Atheromas of the Thoracic Aorta: Clinical and Therapeutic Update

Paul A. Tunick, MD, FACC, Itzhak Kronzon, MD, FACC

New York, New York

Atherosclerotic lesions of the thoracic aorta have recently been recognized as an important cause of stroke and peripheral embolization, which may result in severe neurologic damage as well as multiorgan failure and death. Their prevalence is ~27% in patients with previous embolic events. Transesophageal echocardiography is the modality of choice for the diagnosis of these atheromas, although computed tomography, magnetic resonance imaging and intraoperative epiaortic ultrasound are complementary. Two clinical syndromes account for the embolic phenomena, atheroemboli and, more commonly, thromboemboli. In addition to such superimposed thrombi, plaque thickness (especially ≥4 mm) also correlates with embolic risk. This risk is high, with 12% of patients having a recurrent stroke within approximately one year, and up to 33% of patients having a stroke or peripheral embolus. In addition, aortic atheromas (as seen with intraoperative transesophageal echocardiography and intraoperative epiaortic ultrasound) are an important cause of stroke during heart surgery requiring cardiopulmonary bypass. Such strokes occur during ~12% of cardiac operations employing cardiopulmonary bypass when aortic arch atheromas are seen with transesophageal echocardiography (six times the general intraoperative stroke rate). Although anticoagulant strategies have been reported with encouraging results in nonrandomized studies, prospective, randomized data must be developed before an effective and safe treatment strategy can be determined. This review details the current state of knowledge in this area, including the clinical and pathologic evidence that thoracic aortic atherosclerosis is an important embolic source, data which guide current therapy and future directions for clinical investigation. (J Am Coll Cardiol 2000;35:545–54) © 2000 by the American College of Cardiology

Stroke and peripheral embolization are major causes of morbidity and mortality, and stroke is the third leading cause of death in the U.S. (1). The established risk factors for stroke include increasing age, male gender, heredity, previous stroke, hypertension, smoking, diabetes, carotid artery disease, heart disease and polycythemia. There are also many secondary risk factors, such as climate (excessive heat or cold), socioeconomic status and geographic area (2).

As recently as the 1950s, 55% of strokes were thought to be caused by cerebral vasospasm (3). This changed when Harvard neurologist C. Miller Fisher stressed the etiologic role of emboli from carotid artery atherosclerotic plaques (4). Until the 1990s, carotid disease and atrial fibrillation were the two entities that dominated the clinical approach to patients with stroke and peripheral embolization. Despite the recognition of these two important sources of emboli, stroke data banks as late as 1989 still indicated that in up to 40% of patients, no etiology can be found (5,6). Thus, "cryptogenic stroke" has continued to be a diagnostic dilemma.

Transthoracic echocardiography has been ordered frequently but is frustratingly negative in looking for sources of emboli. Transesophageal echocardiography is a safe, minimally invasive procedure with a very low risk of complications (7). In 1990, a new finding was reported in three patients with embolic disease (8). In these patients, transesophageal echocardiography revealed protruding atherosclerotic plaques in the aortic arch. These initial patients were followed by many case-control (9–11) and then prospective (12–14) studies documenting the association between aortic atheromas and embolic phenomena. Moreover, the mobile components seen attached to these atheromas on transesophageal echocardiography have proven to be thrombi (15–17)—the source of the devastating embolic complications that occur in 20% to 33% of these patients in just one year (12).

This review details the current state of knowledge about thoracic aortic atherosclerosis, including the clinical and pathologic evidence that it is an important embolic source, data which guide current therapy and future directions for clinical investigation.

PREVALENCE OF AORTIC ATHEROMAS IN PATIENTS WITH EMBOLI: CASE-CONTROL STUDIES

After several case series (8,18–20) which found aortic atheromas in patients with emboli, retrospective case-control studies documented a significant association between stroke and peripheral emboli and the presence of

thoracic aortic atheromas seen on transesophageal echocardiography (9–11,21), on autopsy (22,23) and with intraoperative epiaortic ultrasound during cardiac surgery (24). The prevalence of atheromas in the aortic arch in patients with embolic disease, found by three different groups of investigators, was remarkably consistent—27% (9), 21% (11) and 26% (21). In contrast, significant atheromas were found in only 9%, 4% and 13% of control subjects, respectively. Multivariate analyses showed a highly significant odds ratio for the prevalence of previous stroke in patients with atheromas—3.2, 8.2 and 3.6, respectively.

