the presence of large aortic arch plaques was not associated with stroke and vascular events (hazard ratio [HR], 1.05; 95% CI, 0.37–3.03).[3] These observations suggest that the risk of stroke from arch plaques incidentally detected in otherwise healthy subjects may be lower than that generally reported in the literature, which was obtained in subjects who had previous stroke or peripheral embolic events or were referred for TEE because of another coexisting condition.

Plaque Morphology and Stroke Risk

The role of aortic plaques as a risk factor for stroke has been established mainly on the basis of the thickness of the plaque, with either 4 mm or 5 mm chosen as the threshold for increased risk. It is unclear, however, whether plaque thickness is directly related to the stroke mechanism or is rather a marker of diffuse atherosclerosis, which may in fact be responsible for the increased stroke risk. We have demonstrated that differences exist in the plaque-related stroke risk between genders.[28] In our study, aortic plaques 4 mm or thicker were significantly more frequent in men than in women (31.5% vs. 20.3%; $P = .025$), and were associated with ischemic stroke in both men (adjusted OR, 6.0; 95% CI, 2.1–16.8) and women (adjusted OR, 3.2; 95% CI, 1.2–8.8), after adjustment for other established stroke risk factors. Plaques 3 to 3.9 mm in thickness, however, were significantly associated with stroke in women (adjusted OR, 4.8; 95% CI, 1.7–15.0) but not in men (adjusted OR, 0.8; 95% CI, 0.2–3.0). This observation suggests that plaque thickness, instead of identifying the actual culprit lesion for the stroke, may be a marker of diffuse atherosclerosis, including intracranial atherosclerosis, or of other conditions that may differ between genders and are possibly related to the stroke mechanism.[25] In any case, plaque progression, defined as increase in thickness over time, has been shown to be associated with a higher incidence of vascular events. In 117 patients with stroke or transient ischemic attack, those who showed plaque progression over 1 year were significantly more likely to experience a vascular event (stroke, transient ischemic attack, myocardial infarction. or death) over a median follow-up of 1.7 years than those with no plaque progression (51% vs. 11%; $P < .0001$).[29]

The complex morphology of a plaque appears to be more directly related to the stroke mechanism. As mentioned earlier, morphologic features of the plaque, such as ulceration and mobility, have been linked with an increased stroke risk,[1,5,8-11,20] especially in the case of cryptogenic stroke. Stone and associatees[11] showed a significantly greater frequency of ulcerated plaques in 23 patients with cryptogenic stroke than in 26 patients with stroke of determined origin (39% vs. 8%; $P < .001$). In our experience in 152 elderly patients with stroke and 152 age-matched controls,[20] ulcerated or mobile plaques were found to be a much stronger risk factor for stroke than large but noncomplex plaques (Table 38-3). Our study confirmed that plaques 4 mm or thicker were indeed associated with an increased stroke risk (adjusted OR, 4.3; 95% CI, 2.1–8.7); however, when these large plaques were divided on the basis of the presence or absence of ulceration (defined as a discrete indentation of at least 2 mm in width and depth) or mobile components, the stroke risk associated with those complex feature was exceedingly high (adjusted OR, 17.1), whereas large but noncomplex plaques carried only a modest increase in risk (adjusted OR, 2.4; see Table 38-3). This difference remained even after patients with other conditions possibly related to stroke, such as atrial fibrillation, carotid stenosis of 60% or greater, and intracranial atherosclerosis, were excluded from the analysis. Cohen and coworkers[30] studied the impact of plaque morphology (ulceration, hypoechoic components, or calcification) on the risk of recurrent vascular events in a prospective study of 334 patients with stroke older than 60 years and followed up for 2 to 4 years. In patients with plaques 4 mm or greater, the presence of ulcerations or hypoechoic components was not found to increase the risk of vascular events. However, the absence of calcification was associated with the strongest increase in risk (adjusted RR, 10.3; 95% CI, 4.2–25.2), and the presence of calcification was found to decrease the risk of subsequent events (adjusted RR, 1.2; 95% CI, 0.6 to 2.1), possibly signaling a more stable lesion.

These observations suggest that although the thickness of the plaque represents the most readily available marker of the risk of embolization associated with arch aortic plaques, the plaque's morphologic features strongly affect the embolic potential of the lesion, possibly opening the field to new therapeutic approaches in individual patients. It should be remembered that whenever TEE identifies a protruding mobile component on a plaque, that component represents thrombus superimposed on atherosclerotic material and usually occurs on ulcerated plaques. This observation has been confirmed by several

TABLE 38-3 EFFECT OF AORTIC PLAQUE MORPHOLOGY ON THE RISK OF ISCHEMIC STROKE

	Patients with Stroke (N = 152)		*Control Subjects (N = 152)*		Unadjusted Odds Ratio* (95% CI)	Adjusted Odds Ratio* (95% CI)
	N	%	N	%		
No plaque	28	18.4	55	36.2	—	—
Small plaque (<4 mm)†	56	36.8	68	44.7	1.6 (0.9–2.9)	1.9 (1.0–3.6)
Large plaque (≥4 mm)	68	44.8	29	19.1	4.6 (2.5–8.6)	4.3 (2.1–8.7)
Noncomplex plaque	34	22.4	25	16.5	2.7 (1.3–5.3)	2.4 (1.1–5.1)
Complex plaque	34	22.4	4	2.6	16.7 (5.4–51.8)	17.1 (5.1–57.3)
Ulcerated	24	15.8	3	2.0	15.7 (4.4–56.7)	15.8 (4.1–61.4)
Mobile	10	6.6	1	0.7	19.6 (2.4–161.3)	21.3 (2.4–193.2)

*Adjusted for age, gender, arterial hypertension, diabetes mellitus, and hypercholesterolemia.
†No complex forms were present among small plaques.
CI, confidence interval.

