Atherosclerosis of the Ascending Aorta
Prevalence and Role as an Independent Predictor of Cerebrovascular Events in Cardiac Patients

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Background and Purpose The cause of cerebral and peripheral embolism remains undetermined in a significant number of patients. An atherosclerotic thoracic aorta has thus far been considered to be an uncommon one.

Methods To define the potential role of the ascending thoracic aorta as an embolic source, intraoperative ultrasonic aortic imaging was performed in 1200 of 1334 consecutive patients aged 50 years and older who were undergoing cardiac surgery. Patients were divided into two groups according to the results of the ultrasound study in terms of presence or absence of atherosclerotic disease. The prevalence of previous neurological events in the two groups was characterized and compared.

Results Ascending aortic atherosclerosis was present in 231 (19.3%) of the patients studied. Patients in this category were older (P<.0001). A higher percentage of them were smokers (P<.0001) compared with patients with less severe disease. Coronary artery disease was more extensive (P=.012), and a higher percentage of these patients had a history of peripheral vascular disease (P<.0001). Univariate analysis of the subjects with (n=158) and without (n=1042) previous neurological events indicated that age, body mass index, atrial fibrillation, hypertension, and atherosclerosis of the ascending aorta were associated significantly with previous occurrence of a cerebrovascular accident. For the group as a whole, multiple logistic regression analysis demonstrated that hypertension (odds ratio, 1.81; P=.002), atherosclerosis of the ascending aorta (odds ratio, 1.65; P=.013), and atrial fibrillation (odds ratio, 1.54; P=.060) were significantly and independently associated with the occurrence of previous neurological events.

Conclusions Atherosclerosis of the ascending aorta is an independent risk factor for cerebrovascular events. An atherosclerotic ascending aorta may represent a potential source of embol or may be a marker of generalized atherosclerosis.

Cerebrovascular events in cardiac disease and cerebrovascular arterial disease are common causes of embolic neurological events in a significant number of patients.1 Cardiac emboli can arise from thrombi in the left ventricle, left atrium, or left atrial appendage or paradoxically from the right atrium through an atrial septal defect or patent foramen ovale.2,3 Mitral and aortic prosthetic valves can develop thrombi or vegetations that also can embolize.4 A significant number of these abnormalities can be readily identified by transthoracic or transesophageal echocardiography.5 However, the specific cause of cerebral infarction is often elusive. The National Institute of Neurological Disorders and Stroke (NINDS) Stroke Data Bank, a large prospective study of more than 1800 patients, showed that 40% of cases of cerebral infarction were "of undetermined cause."6

Generally, the atherosclerotic thoracic aorta has not been considered to be an important or common cause of cerebral and peripheral embolism. However, case reports have implicated it as a likely source of thrombotic or cholesterol embolism to the brain7-10 or the periphery11-13 occurring spontaneously, after initiation of anticoagulation,14-16 after cardiac surgery,17-22 or after other invasive procedures.23,24

Recently an autopsy study evaluated the relation between ulcerated plaques in the ascending aorta and aortic arch in 500 consecutive patients with cerebrovascular events and other neurological disorders. Patients with ulcerated plaques in the ascending aorta and aortic arch had a significantly greater prevalence of cerebral embolic events compared with the prevalence in those without such plaques.25 Accordingly, atherosclerotic involvement of the thoracic aorta may be an insufficiently recognized cause of cerebral and/or peripheral embolization.

To define the potential role of the ascending thoracic aorta as an embolic source, intraoperative epiaortic ultrasonic aortic imaging was performed in patients undergoing cardiac surgical procedures. This patient population was chosen because high-quality ultrasonic images of the ascending aorta can be obtained at the time of surgery. Our group and others have shown that intraoperative epiaortic ultrasound can be used to accurately assess atherosclerosis of the ascending aorta.26-31 The presence or absence of atherosclerosis of the ascending aorta was characterized and compared with the incidence of previous neurological events (transient ischemic attacks [TIAs] and/or stroke). Our hypothesis was that atherosclerosis of the ascending aorta would be...
a significant and independent risk factor for cerebrovascular events.