Perhaps most importantly, the prevalence of aortic atheromas seen in these studies of stroke patients (21% to 27%) is about the same magnitude as the prevalence of carotid disease (10% to 13%) and atrial fibrillation (18% to 30%) reported in two recent large series of consecutive stroke patients (10,11).

Thus, these case-control data documented a significant association between aortic plaque and embolic disease, but because all of these studies were retrospective, a causal relation was not yet established. Intriguing information from an early case-control study did suggest causality. Most of the arch atheromas were located distal to the innominate artery, and only 18% of embolic events had occurred in the right brain (vs. the left brain or periphery) (9). Obviously, arch atheromas distal to the innominate artery cannot embolize in a retrograde fashion to the right brain and may embolize to the left carotid system or the periphery.

AORTIC ATHEROMAS AND CAROTID ARTERY DISEASE

The association between atheromas and embolic disease in the studies discussed earlier was independent of other risk factors for stroke, most prominently carotid disease and atrial fibrillation (patients with these findings were excluded from the first study [9], and multivariate analysis controlled for them in the other two studies [11,12]). Although aortic atheromas are therefore 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 those without carotid disease, and therefore they have more than one potential source of embolization. In one retrospective study,

aortic arch atheromas were found in significantly more who had a stroke/transient ischemic attack (TIA) patients with carotid stenosis (38% vs. 17% of patients who had a stroke/TIA without carotid stenosis) (25). That study also found that mobile thrombi superimposed on the aortic arch atheromas were exclusively found in patients whose carotid stenosis exceeded 80%. Thus, the patients with the highest risk carotid lesions also had the highest risk aortic plaques. Therefore, when presented with a patient with stroke and significant carotid stenosis, it is important to also consider the possibility that the embolic event may have originated in the aorta. When the neurologic event is contralateral to the carotid stenosis or is associated with peripheral (e.g., renal, lower extremity) emboli, the aorta should be evaluated with transesophageal echocardiography. This is also true in patients who have neurologic events after recovery from a technically successful carotid endarterectomy.

AORTIC ATHEROMAS AND ATRIAL FIBRILLATION

The Stroke Prevention in Atrial Fibrillation (SPAF) investigators have reported a series of 382 patients with "high risk" nonvalvular atrial fibrillation (age >75 years, hypertension, previous stroke) who had transesophageal echocardiography (26). Of these, 134 (35%) had complex aortic plaque (mobile, ulcerated, size ≥4 mm) on transesophageal echocardiography. These patients with plaque had a stroke risk in one year of 12% to 20%. The risk was dramatically lower, only 1.2%, in the patients with high risk nonvalvular atrial fibrillation who did not have significant aortic plaque, regardless of therapy with warfarin or aspirin. Therefore, if a stroke occurs in the setting of high risk nonvalvular atrial fibrillation, and when an "upstream" aortic atheroma is present, the atrial fibrillation may not be the cause of the embolic event.

PLAQUE SIZE AND EMBOLIC RISK

The earliest case series and case-control studies in the U.S. used a cutoff of ≥5 mm thickness to classify significant aortic atheromas (8,9,19). However, the French Aortic Plaque in Stroke (FAPS) group evaluated a large number of patients with varying plaque thicknesses and found not only that increasing plaque thickness imparted increasing risk, but also that with a plaque thickness of ≥4 mm the odds ratio was significantly greater (10). The odds ratio for 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 much higher, 13.8. This study also supports causality with respect to arch atheromas and stroke, instead of these plaques being just a marker for stroke risk, as the odds ratio for stroke in patients with plaque in the descending aorta (which could not embolize to the head) was only 1.5 for the largest plaques, ≥4 mm (vs. an odds ratio of 13.8 for those in the arch, upstream from the cerebral circulation).

PLAQUE MORPHOLOGY AND EMBOLIC RISK

From the earliest studies, the presence of mobile lesions (thrombi) superimposed on aortic atheromas has been recognized to impart a high embolic risk, which will be discussed subsequently. Other characteristics of the lesions seen on transesophageal echocardiography have been evaluated as well. In one study, the presence of ulceration ≥2 mm in aortic plaques seen on transesophageal echocardiography was found to correlate with cryptogenic stroke; ulcerations were present in 9 (39%) of 23 patients with cryptogenic stroke, but were seen in only 2 (8%) of 26 patients with stroke of known cause and 4 (7%) of 57 patients without stroke (27).