studies that have correlated the TEE findings with data derived from the histopathologic examination of the aorta.[4,5,24,25,31,32] Mobile components superimposed on an aortic plaque are infrequently seen in elderly patients with stroke, at a rate ranging from 1.6% to 8.7% in different studies (Table 38-4).[2,8,11,19,20,22,33,34] When present, however, they represent a very strong risk factor for brain embolization. In our study, mobile components superimposed on a plaque were present in 6.6% of elderly patients with stroke and were associated with a more than 20-fold increase in the risk of stroke, after adjustment of data for other conventional stroke risk factors (see Table 38-4).[20] Occasionally, mobile thrombi without severe atherosclerotic changes can be seen in the aortic arch of patients younger than 60 years who present with an embolic event (23 cases out of 27,855 TEE examinations in a multicenter cardiology study).[35] These thrombi, which usually have an insertion site on small atherosclerotic plaques, appear to represent a rare variant of atherosclerotic disease associated with embolic events in younger patients.[35]

The potential for embolism to the brain of large plaques, and even more of complex plaques, has been confirmed with transcranial Doppler ultrasonographic monitoring. With this technique, continuous monitoring of the blood flow into the middle cerebral arteries is obtained. Monitoring can be done simultaneously on the arteries of both sides and maintained for prolonged periods. The passage of small particles in the area interrogated by the ultrasound beam produces a characteristic high-intensity transient signal (HITS) (Fig. 38-8), the identification of which can be made more accurate through the application of appropriate filters. Using this technique over 30 minutes in 46 patients with acute ischemic stroke, Rundek and colleagues[36] showed the presence of HITS in a much larger proportion of patients with stroke and plaques 4 mm or thicker than in patients with small or no plaques, even in the absence of other TEE-detected possible embolic sources (70% vs. 18%; $P = .007$). Moreover, all patients with large and complex plaques were found to have HITS, compared with 39% of patients with large but noncomplex plaques ($P = .005$). Similar results about the association between plaques 4 mm or thicker and HITS were obtained in patients with cryptogenic stroke in a study by Castellanos and associates,[37] in which data on plaque complexity were not reported.

TABLE 38-4 PREVALENCE OF MOBILE THROMBI SUPERIMPOSED ON PROXIMAL AORTIC PLAQUES IN PATIENTS WITH ISCHEMIC STROKE

Study	Patients (N)	*Mobile Thrombi*	
		N	%
Toyoda et al[8]	62	3	4.8
Nihoyannopoulos et al[33]	152	3	2.0
Jones et al[2]	202	11	5.4
Amarenco et al[19]			
Unselected	250	7	2.8
Cryptogenic	78	6	7.7
Stone et al[11]			
Unselected	49	2	4.1
Cryptogenic	23	2	8.7
Di Tullio et al[20]	152	10	6.6
Ueno et al[34]	167	12	7.2
Di Tullio et al[22]	255	4	1.6

In summary, aortic plaque thickness of 4 mm or greater has been shown to be associated with increased risk of stroke and remains a useful tool for risk stratification, although part of the risk may come from superimposed thrombus included in the measurement of plaque thickness. Plaque thickness is also a marker of diffuse atherosclerosis, which may also play an important role in the stroke mechanism. The presence of complex morphologic features of a plaque, and especially of mobile components, appears more directly related to stroke mechanism in individual patients. Overall, the incidence of recurrent embolic events in patients with large or mobile aortic plaques has been estimated to be more than 14% per year, underscoring the need for effective secondary prevention strategies.[38]

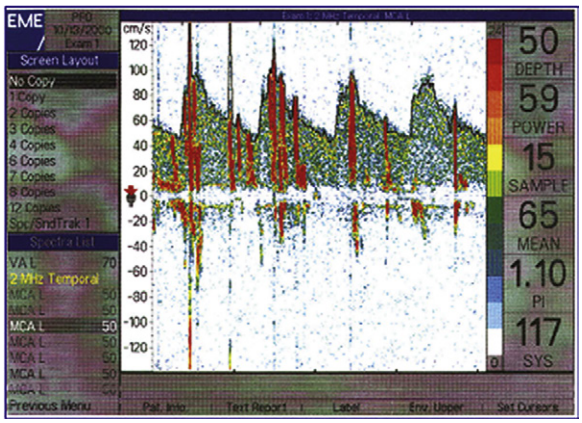

Figure 38-8 Transcranial Doppler examination of the middle cerebral artery. High-intensity transient signals (HITSs) are visualized as vertical high-amplitude signals with narrow spectrum superimposed on the normal blood flow.

Natural History of Aortic Plaques

The natural history of atherosclerotic plaques in the proximal aorta has not been extensively studied. From the information available, however, it appears that plaque size and morphology are important in determining the evolution of a plaque over time. Montgomery and colleagues[39] followed 30 patients who were found to have aortic atherosclerosis (12 with plaque thickness <5 mm, 8 with plaque thickness <5 mm, and 10 with mobile components) on initial TEE. A second TEE examination was then performed at 12 months. Although no significant changes were seen in subjects with smaller plaques, new mobile lesions had developed in 4 of 8 patients with plaques of 5 mm or greater. In patients who had mobile lesions at the time of the initial study, such lesions had resolved in 70% of cases, but new mobile lesions were observed in another 70%. Overall, although 20 of 30 patients (67%) had no change in the degree of atherosclerosis, substantial changes had occurred in the plaque morphology. In another study on 78 patients with stroke or transient ischemic attack, plaque progression over 9 months was observed in 37% of cases and was more frequent in the arch than in other aortic segments.[40] Using transthoracic echocardiographic examination of the aortic arch from a suprasternal window, Geraci and Weinberger[41] studied the plaque progression in 89 patients followed for up to 18 months (mean 7.7 months). Although plaques less than 4 mm thick at baseline showed changes in thickness in only 23% of cases, plaques 4 mm or thicker showed changes in thickness, upward or downward, in 52% of cases. It therefore appears that large aortic plaques are extremely dynamic lesions whose appearance may change considerably over a relatively short period.

