Association Between Large Aortic Arch Atheromas and High-Intensity Transient Signals in Elderly Stroke Patients

Tanja Rundek, MD; Marco R. Di Tullio, MD; Robert R. Sciacca, PhD; Inna V. Titova, BS; Jay P. Mohr, MD; Shunichi Homma, MD; Ralph L. Sacco, MD

Background and Purpose—Aortic arch atheromas (AAs) have been shown to be a risk factor for ischemic stroke (IS) in the elderly because of their potential for cerebral embolization. However, the association between AAs and the presence of cerebral microemboli has not been clearly established. The aim of this study was to determine whether large AAs are associated with an increased frequency of high-intensity transient signals (HITS) in elderly patients with IS.

Methods—We performed bitemporal simultaneous HITS monitoring of both middle cerebral arteries in 62 consecutive elderly patients with acute IS (mean age 72.5 ± 8.8 years, 65% men). In 16 patients, one or both temporal windows were inadequate; therefore, the analysis of HITS was performed in the remaining 46 patients. All patients underwent omniplane transesophageal echocardiography (TEE), and they had no significant extracranial or intracranial artery disease and no cardiac prosthetic valves. Large AA was defined as ≥4 mm in thickness. Complex AA was defined as ulcerated or mobile, regardless of plaque thickness. HITS monitoring was performed within 24 hours of TEE and analyzed by an experienced neurologist-sonographer blinded to TEE findings. A 9-dB threshold was chosen to discriminate HITS from background Doppler signal. The HITS counts in the left and in the right middle cerebral arteries were added and reported as a total number of HITS in 30 minutes.

Results—HITS were detected in 14 (78%) of 18 patients with large AAs versus 8 (29%) of 28 patients with no or small AAs (odds ratio [OR] 8.8, 95% CI 2.2 to 34.8; P = 0.001). The association was also present in 27 patients with no other cardiac embolic sources, such as atrial fibrillation, patent foramen ovale, spontaneous echo contrast, and thrombus (7 of 10 patients with large AAs versus 3 of 17 patients with small or no AA; OR 10.9, 95% CI 1.7 to 68.5; P = 0.013). Complex AAs were associated with a higher frequency of HITS than were noncomplex AAs (6 of 6 patients with complex AAs versus 15 of 39 patients with noncomplex AAs; OR 2.6, 95% CI 1.7 to 3.9; P = 0.005).

Conclusions—HITS are significantly associated with large AAs in elderly stroke patients. This observation may support the causal role of large AAs in IS. (Stroke. 1999;30:2683-2686.)

Key Words: aortic arch • embolism • stroke, ischemic • ultrasonography, Doppler, transcranial

Aortic arch atheromas (AAs) have been shown to be associated with an increased risk of ischemic stroke (IS) in the elderly because of their potential for embolization in the cerebral circulation.1-4 After the embolic potential of AAs had been recognized from pathological studies,5,6 the introduction of transesophageal echocardiography (TEE) allowed for the accurate visualization of the proximal portion of the aorta and provided a tool for assessing the role of AAs as a risk factor for cerebral and peripheral embolism in vivo.4-12 AAs have been linked to an increased risk of embolic events in numerous case-control and cross-sectional studies as well as in some prospective cohort studies.2,4,13 However, the causal role of AA for cerebral microembolism in individual patients has not been clearly established.

Transcranial Doppler (TCD) ultrasound is capable of detecting microembolic material in the arteries of the circle of Willis by recording high-intensity transient signals (HITS) within regular Doppler frequency spectra.14-16 Although these HITS can be clinically silent, they may be clinically important as a marker of increased risk of stroke.17-22 The clinical relevance of HITS, however, remains uncertain. Their detection may be important in patients with AAs, indicating the propensity of AAs to act as a source of cerebral emboli. The examination of AAs by TEE and monitoring of HITS by TCD may therefore be helpful in the selection of stroke patient for prophylactic treatment.

Although multiple studies have linked the presence of AAs with cerebral embolism, the association of large AAs with

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HITS has never been shown in a series of consecutive elderly patients with IS. The present study was aimed at determining whether large AAs are associated with an increased frequency of HITS in elderly patients with acute IS.

Subjects and Methods
As part of the APRIS (Aortic Plaque and Risk of Ischemic Stroke) study, 62 consecutive patients over the age of 60 with first-ever acute IS in the anterior circulation were studied. All patients underwent omniplane TEE and TCD monitoring for HITS within 1 week of stroke onset. All patients also underwent color duplex Doppler of carotid and vertebral arteries, TCD scanning of the circle of Willis and vertebrobasilar system, and brain CT or MRI. Patients with stenosis of >40% of at least one artery in the extracranial (carotid or vertebral arteries) or intracranial (arteries of the circle of Willis or intracranial segment of the vertebral arteries and basilar artery) circulation and patients with prosthetic cardiac valves were excluded from the study before TCD monitoring because of the possible presence of a confounding embolic source.