Subjects and Methods

Patient Population

From January 15, 1990, through July 7, 1992, 1200 of 1334 consecutive patients 50 years of age and older who were undergoing open heart surgery at The Jewish Hospital of St Louis underwent intraoperative epicardiac ultrasound of the ascending aorta. This group of patients represented 91% of those undergoing cardiac surgery during this period. Written informed consent, in a format approved by the Human Studies Committee at the Jewish Hospital of St Louis, was given by all patients before surgery. Ultrasonic imaging was not performed in 134 patients because of unavailability of the equipment or in some emergency procedures. Patients not included in this series were younger than 50 years of age (8.5%) or were undergoing emergency surgery (0.5%). The group included 742 men and 458 women with a mean age of 68 years (range, 50 to 90 years). The majority of the patients (n=830, 69.2%) underwent isolated coronary artery bypass graft surgery; 229 (19.1%) underwent a coronary artery bypass graft combined with another procedure. The remaining 11.7% of patients had insignificant coronary artery disease and required other cardiac surgical procedures including tricuspid, aortic, and/or mitral valve repair/replacement; left ventricular aneurysmectomy; septal myectomy; and closure of ventricular or atrial septal defects.

Ultrasonic Methods and Data

Ultrasonic epicardiac imaging of the ascending aorta was performed during cardiac surgery in each patient. After induction of anesthesia, the chest was opened, and the heart was suspended in a pericardial cradle filled with sterile saline. A 7.0-MHz linear ultrasound transducer (Acuson Computed Sonography) was inserted in a sterile sheath and placed directly over the ascending aorta. Transverse and longitudinal images of the ascending aorta were obtained from the level of the aortic root to the level of the proximal aortic arch, just distal to the innominate artery (Fig 1). The images were evaluated for the presence of atherosclerosis, and the patients were divided into two groups: those with no atherosclerosis (intimal thickening <3.0 mm, without intimal irregularities) and those with ascending aortic atherosclerosis (intimal thickening ≥3.0 mm, with diffuse irregularities, calcification, and/or one or more of the following: large protruding or mobile atheromatous debris, ulcerated plaques, and/or thrombi). The proximal, mid, and distal thirds of the ascending aorta were graded as described above, and the poorest grade for each segment was used in the final analysis of the data. All aortic scans were analyzed independently by two investigators who were blinded to the patients' clinical histories and to all other variables. Inconsistencies in the observations of these two investigators were reconciled by consensus.

Definition of Cerebral Event

At the time of hospital admission, each patient was questioned to determine the presence or absence of history of cerebral neurological events such as stroke or TIA. Positive histories were verified by communication with the patient's neurologist or by review of the medical records, including documentation by computed tomography or magnetic resonance imaging. Patients with known primary neurological disorders were not classified as having had "neurological events" (TIA or stroke). Those in whom neurological events could not be documented were considered to have had no neurological events.

Definition of Variables Analyzed

A total of 14 variables were correlated with atherosclerosis of the ascending aorta. All the data were collected prospectively by one investigator who was blinded to the results of the epicardiac ultrasonic scanning.

Demographic and historical data recorded included the following: age, sex, body mass index (in kilograms per meter squared), history of hypertension requiring treatment with antihypertensive medication, history of diabetes mellitus (insulin or oral hypoglycemic therapy or a carbohydrate-restricted diet), history of smoking (yes/no), the presence of left-sided prosthetic valves, history of peripheral vascular disease, and use of aspirin and/or warfarin at the time of admission.

The presence or absence of mitral stenosis (valve area <2 cm²) was judged from data obtained by cardiac catheterization or by echocardiographic examination. Left ventricular function was assessed angiographically in the right anterior oblique projection according to the Coronary Artery Surgery Study (LV posterior score of 5, normal; 6 to 10, mild LV posterior dysfunction; 11 to 15, moderate dysfunction; and >16, severe dysfunction) or from the echocardiographic ejection fraction (ejection fraction >55%, normal [score=5]; 40% to 54%, mild dysfunction [score=8]; 25% to 39%, moderate dysfunction [score=12]; and <24%, severe dysfunction [score=16]). The number of major epicardiac vessels with 50% obstruction or more was used to compare the extent of coronary artery disease.

Carotid duplex scanning was performed in all patients aged 65 years and older and in younger patients with a history of TIA or stroke. The carotid ultrasound study was considered indicative of severe disease if a diameter reduction of 75% or greater was present in one or both internal carotid arteries. The presence or absence of anterior myocardial infarction was assessed by 12-lead electrocardiography (Q waves in V
through $V_{j}$). The serum cholesterol level was assessed as a continuous variable.