Aortic Plaques in Patients with Stroke of Different Race or Ethnicity

Most studies on the association between atherosclerotic plaques in the proximal portion of the aorta and ischemic stroke have been conducted in white populations. Some information, however, is available for black and Hispanic patients that allows a comparison of plaque frequencies, which is important in the light of the different prevalence of risk factors for atherosclerosis in different race and ethnic groups. In a retrospective study of 1553 patients with ischemic stroke (889 white, 664 black), Gupta and colleagues[42] found a higher prevalence of aortic plaques in white than in black patients in the ascending aorta (14.7% vs. 11.1%; $P = .04$), aortic arch (67.7% vs. 62.2%; $P = .03$), and descending aorta (58.4% vs. 50.3%; $P = .002$). The plaque burden (sum of maximum plaque thickness at the three aortic locations) was also significantly higher in white patients (4.97 mm vs. 4.28 mm; $P = .007$); prevalences of plaques 4 mm or thicker (25.9% vs. 18.7%; $P < .001$) and of complex plaques—defined as protruding, ulcerated, mobile, or calcified regardless of plaque thickness (26.3% vs. 19.0%; $P < .001$)—were also greater in white patients, but *only* in the aortic arch. These findings were observed despite a higher prevalence of arterial hypertension and diabetes mellitus in black patients and cannot therefore be explained by differences in conventional stroke risk factor distribution. In our case-control study in patients with ischemic stroke older than 59 years from the triethnic community of northern Manhattan, plaques 4 mm or thicker had similar frequencies in white, black, and Hispanic subjects (24.1%, 20.0%, and 22.5%, respectively).[20] However, complex plaques were twice as frequent in white subjects than in black and Hispanic subjects (32.3%, 15.6%, and 16.3%, respectively). Complex plaques were associated with a strong increase in stroke risk in all three race-ethnic subgroups. As in the Gupta study,[42] the frequency of arterial hypertension and diabetes mellitus in our study was significantly lower in white subjects than in the other two race-ethnic subgroups, and that of hypercholesterolemia was significantly lower in white subjects than in black subjects. The prevalence of plaques 4 mm or thicker in the overall study population (44.8%) was much higher in our study than in the similar study from France (14.4%)[19] and also higher than the frequency of plaques that were either 5 mm or thicker or complex in the similar study from Australia (22%).[2] Therefore, even though the stroke risks associated with large or complex plaques appeared similar in the three studies, the attributable risk of stroke from proximal aortic plaques may be greater in the population of the United States, underscoring the need for effective preventive measures and risk factor reduction.

Factors Associated with Aortic Plaques in Patients with Stroke

Although differences in traditional risk factors for stroke and atherosclerosis alone do not seem to explain racial and ethnic differences in frequency of aortic plaques, some of these risk factors are indeed associated with the presence of these plaques. Age is the strongest and universally accepted predictor of aortic atherosclerosis.[1,2,4,5,10,19-21,43,44] Cigarette smoking has consistently been shown to be associated with aortic atherosclerosis[2,19,21,43,44] and is the most important modifiable risk factor for the development of aortic plaques. Arterial

hypertension has also been shown to be associated with proximal aortic atherosclerosis,[4,44] especially in the case of ulcerated lesions.[4] In the SPARC study, systolic and pulse pressure variables (office and ambulatory), but no diastolic variables, were associated with atherosclerosis and complex atherosclerosis in the aorta after adjustments for age and smoking history.[44] The association between diabetes mellitus and aortic atherosclerosis has been supported in some studies,[2] and negated in others,[43,44] at least after adjustment for other risk factors.[43] Hypercholesterolemia has been found to be associated with aortic atherosclerosis in some studies,[21,43,45] and treatment with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) has been shown to induce regression of aortic atherosclerotic lesions in humans.[46-48]

Variables besides traditional risk factors have been identified that are associated with aortic atherosclerosis and are possibly cofactors in increasing the embolic risk associated with aortic plaques. As mentioned earlier, the embolic potential of aortic plaque is related at least in part to the presence of superimposed thrombus. It is therefore conceivable that the coexistence of a hypercoagulable state in a patient with aortic arch plaque may increase the likelihood of superimposed thrombus formation, further enhancing the embolic potential of the lesion. Procoagulant properties have been demonstrated in atherosclerotic aortas; increased tissue factor expression and activity have been observed in the atherosclerotic intima that may lead to thrombus formation as the result of its exposure to the flowing blood.[49] Among coagulation factors, an increased fibrinogen level has been shown to be a risk factor for cardiovascular disease and ischemic stroke[50,51] and to be associated with degree of carotid stenosis,[52-54] abdominal aortic atheromas,[52] and peripheral atherosclerotic disease.[55,56] Atherogenic effects of fibrinogen have been described and possibly result from its interactions with some lipoproteins. In fact, fibrinogen has been shown to modulate the atherogenic effects of lipoprotein(a) [Lp(a)][57] and to increase the risk of severe carotid atherosclerosis and stroke in patients with low levels of high-density-lipoprotein cholesterol.[58] The association between fibrinogen and carotid artery disease has been shown to be particularly strong in the elderly.[59] Moreover, interracial differences have been reported in the levels of fibrinogen, with black subjects having higher levels than white subjects[60] and both groups having higher levels than Asian subjects.[61] Fibrinogen has also been shown to be independently associated with aortic atherosclerosis in a group of 148 patients who underwent TEE for valvular heart disease.[43] In that study, there was a relation between fibrinogen levels and severities of both aortic atherosclerosis and coronary artery disease.

Plasma homocysteine has also been found to be independently associated with aortic atherosclerosis diagnosed by TEE. In 82 cardiac patients, Tribouilloy and coworkers[62] found, in a multivariate analysis including usual risk factors for atherosclerosis, that age, male gender, and low-density-lipoprotein (LDL) cholesterol and homocysteine levels were the only factors independently associated with severity of aortic atherosclerosis. These findings suggest that homocysteine may be a marker of atherosclerotic lesion in large arterial vessels. Homocysteine was also shown to be independently associated with aortic arch atheroma progression over a period of 9 months in a group of 78 patients with stroke or transient ischemic attack, whereas no conventional risk factor for atherosclerosis was shown to have similar independent effect. Endothelial dysfunction causing plaque progression and a hypercoagulable state resulting in thrombus deposition were invoked as possible mechanisms for the finding.[40]

As mentioned earlier, the presence of a hypercoagulable state in patients with large aortic plaques could increase the embolic potential. In the APRIS study, prothrombin fragment 1.2 (F1.2), an indicator of thrombin generation, was associated with large plaques in patients with stroke (P = .02) but not in control subjects. Over a mean follow-up of 55.1 ± 37.2 months, patients with stroke who had large plaques and F1.2 levels over the median value had significantly higher risk of recurrent stroke and death than those with large plaques but lower F1.2 levels (230/1000 person-years vs. 85/1000 person-years; P = .05).[22] This observation indicates that in patients presenting with acute ischemic stroke, large aortic plaques are associated with blood hypercoagulability (as indicated by F1.2 level), suggesting a role for coagulation activation in the stroke mechanism.