Transesophageal Echocardiography
TEE was performed by use of a 5-MHz omniplane transducer. The aorta was imaged in transverse and longitudinal views. The aortic arch was defined as the portion of aorta between the curve at the end of the ascending portion and the origination of the left subclavian artery. An atheroma was defined as a discrete protrusion of the intimal surface of the vessel at least 2 mm in thickness and different in appearance and echogenicity from the adjacent intact intimal surface. The presence and location of any atheroma was recorded. In the case of multiple AAs, the most advanced lesion was considered. Aortic arch plaques were characterized according to previously described criteria as large (≧4 mm in thickness), smaller (<4 mm in thickness), or not present. Atheromas with ulceration and/or mobile components were classified as complex, according to the previously published definition. An ulceration was defined as a discrete indentation of the luminal surface of the plaque with base width and maximum depth of at least 2 mm each. The videotapes were reviewed by a single experienced echocardiographer who was blinded to the TCD-HITS results.

TCD Monitoring
The bitemporal simultaneous HITS monitoring of both middle cerebral arteries (MCAs) was performed within 24 hours of TEE according to the standardized protocol published previously. The recording was performed with a 2-channel transcranial Doppler system (TC 2020 EME/Nicolet, 486 processor and 128–fast Fourier transform [FFT] and 2–MHz multiplane probes) equipped with the automated software for HITS detection (EME/Nicolet, version 1.0). The Doppler frequency spectra of both MCAs were recorded continuously for 30 minutes by using a standardized procedure (supine position of patient whenever possible, depth of insonation of 45 to 58 mm from the probe, low to medium gain, and sample volume 10 to 12 mm). The pulse repetition frequency ranged from 4 to 8 kHz, and sweep time for simultaneous monitoring was 3.1 seconds. Based on these parameters, the FFT time-window overlap varied from 25% to 81%, missing <0.2% of embolic signals because of the inadequacy of the equipment characteristics.

HITS were identified by their transient, short (<0.1 second), and unidirectional high-amplitude signal with a narrow spectrum. A 9-dB threshold was chosen to discriminate microembolic signals from background noise, which was in accordance with the recommendations of the International Consensus Group on Microembolus Detection.

An experienced neurologist-sonographer who was blinded to the TCD findings identified HITS. The count was performed by a combination of different methods: (1) visual, by displaying the FFT of the color-coded Doppler spectra, (2) acoustical, by continuous on-line observation, and (3) off-line, by specially designed software for automated HITS detection. Artifacts were excluded during the on-line analysis by means of the characteristic bidirectional occurrence within the Doppler spectrum and of the chirping sounds produced by the probe movement, patient motion, coughing, narrow window, or inappropriate gain used during monitoring.

The HITS counts in the left and in the right MCAs were added, reflecting the total number of HITS in 30 minutes. The side of HITS was compared with the stroke side assessed clinically and by CT or MRI. The embolic signal amplitudes in decibels were also analyzed.

Statistical Analysis
The association of aortic plaque size and complexity with the presence of HITS and HITS amplitude was analyzed by the χ² test or Fisher exact test when appropriate. Crude odds ratios (ORs) for the association between AA size and complexity and the presence of HITS were calculated. The Spearman correlation coefficient (r) was calculated to determine the relationship between AA thickness and the frequency of HITS. All probability values were 2-tailed and considered significant at P<0.05. In the case of multiple comparisons, a Bonferroni correction was performed. For all statistical analyses, SAS statistical package version 6.12 (SAS Institute) was used.

Results
The initial study population consisted of 62 patients (mean age 72.5±8.8 years; 65% men; 50% Hispanics, 26% whites, and 24% African Americans). In 16 (26%) of 62 patients, TCD was not able to detect any signals in either MCA because of the temporal bone thickness (“poor or no” temporal windows). There was a greater proportion of women and African Americans among these 16 patients with inadequate temporal windows (13 women [81%] and 6 African Americans [38%]) compared with the 46 patients with adequate windows (16 women [35%] and 9 African Americans [20%]; P<0.05). Although the average age was slightly greater in patients with inadequate windows (76.6±7.4 years) than in those with adequate windows (72.6±8.9 years), the proportion of the patients aged >75 years was the same (44% in both groups).

Data analysis was therefore performed among the 46 patients with the interpretable TCD findings. Demographic and clinical characteristics of these 46 study patients are summarized in Table 1.

TCD detected HITS in 22 (48%) of 46 patients. The majority of these patients showed a low frequency of HITS, with an average number of 1.6±1.1 per 30 minutes (range 1 to 5). Fifteen patients (68%) had 1 HITS, 3 patients (13%) had 2 HITS, 2 (9%) had 3 HITS, 1 (5%) had 4 HITS, and 1 (5%) had 5 HITS. The amplitude of HITS ranged from 9 to 13 dB (average 10.6±1.7 dB). Patients with HITS did not differ from those without HITS with respect to age, sex, and race/ethnicity (except for the higher proportion of HITS detected among African Americans, 8 [42%] of 22 versus 2 [10%] of 24; P=0.025) and with respect to most of the common risk factors (Table 1). There was a higher frequency of HITS among patients with coronary heart disease (8 [42%] of 22 versus 3 [14%] of 24; P=0.049) or hypercholesterolemia (10 [53%] of 22 versus 4 [19%] of 24; P=0.026). HITS were detected more frequently on the symptomatic side (14 [64%] of 22 versus 7 [29%] of 24; P=0.019). HITS were less frequently observed in lacunar strokes (8 [33%] of 24 versus 1 [6%] of 22; P=0.016).
TABLE 1. Demographic and Clinical Characteristics of Study Patients According to Presence of HITS