**Statistical Analysis**

Data were analyzed by SAS as implemented on the SUN computer system of the Division of Biostatistics at Washington University. Results are expressed as mean±SD. Between-group comparisons were made with $t$ tests for continuous variables and $\chi^2$ tests for discrete variables. However, because the distributional requirements of a $t$ test could not be satisfied, Wilcoxon's test was used to compare body mass index and the number of atherosclerotic coronary arteries in patients with, versus those without, a history of an event. To determine the best set of independent predictors of an event, PROC LOGISTIC of the SAS system was used to perform a stepwise logistic regression analysis. Ninety-five percent confidence intervals (CIs) on odds ratios (ORs) were computed by use of a standard formula. Statistical significance was attributed at $P<.05$.

Because the predictive power of atherosclerosis of the ascending aorta may be mediated in part by the concomitant presence of carotid atherosclerosis and because delineation of carotid disease was undertaken routinely only in subjects 65 years of age and older, our analysis of factors associated with cerebral embolic events was performed in two parts. In the first we evaluated risk factors for cerebral events in all 1200 subjects. This analysis excluded considerations of the impact of carotid disease. In the second analysis we considered only the 789 subjects aged 65 years and older for whom data regarding carotid disease were available.

ORs provide a useful measure of the odds of a particular disease in a patient with a given risk factor compared with a patient without a given risk factor. However, these ratios say nothing about the public health consequences of a given risk factor because they do not incorporate information about its prevalence. Thus, we computed the attributable risk associated with each factor in our final regression model. The attributable risk provides a measure of the percentage of cases of a particular disease that is associated with exposure to a given risk factor and can be computed with a standard formula.33

**Results**

**Prevalence of Atherosclerosis**

Characteristics of the two patient groups are presented in Table 1. Ascending aortic atherosclerosis was present in 231 patients (19.3%); these patients were older (71.1±8.0 versus 67.7±8.5 years; $P<.0001$) and had a lower body mass index (25.6±4.8 versus 27.3±9.7 kg/m²; $P<.0001$) than those with no atherosclerosis. These patients also had more extensive coronary artery disease, as determined by the number of vessels affected (3.02±1.3 versus 2.76±1.4 diseased coronary vessels; $P<.0001$), and a higher incidence of peripheral vascular disease (19.5% versus 6.8%; $P<.0001$) than those with no atherosclerosis of the ascending aorta. A higher percentage of patients with atherosclerosis of the ascending aorta were smokers (61.3% versus 46.4%; $P<.0001$), and their mean cholesterol level was higher than the other group ($P=.030$). No significant difference was found between the two groups for the other variables analyzed.

As shown from a plot of the percentage of patients with moderate or severe atherosclerosis of the ascending aorta as a function of age (Fig 2), the percentage of patients with significant atherosclerosis of the ascending aorta increased with increasing age (from 9.6% in the sixth to 32.6% in the ninth decade of life). Epi-aortic ultrasound images typical of patients with atherosclerosis of the ascending aorta and corresponding pathological specimens are shown in Fig 3.
Risk Factors Associated With Cerebral Embolic Events

A total of 158 patients (13%) had a history of previous neurological events (50 TIAS and 108 strokes). The left side of Table 2 summarizes the characteristics of all 1200 subjects with and without a history of neurological events. Factors associated with an increased likelihood of previous neurological events were advanced age (P=.023), lower body mass index (P=.033), atrial fibrillation (P=.053), the use of warfarin (P=.011), hypertension (P=.001), and the presence of ascending aortic atherosclerosis (P=.012). With the exception of warfarin use, all of these variables were entered into a stepwise logistic regression analysis, with the final model consisting of all variables with a value of P<.1.

Table 3 summarizes the results of the multiple logistic regression analysis. For all subjects, the three factors independently associated with a history of neurological events were hypertension (P=.002), ascending aortic atherosclerosis (P=.013), and atrial fibrillation (P=.060). ORs were 1.81 (95% CI, 1.24 to 2.66) for hypertension, 1.65 (95% CI, 1.11 to 2.43) for ascending aortic atherosclerosis, and 1.54 (95% CI, 0.98 to 2.43) for atrial fibrillation.