The embolic potential of an aortic atheroma is also related to its lipid content. Cholesterol crystal emboli have been documented pathologically in peripheral arteries of patients in whom large atheromas are seen on TEE.[63-65] In addition to the association of total and LDL cholesterol with aortic plaques, mentioned earlier, Lp(a) has been shown to be an independent marker of aortic atherosclerosis.[66] Lp(a) is a complex between LDL and apoprotein(a). In spite of the close structural resemblance between LDL and Lp(a), these particles have very different metabolic properties. Serum Lp(a) levels are under strong genetic influence and are determined mainly by the synthetic rate of apoprotein(a), a protein with a striking similarity to plasminogen. This homology to plasminogen has prompted the speculation that Lp(a) may be an important risk factor for both atherosclerosis and thrombosis. It has been suggested that the atherogenic activity of Lp(a) might result from its inhibiting effect on plasminogen activation, with consequent decrease in plasmin formation. This in turn reduces the activation of transforming growth factor-β, a potent inhibitor of smooth muscle cell proliferation.[67] In addition, Lp(a) has been detected in atherosclerotic plaques, where it combines with fibrin and attenuates the clearance of this protein, promoting atherogenesis and vascular dysfunction.[68]

In summary, some lipid and coagulation abnormalities are associated with proximal aortic atherosclerosis; such abnormalities may be of importance in the progression of the atherosclerotic plaque and are possibly implicated as cofactors in determining the plaque's embolic potential. The study and consequent better understanding of the relation between lipid metabolism, coagulation, and proximal aortic atherosclerosis might provide indications for preventive and therapeutic measures in patients with proximal aortic plaques.

Proximal Aortic Plaques and Carotid Artery Disease

The relation between proximal aortic plaques and carotid artery disease, another important risk factor for ischemic stroke, has been investigated in several studies. In the autopsy study by Amarenco and colleagues,[4] ulcerated aortic plaques were as frequent in patients with carotid stenosis greater than 75% than in patients without it. In the case-control TEE study by Amarenco and associates,[19] no correlation was observed between aortic plaques 4 mm or thicker and carotid stenosis greater than 70%. We observed that the frequency of carotid stenosis greater than 60% rose with increasing aortic plaque thickness[10]; however, the positive predictive value of carotid stenosis greater than 60% for arch plaque 5 mm or thicker was only 16%, suggesting that although a general correlation exists between aortic and carotid atherosclerosis, one condition cannot be predicted on the basis of the other in individual patients. Jones and coworkers[2] obtained similar results, reporting a positive predictive value of carotid disease for aortic plaque of 57%. In a later study, Kallikazaros and colleagues[69] reported, in a group of 62 patients with cardiac disease, that presence of carotid plaque had good positive predictive value (83%) and acceptable sensitivity (75%) and specificity (74%) for presence of aortic plaque, but lower negative predictive value (63%). In summary, a general correlation exists between carotid atherosclerosis and aortic atherosclerosis, but one cannot be reliably predicted from the presence of the other, with the possible exception of patients with cardiac disease, in whom the relation appears to be closer.[69]

Proximal Aortic Plaques and Coronary Artery Disease

The relation between aortic atherosclerosis and coronary artery disease has been extensively studied. In a TEE study of 61 patients who had previously undergone coronary angiography, Fazio and associates[70] found atherosclerotic plaques in the thoracic aorta in 37 of 41 patients (90%) with obstructive coronary disease (defined as ≥50% left main coronary artery stenosis or ≥70% stenosis in the left anterior descending, circumflex, or right coronary arteries), but in only 2 of 20 patients (10%) with no or nonobstructive coronary disease. In that study, the presence of aortic plaque on TEE had 90% sensitivity and 90% specificity for obstructive coronary artery disease. In 153 consecutive patients undergoing coronary angiography and TEE, Khoury and colleagues[71] detected plaques in the aorta of 90 of 97 patients (93%), in comparison with 12 of 55 patients (22%) with normal coronary arteries.The aortic arch had evidence of plaque in 80% of patients with coronary stenosis greater than 50%. In the SPARC study,[1] aortic plaques were independently associated with history of myocardial infarction and coronary bypass surgery. In the population-based Rotterdam Coronary Calcification Study,[72] coronary calcification, assessed in 2013 subjects by electron-beam CT, showed a graded association with aortic calcification, considered a marker of atherosclerosis. In that study, the association was stronger than that between coronary calcification and carotid disease.

Therefore, a strong association between aortic atherosclerosis and coronary artery disease has been widely documented. However, the strength of this association appears slightly lower in elderly patients. In the study by Khoury and colleagues,[71] the specificity of the presence of aortic plaques for the diagnosis of coronary artery disease was found to be decreased in patients older than 63 years in comparison with younger patients (64% vs. 90%, respectively). In another study of 84 patients with cardiac disease,[73] the presence of aortic plaques failed to predict significant coronary artery disease in patients older than 69 years, but it was a strong predictor in younger patients.

Aortic Plaques and Atheroembolism

Besides being the site of origin of thromboembolism to the brain and the peripheral circulation, the atherosclerotic aorta can also give origin to atheroembolic phenomena, in which cholesterol crystal emboli are sent to various segments of the arterial circulation. Atheroembolism is generally characterized by small embolic particles that lodge in small arterioles (<200 μm in diameter)[74] and may occur spontaneously or following vascular surgery, arteriography, or anticoagulation.[75,76] The clinical consequences of atheroembolism are variable, depending on the location of the target organ and the number and frequency of embolic episodes. Therefore, atheroembolism has a wide spectrum of clinical presentations, from clinically silent episodes recognized only during diagnostic procedures[77-79] to complex clinical pictures characterized by multiple organ involvement (brain, retina, kidneys, gastrointestinal tract, lower limbs).[80,81] The simultaneous or consecutive involvement of different body segments may, in fact, greatly facilitate a correct diagnosis in cases of subtle or subacute clinical presentation.