One large group of 334 patients >60 years old with stroke was evaluated with transesophageal echocardiography and was followed for two to four years (28). These authors found that hypoechoic plaques, calcification and ulceration were more common in plaques ≥4 mm in thickness. In that study, the presence of ulceration did not increase the relative risk of vascular events in patients with plaques ≥4 mm (the relative risk was 4.3 in those with ulceration and 5.7 in those without ulceration). However, the absence of calcification did increase the risk in patients with plaques ≥4 mm. The highest risk was found in patients with noncalcified plaques ≥4 mm, in whom the relative risk was 10.3. The lack of calcification was associated with a higher risk, regardless of the other morphologic features of the plaque.

It is possible that these noncalcified plaques may be the ones that are lipid-laden and therefore "vulnerable." This theory is supported by a pathologic study that evaluated the size of the lipid pool and the number of smooth muscle cells and macrophages in human aortic plaques that were intact as compared with those that had superimposed thrombi (29). These authors found that the presence of superimposed thrombi is characteristic of plaques with a high proportion of their volume occupied by extracellular lipid and in which there was a shift toward a preponderance of monocytes/macrophages as compared with smooth muscle cells in the cap.

PATHOLOGIC CORRELATES AND SUPERIMPOSED THROMBI

In 1992, an important autopsy study examined 500 patients with stroke and other neurologic diseases (22). The major finding was that ulcerated plaques were present in the aortic arch in 62 (26%) of 239 patients with cerebrovascular disease, but in only 13 (5%) of the 261 patients with other neurologic diseases (p < 0.001). Furthermore, the prevalence of ulcerated plaques in the aortic arch was much higher (61%) in 28 patients with "cryptogenic stroke," as compared with 22% in those with stroke and carotid disease or another known cause of stroke. These authors did not identify thrombi on the aortic lesions; however, thrombi

may have been lost due to washing and preparation of the specimens or lysis before pathologic examination.

Since the earliest reports, investigators have found that a significant proportion (25% to 50%) of protruding atheromas seen on transesophageal echocardiography have a mobile component that moves freely with the blood flow. These may range in size from 1 mm to several centimeters. Early case reports of two such patients who underwent heart surgery documented that these mobile lesions were in fact thrombi superimposed on atherosclerotic plaque (15,30). The following year, thrombi were also documented in an another three patients with mobile lesions on transesophageal echocardiography (31), and mobile lesions have been reported to disappear after heparin or warfarin therapy (32,33) or thrombolysis (34).

The presence of thrombi on aortic plaques was further documented in a recent autopsy series (35). This study reported aortic thrombi in 17 of 120 consecutive autopsies, as well as a significant association between complex plaque (thrombus, ulceration or debris) and previous emboli. In addition, pathologic examination of mobile lesions in the aorta seen on transesophageal echocardiography was recently reported in six patients with aortic aneurysm or dissection, and thrombi were found at the time of surgery (17).

In a study using repeat transesophageal echocardiography over a period in the same patients with aortic atheromas, changes in lesion morphology were noted (36). On the second transesophageal echocardiographic examination, there were new mobile lesions present on plaques where there had been none initially in 11 (61%) of 18 patients. Furthermore, 7 of 10 mobile lesions present on the first examination had resolved (or embolized?) by the time of the second examination. It is not surprising that these plaques in the aorta may be unstable, and that superimposed thrombosis may occur and recur in the same way that it does in the coronary circulation. This has important therapeutic implications, which will be discussed subsequently.

EMBOLIC SYNDROMES IN PATIENTS WITH AORTIC ATHEROMAS: THROMBUS EMBOLIZATION VERSUS ATHEROEMBOLI (CHOLESTEROL CRYSTAL EMBOLI)

It is common for thrombi to form on aortic atheromas, and embolization to the femoral arteries has been found at surgery to be due to thrombus (15,30). A different clinical picture—the atheroemboli syndrome—is also associated with aortic disease. This consists of renal failure, skin lesions, blue toes and multiorgan findings caused by cholesterol emboli (37). It may develop spontaneously or may result from arterial manipulation during cardiac catheterization, intra-aortic balloon pumping or the institution of cardiopulmonary bypass. The atheroemboli may occlude small arteries and they can be seen as refractile bodies in the retinal arteries. They can also be diagnosed microscopically with biopsy of the skin, muscle or kidney. Recent reports

have shown protruding aortic atheromas on transesophageal echocardiography in patients with atheroemboli in the skin, muscle and kidneys (38,39). However, the syndrome of blue toes and renal failure has not often been observed in patients with aortic atheromas on transesophageal echocardiography and was reported in only one patient treated with warfarin in the SPAF III study of patients with aortic atheromas (26). More subtle findings may occur, as was reported in a study of patients undergoing cardiac surgery. Increasing levels of creatinine were noted to be associated with increasing severity of aortic atherosclerosis (40).