Results of the univariate analysis of the 789 subjects (aged ≥65 years) for whom data defining the presence or absence and severity of carotid disease were available are summarized on the right side of Table 2. The only factors that were associated with neurological events were hypertension (P=.004), diabetes (P=.045), ascending aortic atherosclerosis (P=.033), and severe carotid artery disease (P=.002).

Table 3 also lists the results of the multiple logistic regression analysis with data from patients for whom carotid artery disease data were available. Among these patients, factors independently associated with a history of neurological events were severe carotid artery disease (P=.008), hypertension (P=.014), and ascending aortic atherosclerosis (P=.053). Associated ORs were 2.70 (95% CI, 1.29 to 5.62) for severe carotid artery disease, 1.77 (95% CI, 1.12 to 2.81) for hypertension, and 1.54 (95% CI, 0.99 to 2.38) for ascending aortic atherosclerosis. The ORs strongly suggest that among the three variables in this model, severe carotid artery disease has the strongest association with neurological events. However, ORs do not reflect the prevalence of the risk factor. Among these patients, risk factor prevalences were 4.6% for severe carotid artery disease, 23.4% for ascending aortic atherosclerosis, and 64.2% for hypertension. Attributable risks associated with the
TABLE 2. Characteristics of Patients With and Without Previous Neurological Events

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Subjects (n=1200)</th>
<th>Subjects With Carotid Artery Ultrasound Data (n=789)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Event (n=1042)</td>
<td>Event (n=158)</td>
</tr>
<tr>
<td>Age,*y</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>68.1±8.6</td>
<td>69.8±8.1</td>
</tr>
<tr>
<td>Body mass index,* kg/m²</td>
<td>27.1±9.5</td>
<td>26.0±4.1</td>
</tr>
<tr>
<td>Left main disease, %</td>
<td>22.4</td>
<td>20.2</td>
</tr>
<tr>
<td>Extent of coronary artery disease†</td>
<td>2.83±1.4</td>
<td>2.72±1.5</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>38.0</td>
<td>39.9</td>
</tr>
<tr>
<td>Mitral stenosis, %</td>
<td>2.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>12.8</td>
<td>18.5</td>
</tr>
<tr>
<td>Warfarin, %</td>
<td>12.6</td>
<td>23.7</td>
</tr>
<tr>
<td>Aspirin, %</td>
<td>54.3</td>
<td>51.9</td>
</tr>
<tr>
<td>Anterior myocardial infarction, %</td>
<td>8.7</td>
<td>11.4</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>60.9</td>
<td>74.2</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>26.7</td>
<td>31.8</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>49.1</td>
<td>50.0</td>
</tr>
<tr>
<td>Peripheral vascular disease, %</td>
<td>9.0</td>
<td>10.8</td>
</tr>
<tr>
<td>Ascending aorta atherosclerosis, %</td>
<td>18.1</td>
<td>26.6</td>
</tr>
<tr>
<td>Cholesterol,* mg/dL</td>
<td>212±46</td>
<td>207±53</td>
</tr>
<tr>
<td>Severe carotid artery disease, %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Patients aged ≥65 years.
†Mean±SD.
‡Determined by number of vessels affected.

three variables are 5.8% for severe carotid artery disease, 9.9% for ascending aortic atherosclerosis, and 32.8% for hypertension.

Discussion

In this study we compared the results of ultrasonic scanning of the ascending aorta with the incidence of previous neurological events. One hundred fifty-eight of the 1200 patients in our study had such a history, and the percentage of those in this group with atherosclerosis of the ascending aorta was significantly higher than that in the group without previous neurological events. Ascending aortic atherosclerosis remained a significant risk factor even when other risk factors, such as atrial fibrillation and hypertension, were included in the analysis.