Older age appears to be the strongest risk factor for atheroembolism from an aortic source. All 16 patients with atheroembolism reported by Gore and Collins[80] were older than 60 years. In that study, 12 of 13 autopsied patients had evidence of embolism to multiple sites. Older age and aortic atherosclerosis have a major impact on the risk of atheroembolism following cardiac surgery, as discussed in the next section.

Proximal Aortic Plaques and Cardiac Surgery

Aortic atherosclerosis is widely recognized as a strong risk factor for atheroembolic events, especially stroke, after cardiac surgery. As the mean age of the general population increases and indications for cardiac surgery in the elderly expand, an ever-increasing number of elderly subjects undergo open heart surgery, raising the number of subjects at high risk for atheroembolic events. Blauth and colleagues,[82] studying the autopsies of 221 subjects who had undergone cardiac surgery, identified embolic disease in 69 (31%), which was atheroembolic in nature in more than two thirds of cases. The brain was the most common target organ (16%), followed by spleen (11%), kidney (10%), and pancreas (7%). Atheroembolism was

multiple in 63% of subjects and was more common after coronary artery procedures than after valvular procedures (26% vs. 9%; $P = .008$). Atheroembolic events occurred in 37% of patients with severe atherosclerosis of the ascending aorta but in only 2% of patients without significant aortic disease ($P < .0001$), and 96% of patients who had evidence of atheroemboli had severe atherosclerosis of the ascending aorta. In that study, there was a strong relationship between age, severe aortic atherosclerosis, and atheroembolism.

The consequences of atheroembolism during or after cardiac surgery may be devastating. In a 2003 autopsy study, death was directly attributed to the embolic event (intraoperative cardiac failure due to coronary embolization in 3, massive stroke in 2, and extensive gastrointestinal embolization in 1) in 6 of 29 patients (21%) who had evidence of atheroemboli.[83] Proximal aortic atherosclerosis is also associated with the severity of postoperative neurologic complications. In a multicenter prospective study on adverse cerebral outcomes after coronary bypass surgery in 2108 patients from 24 U.S. institutions, the most severe complications (focal injury, or stupor or coma at discharge) were predicted by proximal aortic atherosclerosis, history of neurologic disease, and older age.[84] In 921 consecutive patients undergoing cardiac surgery in another study, the incidence of postoperative stroke was 8.7% in patients with atherosclerotic disease of the ascending aorta and 1.8% in patients without it ($P < .0001$).[85] Logistic regression indicated that aortic atherosclerosis was the strongest predictor of perioperative stroke. In yet another study, aortic atherosclerosis was shown to be a predictor of both early (immediately after surgery) and delayed (after initial uneventful recovery) stroke in 2972 patients undergoing cardiac surgery.[86] In that study, 82% of early strokes and 71% of delayed strokes occurred in patients 65 years of age or older.

The increased risk of stroke during coronary artery bypass in patients with proximal aortic plaques has been related to the effects of cannulation of the aorta to establish extracorporeal circulation. Ura and colleagues[87] performed epiaortic echocardiography before cannulation and after decannulation in 472 patients undergoing cardiac surgery with extracorporeal circulation. In 16 patients (3.4%), these investigators found a new lesion in the intima of the ascending aorta after decannulation. In 10 of 16 patients (63%), the new lesions were severe, with mobile components or disruption of the intimal layer. Three patients in this group had a postoperative stroke. Thickness of the plaque near the site of aortic manipulation was associated with the development of a new lesion. The frequency of new lesion was 33.3% with plaque thickness 4 mm or greater, 11.8% with plaque thickness 3 to 4 mm, and only 0.8% with plaque thickness less than 3 mm. It has been suggested that the incidence of perioperative stroke and vascular events in patients with severe proximal aortic atherosclerosis can be reduced by modifications in surgical approach. Trehan and associates[88] performed TEE in 3660 patients scheduled for coronary artery bypass surgery and found proximal aortic atheromas with mobile components in 104 (2.84%). In those patients, these researchers modified the surgical approach, the most frequent change being off-pump surgery (88 of 104 patients). The incidences of stroke and vascular events at 1 week after surgery were 0.96% and 1.92%, respectively, and there were no embolic events in the 88 patients who had undergone off-pump surgery. Therefore, preoperative TEE evaluation of the proximal aorta and evolution in surgical techniques may decrease the incidence of stroke associated with coronary artery bypass surgery.

Proximal Aortic Plaques and Cardiac Catheterization

There is a high risk of embolism to the brain when severe proximal atherosclerosis is present in subjects undergoing catheter-based diagnostic or therapeutic procedures involving the aortic arch. Because a TEE examination of the aorta is not usually performed before intraaortic procedures, the presence of aortic plaques is not known to the operator, a circumstance that increases the risk of embolic events after the procedure, especially in elderly patients. The awareness of the presence of aortic plaques, and the consequent modification of the catheterization technique, can be of great importance in reducing the risk of embolic sequelae. Karalis and associates[89] performed cardiac catheterization via the usual femoral approach in 59 patients with aortic atherosclerosis and in 71 control patients. The incidence of embolic events was 17% in patients with aortic atherosclerosis and 3% in controls ($P = .01$). No embolic events occurred in 11 patients with aortic atherosclerosis in whom a brachial approach instead of a femoral approach was used. It is therefore evident that the identification of subjects at high risk for atheroembolism (elderly, with history of prior embolic events or evidence of atherosclerosis in other body segments, or with multiple risk factors for atherosclerosis) can be invaluable in identifying the patients who should be referred for TEE before intraaortic procedures and could drastically reduce the incidence of embolic complications.

Obviously, the same consideration just discussed for diagnostic cardiac catheterization applies to therapeutic procedures involving the aorta. Keeley and Grines[90] evaluated the frequency of aortic debris retrieval during placement of guiding catheters in 1000 consecutive patients undergoing percutaneous revascularization procedures. In more than 50% of cases, guiding catheter placement was associated with scraping of debris from the aorta. The investigators underscored the fact that great attention to allowing debris to exit the back of the catheter was essential to prevent the injection of atheromatous debris into the bloodstream. Karalis and associates[89] also compared the results of intraaortic balloon pump placement in 10 patients with aortic atherosclerosis and in 12 patients without it. An embolic event related to the procedure was observed in 5 patients (50%) in the former group, and in none in the latter ($P = .02$). The researchers concluded that when aortic debris is detected, and especially when mobile components are identified, performing brachial rather than femoral catheterization and avoiding placement of an intraaortic balloon pump may reduce the risk of embolism.