Because the mobile lesions seen on transesophageal echocardiography are thrombi, it is likely that the large majority of medium to large artery occlusions (cerebral, femoral, renal) that occur in patients with aortic atheromas are due to the embolization of thrombus.

AORTIC ATHEROMAS AND RISK FACTORS FOR ATHEROSCLEROSIS

Not surprisingly, the presence of aortic atheromas is related to the traditional risk factors for atherosclerosis. Atheromas are most often seen in the elderly (the average age of those with aortic atheromas is ~70 years [12]), although atheromas have been seen in patients as young as 43 years (15). Hypertension and hypercholesterolemia are also significantly more common in patients with aortic atheromas (41), and a positive correlation between aortic atherosclerosis and smoking has also been documented (42).

In addition to these "traditional" risk factors, both fibrinogen levels (43) and homocysteine levels (44) have been positively correlated with aortic atherosclerosis. In the latter study, which measured plaque in three locations in the thoracic aorta on transesophageal echocardiography, a significant correlation between total plaque burden and homocysteine levels was seen, as well as an inverse relation between plaque burden and pyridoxal-5′-phosphate (vitamin B_6) levels.

AORTIC ATHEROMAS AS A MARKER FOR CORONARY ARTERY DISEASE (CAD)

Radiographic studies have reported an association between aortic plaque seen on chest X-ray and the subsequent development of clinical CAD (45). Aortic plaque seen on transesophageal echocardiography has been correlated with a higher prevalence of CAD (33) and the presence of significant angiographic coronary artery stenosis (46). In addition, the lack of aortic plaque on transesophageal echocardiography has also been shown to be predictive of the absence of CAD (47).

Transesophageal echocardiography was performed on 61 patients who had previously undergone coronary angiography for the evaluation of CAD or valvular heart disease or for miscellaneous indications (46). 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 transesophageal echocardiography was 95%, and the negative predictive value was 82%. The authors concluded that the detection of aortic plaque by transesophageal echocardiography appears to be a marker for the presence of obstructive coronary artery disease. In 1997, another group also found that the presence of aortic plaque on transesophageal echocardiography correlated with angiographic coronary stenosis, but only among 60 patients <70 years old (48). Among 24 patients >70 years old, aortic plaque found on transesophageal echocardiography failed to be a significant predictor of coronary disease (plaque was seen in 12 of 13 older patients with coronary disease, but also in 9 of 10 older patients without coronary obstruction). Further investigation in larger groups of patients is necessary.

OTHER IMAGING MODALITIES

Although transesophageal echocardiography was the first procedure to gain acceptance for imaging of thoracic aortic atheromas, other imaging modalities have a role. Dual helical computed tomographic (CT) scanning was used to evaluate 32 patients who also had transesophageal echocardiography (49). The sensitivity and specificity of the CT study for the detection of protruding aortic atheromas seen on transesophageal echocardiography were 87% and 82%, respectively. Magnetic resonance imaging (MRI) has also been used to detect thrombus in the aortic arch (50,51) and to differentiate aortic thrombus from intravascular tumor (pulmonary artery metastatic melanoma) (52). Rapid acquisition techniques employed in the last study (52) may help to overcome flow artifacts which may obscure intra-arterial masses on contrast-enhanced electrocardiographic-gated MRI studies. Because of the potential of MRI to detect aortic atheromas, a study was done to compare breath-hold, gadolinium-enhanced three-dimensional magnetic resonance angiography (MRA) with transesophageal echocardiography (53). This study showed that although transesophageal echocardiography and MRA were comparable for detecting atheromas in the ascending aorta and descending aorta, plaque thickness was significantly larger in the aortic arch on transesophageal echocardiography as compared with MRA. Fewer "high risk" plaques ≥5 mm were detected by MRA. Both CT and MRI studies have the potential to visualize plaques in the small area masked by the tracheal air column on transesophageal echocardiography, and the three modalities appear to be complementary.

Intraoperative epiaortic ultrasound has been used in the operating room to visualize atheromas in the ascending aorta (24,54). For patients undergoing cardiac surgery, two studies have reported that this technique is more sensitive than transesophageal echocardiography for finding disease in the ascending aorta (55,56). Transthoracic echocardiography has also been used to visualize plaque in the ascending aorta and aortic arch. In one initial study, 20 patients were

evaluated with both transthoracic and transesophageal techniques (57). However, the resolution of images obtained by the transthoracic approach is currently not as high as that of those images obtained with a transducer in the esophagus. At this time, transesophageal echocardiography is the procedure of choice for the detection, measurement and characterization of thoracic aortic atheromas in both inpatients and outpatients. For patients undergoing cardiac surgery, intraoperative epiaortic ultrasound has been found to be superior for evaluating the ascending aorta, and this technique can be used to complement the information on the aortic arch that is obtained by intraoperative transesophageal echocardiography.