Clinical entities associated with an increased risk of cerebral neurological events include atrial fibrillation,36,37 hypertension,38,39 severe carotid artery disease,40,41 diabetes mellitus,42 valvular heart disease,43,44 and mitral annular calcification.45 However, the specific cause of cerebral neurological events often cannot be identified.4 The atherosclerotic thoracic aorta has been recognized for years as a probable contributor to the development of renal failure,16,23,24,46 peripheral embolism,11,13,47 and TIA or stroke.7-10 In particular, the problem of intraoperative atheroembolism during cardiac surgery has become increasingly recognized.17,22,48 Strategies for the identification of atherosclerosis26,27,29-31,49 and prevention of embolization have been discussed recently.26,27,29,31,20-22

Case reports have implicated the thoracic aorta proximal to the arch vessels as a likely source of embolism to the brain and other organs, but large studies to ascertain its true significance have not been undertaken. In a recent autopsy study the presence of ulcerated plaques in the aortic arch was correlated with a premorbid history of cerebrovascular and other neurological diseases in 500 consecutive patients. A prevalence of ulcerative plaques of 58% was found in the aortic arches of patients with ischemic stroke of unknown cause, a prevalence of ulcerative plaques of 20% was found in those with ischemic stroke of known cause, and a prevalence of only 5% was found in those with other neurological diseases, suggesting a link between aortic arch atherosclerosis and cerebral embolic events.23 Un-
Unfortunately, this study suffered from the selection bias inherent in all autopsy studies. Furthermore, other risk factors, such as hypertension and diabetes mellitus, were not considered.

Until recently it was not possible to identify atherosclerosis of the ascending aorta without direct visualization of the vessel (ie, at surgery or autopsy). However, with the development of techniques such as magnetic resonance imaging, computed tomography,23-24 and transesophageal echocardiography,25-28 it has become possible to assess atherosclerosis of the thoracic aorta noninvasively. Our group and others have shown that high-frequency ultrasonic probes can be used on the ascending aorta to define the extent of atherosclerosis at the time of cardiac surgery.26,27,29-31

Significance of Atherosclerosis of the Ascending Aorta

When all 1200 patients were evaluated, ascending aortic atherosclerosis was a significant independent predictor (P = .024; OR, 1.65) of neurological events. It achieved borderline significance (P = .055; OR, 1.54) after statistical adjustment for carotid artery disease among the 789 patients in whom data on carotid ultrasound were available. Thus, our data suggest that aortic atherosclerosis is an independent risk factor for the development of neurological events and that it may be associated with an increase of approximately 60% in the likelihood of such events. The OR of 2.70 that was associated with carotid artery disease was much greater than the corresponding ratio for ascending aortic atherosclerosis. However, the attributable risks associated with ascending aortic atherosclerosis and carotid artery disease appear similar. It is possible that atherosclerosis of the ascending aorta is a marker of generalized atherosclerotic disease rather than the cause of neurological events.

Limitations of the Study

Several factors may have limited the apparent strength of the relation we found between aortic atherosclerosis and neurological events. First, our ultrasonic technique was applicable to examination of the ascending aorta only. Unfortunately, we were not able to obtain good views of the aortic arch. Amarenco et al32 found more severe atherosclerosis (ulcerated plaques) in the aortic arch, near the origins of the arch vessels, than in the ascending aorta (81% versus 44%) in a group of patients with atherosclerosis. Thus, if the association between cerebrovascular events and atherosclerosis of the aortic arch is as strong as the association observed between ascending aortic atherosclerosis and cerebrovascular events, additional events could be explained with the use of these data. This implies that the ORs presented here underestimate the true impact of aortic atherosclerosis.

Second, because of limitations of retrospective assessments, we were unable to determine the exact time of occurrence and the anatomic loci of many of the neurological events. If we had been able to confine our analysis to neurological events that occurred within the recent past and those that could not have been explained by significant contralateral carotid artery disease, it may have been possible to ascertain the relative contribution of aortic atherosclerosis more definitively.

Despite the high spatial resolution of the ultrasonic system, we are unable to identify specific patients with significant atherosclerosis who are at high risk of embolic events.

Although the patient population was highly selected and many had significant coronary artery disease, most deaths in patients with stroke and TlsAs occur in patients with coronary artery disease1,59,60 and hypertension.28 Thus, our results may be quite widely applicable.

Conclusions

Atherosclerosis of the ascending aorta is present in approximately 20% of cardiac surgical patients aged 50 years and older, and the percentage increases with age. Patients with atherosclerosis of the ascending aorta have a significantly higher incidence of previous cerebrovascular events, independent of other demographic and clinical data. An atherosclerotic ascending aorta may represent a potential source of emboli or may be a marker of generalized atherosclerosis.

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References

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