Treatment of Proximal Aortic Plaques

Although the role of proximal aortic plaques as a risk factor for cerebral and peripheral embolism has become increasingly evident in the past decade, the best treatment options to reduce the risk of a first or recurrent embolic event in patients with aortic plaque are not yet clearly defined. Several preventive and therapeutic possibilities have been suggested and are reviewed in this section.

Systemic Anticoagulation

Because most embolic events associated with large or complex proximal aortic plaques are thought to be thromboembolic in origin, systemic anticoagulation has been suggested as an option to reduce their incidence in patients with this type of plaque. Dressler and colleagues[91] reported on the frequency of recurrent vascular events in 31 subjects presenting with a systemic embolic event and a mobile aortic plaque on TEE, according to the use of warfarin. Treatment was not randomized, and although 79% of patients (11 of 14) with medium or large mobile components received warfarin, only 53% (9 of 17) of those with small mobile components (diameter ≤1mm) did. Overall, 45% of patients not receiving warfarin had a vascular event over a mean follow-up of approximately 10 months, compared with 5% of those receiving warfarin. Corresponding figures for stroke were 27% and 0%, respectively. Annual incidence of stroke in the group not receiving warfarin was 32%. The investigators concluded that warfarin was protective against recurrent embolic events in patients with mobile plaques and that the dimension of the mobile component should not be used to assess the need for anticoagulation. Prospective results from the Stroke Prevention in Atrial Fibrillation (SPAF) study[92] showed significant reduction of the rate of embolic events in patients with protruding atheromas treated with adjusted-dose warfarin (international normalized ratio [INR], 2 to 3) in comparison with patients treated with low-intensity warfarin (INR, 1.2 to 1.5) plus aspirin (325 mg/day). Overall, patients with complex aortic plaques had a fourfold higher stroke incidence than patients without plaques, and adjusted-dose warfarin decreased the risk by 75% ($P = .005$). Of course, all patients in that study had nonvalvular atrial fibrillation, precluding the direct extrapolation of the results to the general population.

Although the use of oral anticoagulation in patients with mobile plaques appears logical and is supported by the aforementioned studies, its use in patients with large but nonmobile lesions is more controversial. In 50 patients with atheromas 4 mm or larger but without mobile components followed for 22 ± 10 months, Ferrari and coworkers[93] found a substantial incidence of stroke in patients treated with aspirin or ticlopidine (5/23, or 21.7%), compared with no stroke in 27 patients treated with warfarin ($P = .01$). This study was small, however, and the treatment was not randomized. In 2009, we reported on the incidence of recurrent stroke and death in 516 patients with acute ischemic stroke treated with aspirin or warfarin as part of the Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS). Over a follow-up of 2 years, large plaques (≥4 mm) remained associated with an increased risk of events (adjusted HR, 2.12, 95% CI, 1.04–4.32), especially those with complex morphology (HR, 2.55, 95%CI, 1.10–5.89). The risk was highest among patients with cryptogenic stroke, both for large plaques (HR, 6.42, 95% CI, 1.62–25.46) and for large complex plaques (HR, 9.50, 95% CI, 1.92–47.10).[94] Therefore, medical treatment with warfarin or aspirin did not seem to affect the significance of the association between large arch plaques and recurrent events. Although event rates tended to be lower in the warfarin group than in the aspirin group (2-year event rate in patients with large plaques, 23.0% and 30.2%, respectively; $P = .21$), the difference between the two treatments was not statistically significant.[95] Further studies with larger patient populations are needed to evaluate the possibility of differences in efficacy between warfarin and aspirin or other antiplatelet agents in specific patient subgroups, such as patients with cryptogenic stroke.

The safety of systemic anticoagulation in patients with aortic plaques has traditionally been questioned,[96] because anticoagulation might induce bleeding within the plaque, with consequent ulceration and risk of embolization. Moreover, anticoagulation might remove the thrombin coating from ulcerated atheromas and therefore facilitate microembolization of cholesterol crystals.[97,98] Atheroembolism is a real clinical entity, and its sequelae[73-80] and association with anticoagulation[75,76] in patients with aortic atherosclerosis have been discussed earlier in the chapter. However, its incidence after systemic anticoagulation appears to be rather low. In the SPAF study,[99] adjusted-dose treatment with warfarin (INR, 2 to 3) was associated with an incidence of cholesterol embolization of 0.7% per year.

Antiplatelet Medications

As mentioned earlier, antiplatelet therapy with aspirin or ticlopidine has been reported to be less protective against recurrent embolic events than warfarin therapy in patients with large or complex plaques,[91-93] but this has been seen generally in small studies without treatment randomization. The only data from a randomized study come from PICSS[94] and are summarized earlier, in the section on systemic anticoagulation.The combination of aspirin and clopidogrel is being tested against warfarin in patients with large plaques.[100] More data are therefore needed to assess the role of antiplatelet agents in the prevention of aortic plaque–related embolic events, their relative efficacy in comparison with warfarin, and the identification of patients for whom either treatment is suitable.

Thrombolysis

Thrombolysis has occasionally been used to treat large mobile plaques with seemingly very high embolic potential.[101] The high risk of major hemorrhagic complications, especially in elderly patients, and the questionable advantages of thrombolysis over anticoagulation make it an unlikely therapeutic choice in patients with mobile plaques, so thrombolysis should be reserved for selected cases. Like systemic anticoagulation, thrombolysis has also been associated with atheroembolic complications

in patients with aortic atherosclerosis,[102] although the incidence of this complication is probably rather low.[103]

Statins

The use of statins to prevent embolic events in patients with large or complex aortic plaques appears to have a powerful rationale, because statins may induce plaque stabilization through the reduction of the lipid content, with consequent reduced frequency of ulceration and superimposed thrombus formation. As mentioned earlier, statins have been shown to induce plaque regression in humans.[46-48] To date, no randomized trial has assessed the efficacy of statins for this indication. The only available data come from Tunick and colleagues,[104] who retrospectively identified 519 patients with severe thoracic aortic plaques and determined the incidence of embolic events according to treatment status (statins, warfarin, or antiplatelet medications). Treatment was not randomized, and patients taking each class of medication were matched with patients of similar age and embolic risk profile not taking that medication. Over an average follow-up of 34 ± 26 months, embolic events occurred in 111 patients (21%). In multivariate analysis, statin treatment was found to be independently protective against recurring events ($P = .0001$). In the matched analysis, the relative risk reduction was 59%. No protective effect was found for warfarin or antiplatelet medication. Although with the limitations of the retrospective nonrandomized design, this study represents preliminary evidence of the efficacy of statins in preventing embolic events in patients with severe aortic plaques, which deserves confirmation in randomized prospective studies.