PROSPECTIVE STUDIES AND THE INCIDENCE OF FUTURE EVENTS

The case series and case-control studies discussed earlier document a significant association between aortic atheromas and embolic disease, but do not establish a causal relation. More recently, there have been several prospective studies that have looked at the risk of future embolic stroke and peripheral emboli in patients with protruding atheromas in the thoracic aorta seen on transesophageal echocardiography (12–14) and intraoperative epiaortic ultrasound in the operating room during heart surgery (58). The studies using transesophageal echocardiography found both an incidence of stroke averaging 12% in just one year and an incidence of all embolic events (stroke and peripheral) of up to 33% in the same short period. The odds ratios for the risk of future events (4.3, 3.5 and 4.3) were consistent in the transesophageal echocardiographic studies and lower (1.3) in the large series of patients with ascending aortic atherosclerosis on intraoperative epiaortic ultrasound. This may reflect the fact that fewer plaques are seen in the ascending aorta than in the arch or descending aorta. The study using intraoperative epiaortic ultrasound also documented a higher incidence of mortality; the odds ratio was 1.38 for death during the follow-up period of up to seven years. The death rate was 15.4% for patients with a normal ascending aorta and much higher, 43.4%, in those with severe ascending atherosclerosis (>5 mm, or ulcerated or mobile lesions).

It is important to remember that although the brain is the most common site of embolization, many patients have severe morbidity and mortality secondary to peripheral embolization from these lesions. Patients with atheromas may have severe ischemia or infarction of the legs, kidneys or bowel, and in some patients, all of these vascular beds are affected, resulting in multiorgan failure and death (12).

EMBOLIC EVENTS DURING AORTIC MANIPULATION

Left heart catheterization and intra-aortic balloon pumping. Cardiac catheterization or placement of an intra-aortic balloon pump may cause embolization from aortic atheromas (59,60). One group found that in 7 (15%) of 48 patients with protruding atheromas on transesopha-

geal echocardiography, an embolic event occurred as a result of cardiac catheterization through the femoral artery (59). They also found such events in four of seven patients with significant aortic atheromas who had balloon pump placement. The highest risk patients were those with mobile thrombi. Embolic events occurred in 9 (43%) of 21 of these patients, but in only 2 (7%) of 27 patients with atheromas but no mobile thrombi on transesophageal echocardiography. It should be noted that these numbers do not reflect the incidence of embolic complications during cardiac catheterization, which is actually low (0.5% of strokes in one large series) (61). However, when embolic complications do occur, aortic atheromas are a common association.

In a prospective evaluation of 1,000 consecutive patients undergoing coronary interventions, the amount of visible atheromatous material retrieved from guiding catheters that had been passed up the aorta from the femoral artery was recorded (62). The authors found that in >50% of cases, guiding catheter placement is associated with scraping of debris from the aorta, and they recommended allowing the debris to exit the back of the catheter to prevent the injection of atheromatous material into the vascular tree.

Cardiac surgery. Embolic stroke and peripheral emboli may complicate cardiac surgery involving cardiopulmonary bypass, especially in the elderly. These events occur in 2% to 7% of patients in reported series (63–65). Various theories have been advanced to explain these embolic complications, including air emboli and manipulation of the aorta during proximal graft anastomosis, cross-clamping, palpation and "sandblasting" from the cannula flow. In one series, patients with aortic arch atheromas had a significantly higher incidence of intraoperative stroke (3 [15%] of 23) than did those without atheromas (2 [2%] of 107) (66). One of the patients in this study had an intraoperative stroke after the cannula was observed going through an aortic arch plaque with a mobile thrombus. The thrombus was no longer seen after cannulation.

This study (66) also found that palpation of the aorta by the surgeon did not identify the atherosclerotic disease seen on transesophageal echocardiography in 83% of those with significant plaque. Underestimation of atherosclerotic disease of the ascending aorta by palpation had been documented previously in a study of intraoperative epiaortic ultrasound (67) and was confirmed in a subsequent report in which palpation identified only 38% of significant ascending aortic plaques and underestimated their severity (68).

More recently, 268 patients with aortic arch atheromas ≥5 mm on transesophageal echocardiography were evaluated after cardiac surgery (69). Arch atheromas proved to be a highly significant risk factor for intraoperative stroke, which occurred in 11.6% (the general intraoperative stroke risk at that institution is 2.2%). In addition, this study (69) evaluated a subgroup of 43 patients (retrospectively) in whom aortic arch endarterectomy was done in an effort to prevent intraoperative stroke. The stroke risk was nearly

three times higher (34.9%) if an endarterectomy was done just before coronary bypass or valve surgery. Furthermore, the strokes that occur in patients with arch atheromas are major neurologic events. The in-hospital mortality rate in those patients with intraoperative stroke was 39%, and many of the survivors were severely disabled. The patients with intraoperative stroke had a significantly (nearly four times) greater number of days intubated and a significantly (approximately three times) higher incidence of prolonged awakening from anesthesia. As a result, their recovery room and length of stay in the intensive care unit were significantly longer. The total hospital length of stay was also very long for patients with arch atheromas (six weeks), both with and without stroke (comorbidity other than stroke was high in these patients with atheroma as well). Finally, the in-hospital mortality rate for the group of 268 patients with aortic arch atheromas on transesophageal echocardiography was 14.9%, more than double the general rate. Clearly, patients with aortic arch atheromas represent a high risk group for cardiac surgery, and this must be factored into the risk–benefit analysis that is done for these patients when cardiac surgery requiring cardiopulmonary bypass is contemplated.

MANAGEMENT OF PATIENTS WITH AORTIC ATHEROMAS

The proper management of patients with protruding aortic atheromas is not yet known. This section summarizes the current data that may be used to design a therapeutic approach to these patients.

Hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors. These reductase inhibitors, which block cholesterol synthesis and result in an increase in low density lipoprotein (LDL) receptor synthesis (and a drop in serum LDL), have become widely used in the primary and secondary prevention of coronary artery disease. A recent meta-analysis of randomized trials of these drugs in the prevention of myocardial infarction looked at the incidence of stroke (not the primary end point of the trials) (70). Data from a total of 49,477 patients treated with "statins" in 28 trials were pooled and compared with data from 56,636 control subjects. The relative risk of fatal and nonfatal stroke in treated patients was 0.76 (95% confidence interval 0.62 to 0.92). The authors concluded that in hyperlipidemic patients who have not previously had a stroke, HMG-CoA reductase inhibitors reduce the incidence of stroke. Stroke was a prespecified secondary end point in the Cholesterol And Recurrent Events (CARE) trial (71). Pravastatin versus placebo was used in 4,159 subjects with "average" cholesterol and LDL levels (mean 209 vs. 139 mg/dl) who had a myocardial infarction an average of 10 months before the study. Those treated with pravastatin had a 32% reduction in all-cause stroke and a 27% reduction in stroke

or TIA. In addition, there was no increase in hemorrhagic stroke with pravastatin.

In a study of eight patients with familial hypercholesterolemia, plaque area was evaluated using transesophageal echocardiography (72). With LDL-apheresis (n = 5), there was a reduction in plaque area, although with standard therapy in three patients no reduction was seen.

It does seems reasonable to consider the use of HMG-CoA reductase inhibitors in patients with aortic atherosclerosis. As noted earlier, aortic plaques that undergo thrombosis have been found to contain more lipid (29), and lipid reduction is one mechanism by which statins may stabilize plaques and prevent stroke. Statins have also been found to reduce thrombin generation by platelets, which is elevated in hypercholesterolemic patients (73). This could play a role in reducing plaque thrombosis. Actual regression of plaque size in the aorta could be another mechanism, as shown in one recent study in which patients with familial heterozygous hypercholesterolemia and aortic atheromas on transesophageal echocardiography were treated with pravastatin (74). These authors found that the atheroma grade remained stable on treatment in seven patients, progressed in three and regressed in six. Those with regression had a significantly greater reduction in plasma LDL.

Antithrombotic and anticoagulant treatment. Because thrombi have been documented to develop on and embolize from aortic atheromas, it may be logical to assume that anticoagulant treatment with warfarin may be beneficial in these patients. In fact, these mobile lesions have been noted to disappear during anticoagulant therapy (32,75) or with the use of a thrombolytic agent (34). However, there is significant resistance to the use of warfarin in patients with aortic atherosclerosis because of the theoretic risk of plaque hemorrhage aggravating the atheroemboli syndrome ("blue toes," often with renal failure or intestinal infarction [76]). There have been reports of individual patients with this syndrome worsening during anticoagulation (77,78), as well as a report of improvement, with resolution of an aortic thrombus on anticoagulation in a patient with the atheroemboli syndrome (16). Cholesterol emboli have been documented on skin, muscle and renal biopsy in patients with aortic atheromas seen on transesophageal echocardiography (39,40). However, the risk of clinically apparent atheroemboli syndrome during warfarin therapy in patients with aortic atheromas on transesophageal echocardiography appears to be low (only one episode in 134 patients in the SPAF trial) (79).