Surgery

Aortic endarterectomy has been proposed as a preventive measure in patients with large mobile plaques in the proximal aorta at impending risk for embolism, especially when cardiac surgery is performed. However, the surgical procedure on the aorta in itself carries a high risk, especially for the potential to dislodge parts of the mobile component of the plaque and precipitate an embolic event. Stern and colleagues[105] performed intraoperative TEE in 3404 patients undergoing heart surgery, finding complex plaques (≥5 mm, or mobile) in 268 (8%). Arch endarterectomy was performed in 43 patients in an attempt to prevent intraoperative stroke. The intraoperative stroke rate in the 268 patients was high (15.3%), as was mortality (14.9%). On multivariate analysis, age and arch endarterectomy were found to be independently associated with intraoperative stroke. The OR for stroke of arch endarterectomy was 3.6 ($P = .01$). Therefore, the use of arch endarterectomy should be carefully considered only in very selected cases.

Resection and graft replacement of a severely atherosclerotic segment of ascending aorta were performed by Rokkas and Kouchoukos and associates[106] in 81 patients (mean age 71 years) undergoing coronary bypass surgery. In that study, the 30-day mortality was 8.6% (7 patients). Perioperative strokes occurred in 4 patients (4.9%), and transient neurologic deficits in 2 (2.5%). During the follow-up, only one stroke occurred 4 months after the procedure. However, 3-year survival was only 40%, with mortality being secondary mainly to complications from generalized atherosclerosis. In 17 patients who underwent graft replacement of the ascending aorta for severe atherosclerosis during elective coronary bypass grafting, King and colleagues[107] reported a hospital mortality of 23.5%, compared with only 2.3% in 89 patients who underwent replacement for ascending thoracic aortic aneurysm ($P = .006$). Cerebrovascular event rates were 17.6% and 3.4%, respectively ($P = .05$). Nonfatal postoperative complications were observed in 53% of the patients with atherosclerosis, compared with 20% of controls ($P = .01$).

From the cumulative evidence presented, surgical procedures on a severe atherosclerotic proximal aorta are associated with substantial morbidity and mortality and should be reserved for carefully selected cases.

Future Directions

The most important advancements in the field of proximal aortic plaques and ischemic stroke will likely come from the results of randomized clinical trials to test preventive and therapeutic options in patients with proximal aortic atherosclerosis. However, as the general population ages, the number of subjects with atherosclerotic disease will increase, and the identification of subjects at high risk for embolic events to target for primary prevention measures will become more and more important. Better, easier, and noninvasive ways to identify high-risk aortic plaques will be needed. This need may entail both a more accurate assessment of plaque morphology and attempts to identify plaques that are more likely to rupture and give origin to embolic events (vulnerable plaques).

Newer Imaging Modalities

As mentioned earlier, the assessment of stroke risk in patients with proximal aortic plaques has been based on plaque thickness and morphology. The measure of plaque thickness, although very helpful for risk stratification, is a monodimensional measurement of a three-dimensional lesion and may therefore not convey all the information about the plaque embolic potential in individual subjects. Also, plaque thickness and morphology characteristics are usually evaluated by TEE, a semi-invasive technique that does not lend itself to be a screening tool in asymptomatic elderly subjects. Transthoracic echocardiography from a suprasternal or supraclavicular approach would be a much easier and more widely applicable technique, provided that questions on its sensitivity in comparison with TEE, especially for identification of complex plaque morphology, can be addressed. Real-time three-dimensional echocardiographic equipment has become available that with further technical refinements might prove very useful in the noninvasive evaluation of the aortic arch. Figure 38-9 displays an example of an ulcerated plaque in the distal portion of the aortic arch visualized by TEE, commonly available transthoracic echocardiography, and real-time three-dimensional echocardiography. The advantages of the three-dimensional technique over the traditional transthoracic image in displaying the real extension of the

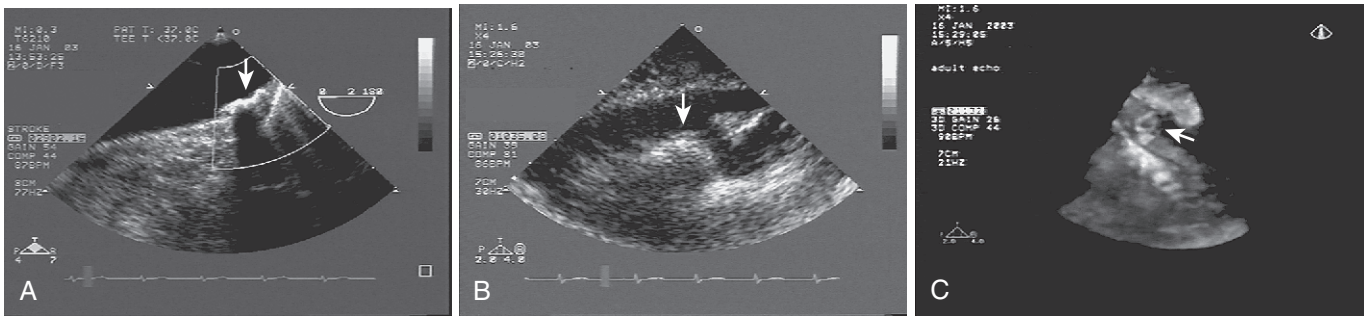

Figure 38-9 A, Transesophageal echocardiography visualization of a calcified plaque in the distal aortic arch. A large ulceration *(arrow)* is shown. B, Same plaque as in A, visualized from the suprasternal transthoracic approach. No definite ulceration is visible. C, Transthoracic three-dimensional imaging of the same plaque. Rotation of the transducer plane has allowed a better visualization of the plaque, and the entire area of ulceration *(arrow)* is now visible.

plaque and the characteristics of its ulceration are apparent; the three-dimensional technique allows a representation of the plaque characteristics that appears at least as good as that obtained by TEE. Further technical refinements, including transducers with smaller footprints to better fit into the suprasternal notch, and studies assessing the accuracy of the new technique in comparison with TEE are needed to evaluate the potential and applicability of this new technique.