Three reports shed light on the question of whether or not warfarin will prove to be beneficial in patients with aortic atheromas. The first described 31 patients with mobile lesions in the aorta on transesophageal echocardiography (80). There was a higher incidence of vascular events in patients who were not treated with warfarin as compared with those given warfarin (at the discretion of the referring physicians) (45% vs. 5%). Strokes occurred in 3 of 11

patients not treated with warfarin, and in none of those treated with warfarin.

The second report is from the Stroke Prevention in Atrial Fibrillation Investigators Committee on Echocardiography (26). This was a randomized trial of patients with "high risk" nonvalvular atrial fibrillation. Because transesophageal echocardiography was done, the results for patients with both atrial fibrillation and aortic plaque could be reported. The risk of stroke in one year in 134 patients with complex aortic plaque was found to be reduced from 15.8% (11 events) in those treated with fixed low dose warfarin plus aspirin (International Normalized Ratio [INR] 1.2 to 1.5) to only 4% (3 events) in those treated with adjusted-dose warfarin (INR 2 to 3). Therefore, there was a 75% risk reduction for patients with atheromas who received "therapeutic range" anticoagulation. Although these patients with atrial fibrillation were randomized to the two treatment arms without regard for the presence or absence of aortic plaque, there were fewer strokes in patients with atheromas who were treated with full anticoagulation. As noted earlier, there was only one episode of the atheroemboli syndrome in warfarin-treated patients.

The third report was an observational study of 129 patients who were found to have aortic atheromas on transesophageal echocardiography, which was done to look for a source of cerebral or peripheral embolization (81) (27.5%) prevalence of atheroma, the same as in previous studies [9]). Treatment with oral anticoagulation, aspirin or ticlopidine was not randomly assigned. There was a significant reduction in the number of embolic events in patients with plaques ≥4 mm who received oral anticoagulants (0 events in 27 patients vs. 5 events in 23 patients treated with antiplatelet agents). For patients with mobile lesions, there was a significant reduction in mortality while they were on anticoagulants, although the trend toward fewer embolic events did not reach statistical significance in this group.

The data from these three reports suggest that warfarin is not harmful in patients with aortic atheromas, and in fact, there were fewer strokes in the patients who were given warfarin by their physicians. However, it is important to note that these studies are not randomized trials of treatment for patients with atheromas, and the numbers are relatively small. Clearly, a trial with sufficient power to detect a significant treatment effect (or harm) should be done to evaluate the possible efficacy of anticoagulation (warfarin) and various antithrombotic therapies in patients with significant thoracic aortic atheromas.

Operative approaches to patients with severe atherosclerosis of the aortic arch and ascending aorta. Aortic arch endarterectomy as a primary procedure for patients with previous emboli has been described in three case reports of relatively young patients (average age 55 years) who had recurrent emboli despite anticoagulation (15,30,82). There have been additional case reports of successful arch endarterectomy, and this operation was proposed as a possible

standard by which to treat the problem (83). However, it is clear from the larger series of patients described earlier (69) that arch endarterectomy greatly increases the risk of major intraoperative stroke, and this procedure should not be done on a routine basis.

In a study of 500 patients having cardiac surgery, the aorta was evaluated with intraoperative epiaortic ultrasound (68). In the 68 patients with ascending aortic atherosclerosis, various changes in technique were used in an attempt to prevent stroke (changing the site of cannulation, clamping or graft anastomosis and graft replacement [n = 10] of the ascending aorta). There was only one neurologic event in these 68 patients (1.5%). This series was expanded in a subsequent report of 231 patients with moderate or severe ascending aortic atherosclerosis (84). Replacement of the ascending aorta in 27 patients resulted in an intraoperative stroke rate of 0%.

In 111 other patients with ascending atherosclerosis, interventions short of replacement of the ascending aorta were undertaken in an attempt to avoid manipulating, cannulating or clamping the diseased segments. These maneuvers included use of the femoral artery or alternate sites in the ascending aorta or arch for cannulation; no aortic clamping or placement of the clamp more proximally in the ascending aorta or arch; retrograde (coronary sinus) cardioplegia installation or the use of hypothermic fibrillatory arrest; and alternate sites on the ascending aorta for attachment of the proximal coronary grafts. The stroke rate in these 111 patients with more minor interventions was nearly fourfold higher than the general stroke rate in 1,200 consecutive patients (6.3% vs. 1.6%).

To summarize the current data regarding operative interventions during cardiac surgery requiring cardiopulmonary bypass in patients with significant atheromas of the aortic arch and ascending aorta, 1) arch endarterectomy is generally counterproductive and its use should be restricted to good (relatively young) operative candidates with recurrent critical events despite other therapy; 2) attempts to avoid manipulation and cannulation of diseased segments appear to be prudent, but do not necessarily prevent stroke; and 3) graft replacement of the ascending aorta is feasible and resulted in no intraoperative strokes in 27 reported cases. Replacement of the ascending aorta does not address significant disease more distally (in the arch), and its successful outcome depends on a surgical group with the skill and experience to accomplish this with excellent results similar to those in the published studies. Finally, the presence of ascending or aortic arch atheromas on transesophageal echocardiography or intraoperative epiaortic ultrasound is a contraindication to the use of the new, minimally invasive port-access techniques for heart surgery, as the intra-aortic endoclamp used with these techniques cannot be advanced safely into the ascending aorta in such patients (85).

Minimally invasive direct coronary artery bypass graft surgery (MIDCAB) is a procedure that allows stabilization

of coronary artery segments so that they can be grafted while the heart is beating. Most often, the left internal mammary artery is grafted to the left anterior descending coronary artery as the primary procedure (with no need for a proximal aortic anastomosis). Because no cardiopulmonary bypass is used, stroke and peripheral embolization due to manipulation of the thoracic aorta may be avoided in patients with aortic atheromas. Early reports of this technique in patients with aortic arch atheromas on transesophageal echocardiography have shown that the procedure can be performed without intraoperative stroke (86,87), although MIDCAB did not prevent neuropsychiatric dysfunction in one small study (88). Further data will help to evaluate the utility of the MIDCAB technique for patients with atheromas who require CABG. The technique obviously does not apply to those requiring valve operations.

Cardiac catheterization. The studies cited earlier document an association between aortic plaque and embolic complications due to the passage of catheters, and debris can be retrieved from coronary guiding catheters in many patients with such plaque (59,62). There are no trials of various maneuvers to prevent embolic complications due to catheterization of the aorta; however, a right brachial approach (rather than femoral), by definition, avoids atheromas in the femoral and iliac arteries, the abdominal and descending aorta and the aortic arch. Ascending aortic atheromas are less common than arch atheromas, and the plaque burden increases further in the descending aorta (53). Innominate atheromas are not visible on transesophageal echocardiography, but they are uncommon (only five were seen in 520 MRI studies of the great vessels in one series (unpublished data). Such an approach must still traverse the innominate artery and ascending aorta, but it is possible that this may entail less risk than that with traditional femoral catheterization, and this brachial approach has been proposed for patients with peripheral vascular disease (89).

Conclusions. Aortic atheromas have been recognized, along with carotid artery disease and atrial fibrillation, as a leading cause of embolic stroke and peripheral organ damage. The prevalence of thoracic aortic atheromas (~27% in patients with previous events) is on the same order of magnitude as the other two etiologies, and atheromas are therefore responsible for many so-called "cryptogenic strokes." Plaque thickness and superimposed mobile thrombi are risk factors for embolic events, and plaque ulceration and the absence of calcification (lipid-rich plaques?) may be as well. When atheromas were present, the incidence of future stroke in three separate studies was 12% in a single year, and the incidence of stroke or peripheral embolic events was as high as 33%. The technique of choice for the diagnosis of this condition is transesophageal echocardiography, which is only minimally invasive and can be performed at the bedside in awake patients. Transesopha-

geal echocardiography has also been shown to be cost-effective in stroke patients (90).

The vital question of therapy remains to be answered. Although aortic arch endarterectomy is technically possible, its routine use as an adjunct to cardiac surgery in patients with arch atheromas should be abandoned, as the procedure greatly increases the stroke risk. Anticoagulant agents have been associated with fewer strokes in the published data; however, their role, as well as that of antithrombotic drugs and strategies to promote atheroma stabilization and regression, must be evaluated in prospective, randomized clinical trials that are sufficiently sized to detect a significant treatment effect or detriment.

Reprint requests and correspondence: Dr. Itzhak Kronzon, Department of Medicine, New York University School of Medicine, 560 First Avenue, New York, New York 10016.

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