Noninvasive techniques besides echocardiography have been shown to have excellent accuracy for the detection of proximal aortic plaques. MRI has been shown to correlate well with TEE for aortic plaque determination[108] and to accurately quantify the fibrotic and lipidic components of the plaque in animal models.[109] Compared with TEE, dual-helical CT has shown sensitivity of 87%, specificity of 82%, and overall accuracy of 84% for the detection of aortic plaques.[110]

A combination of different techniques, such as positron emission tomography (PET) and MRI, has been successfully applied to the imaging of plaques in the aortic arch (Fig. 38-10).

Identification of the Vulnerable (High-Risk) Plaque

The noninvasive identification of the vulnerable plaque, or a plaque that is at higher risk for rupture and consequent superimposed thrombus formation, would be of great importance in trying to prevent embolic sequelae. As discussed before, MRI has shown potential for identifying fibrotic and lipidic components of a plaque.[109] Contrast agents have been introduced that may enhance this capability. Superparamagnetic iron oxide has been found to localize to aortic atherosclerotic plaques in animal models, allowing the detection of iron-laden macrophages in the aortic subendothelium[111] and therefore possibly providing a new noninvasive modality for imaging of inflammatory aortic plaques. Contrast agents have been developed that target activated matrix metalloproteinases, enzymes that have been implicated in the propensity of a plaque to rupture.[112] Positron emission tomography with fludeoxyglucose F 18 is a promising tool for visualizing inflammation in an atherosclerotic plaque and has been shown to be able to visualize statin-induced reduction in the degree of inflammation.[113] Further development of these techniques may improve our ability to identify those plaques that are more likely to become sources of cerebral embolization.

Summary

Large and complex plaques in the proximal portion of the thoracic aorta have been established as a risk factor for ischemic stroke, especially cryptogenic, and other arterial embolic events in patients older than 60 years. The frequency of embolic events, both spontaneous and precipitated by diagnostic or therapeutic procedures on the aorta, has been defined. Progress has been made in aortic plaque imaging and in the understanding of morphologic characteristics and associated factors that affect the plaque-related embolic risk. Initial therapeutic data have been obtained, although further investigation remains to be done in that regard. Further advancement is expected to come from improved techniques for the identification of high-risk plaques and from randomized treatment trials aimed at reducing the risk of embolic events associated with severe proximal aortic atherosclerosis.

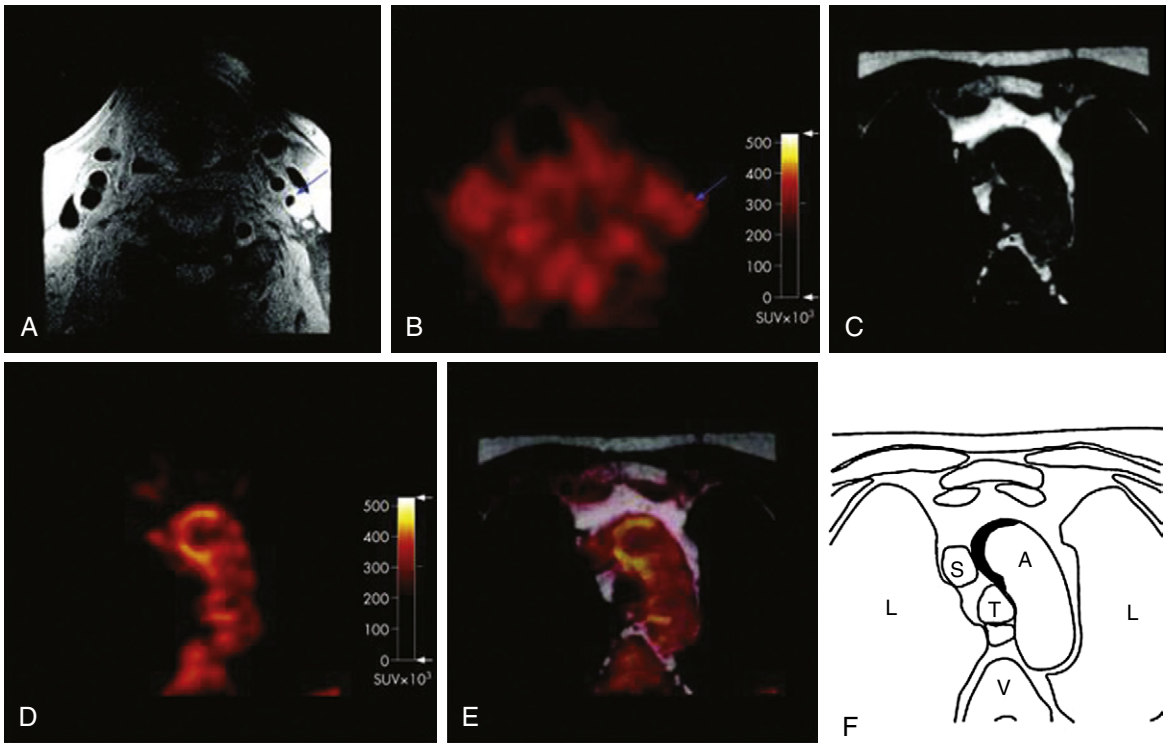

Figure 38-10 Co-registered axial fluorodeoxyglucose F-18 (FDG) positron emission tomography scan and MR image of the neck (A and B) and chest (C to E), showing minimal tracer uptake in the ipsilateral carotid artery *(arrow)* and high uptake into an eccentric plaque in the arch of the aorta. F, Schematic of chest MR images, showing the aortic arch (A) with plaque, lungs (L), superior vena cava (S), trachea (T), and vertebral body (V). (Reprinted with permission from Moustafa RR, Azquierdo D, Weissberg PL, et al: Neurological picture: Identifying aortic plaque inflammation as a potential cause of stroke. *J Neurol Neurosurg Psychiatry* 79:236, 2008. © BMJ Publishing Group Ltd.)

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