<table>
<thead>
<tr>
<th></th>
<th>HITS+ (N=22)</th>
<th>HITS− (N=24)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;75 years</td>
<td>10 45</td>
<td>10 42</td>
<td>0.796</td>
</tr>
<tr>
<td>Sex Male</td>
<td>13 59</td>
<td>17 70</td>
<td>0.404</td>
</tr>
<tr>
<td>Race ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>8 42</td>
<td>2 10</td>
<td>0.025</td>
</tr>
<tr>
<td>White</td>
<td>4 21</td>
<td>6 28</td>
<td>0.422</td>
</tr>
<tr>
<td>Hispanic</td>
<td>7 37</td>
<td>13 62</td>
<td>0.127</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF</td>
<td>5 23</td>
<td>2 8</td>
<td>0.128</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>8 42</td>
<td>3 14</td>
<td>0.049</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 11</td>
<td>4 19</td>
<td>0.664</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8 42</td>
<td>6 25</td>
<td>0.370</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>10 53</td>
<td>4 19</td>
<td>0.026</td>
</tr>
<tr>
<td>Current smoking</td>
<td>4 21</td>
<td>2 8</td>
<td>0.398</td>
</tr>
<tr>
<td>CT/MR stroke side</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>14 64</td>
<td>7 29</td>
<td>0.019</td>
</tr>
<tr>
<td>Stroke subtype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacunar</td>
<td>1 6</td>
<td>8 33</td>
<td>0.016</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>5 23</td>
<td>3 15</td>
<td>0.301</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>16 71</td>
<td>13 52</td>
<td>0.193</td>
</tr>
<tr>
<td>TEE findings AAs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any AA Present</td>
<td>20 90</td>
<td>16 67</td>
<td>0.049</td>
</tr>
<tr>
<td>Complex AA</td>
<td>6 27</td>
<td>0 0</td>
<td>0.008</td>
</tr>
<tr>
<td>PFO</td>
<td>2 10</td>
<td>5 21</td>
<td>0.245</td>
</tr>
<tr>
<td>SPEC</td>
<td>6 27</td>
<td>3 13</td>
<td>0.187</td>
</tr>
<tr>
<td>Thrombus</td>
<td>2 10</td>
<td>0 0</td>
<td>0.223</td>
</tr>
<tr>
<td>Valvular strands</td>
<td>13 59</td>
<td>16 67</td>
<td>0.595</td>
</tr>
</tbody>
</table>

TABLE 2. Association Between AAs and HITS

<table>
<thead>
<tr>
<th>AAs</th>
<th>HITS+ (N=36)</th>
<th>HITS− (N=10)</th>
<th>Large (≥4 mm) (N=18)</th>
<th>Small or None (N=28)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present HITS+</td>
<td>20 56</td>
<td>2 20*</td>
<td>14 78</td>
<td>8 29†</td>
<td></td>
</tr>
<tr>
<td>Not HITS−</td>
<td>16 44</td>
<td>8 80</td>
<td>4 22</td>
<td>20 71</td>
<td></td>
</tr>
<tr>
<td>*P=0.064 (OR 5.0, 95% CI 0.9–26.9); †P=0.001 (OR 8.8, 95% CI 2.2–34.8).</td>
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<td></td>
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</tr>
</tbody>
</table>

TEE detected AAs in 36 (78%) of the 46 patients. Large AAs were found in 18 patients (39%), small AAs in 18 (39%), and no AA was found in 10 patients (22%). Complex AAs were found in 6 (17%) of 36 patients.

HITS were detected in 20 (56%) of 36 patients with AAs and in 2 (20%) of 10 patients without AAs (OR 5.0, 95% CI 0.98 to 26.9; P=0.064). Furthermore, HITS were detected in 14 (78%) of 18 patients with large AAs versus 8 (29%) of 28 patients with no or small AAs (OR 8.8, 95% CI 2.2 to 34.8; P=0.001; Table 2). The AA thickness and the frequency of HITS per 30 minutes were also highly correlated when analyzed as continuous variables (r=0.501, P<0.01).

Complex AAs were associated with a higher frequency of HITS than were noncomplex AAs (6 of 6 patients with complex AAs versus 15 of 39 patients with noncomplex AAs; OR 2.6, 95% CI 1.7 to 3.9; P=0.005).

After exclusion of patients with other possible TEE findings that may contribute to HITS (7 patients with atrial fibrillation, 7 with patent foramen ovale (PFO), 9 with spontaneous echo contrast (SPEC), and 2 with thrombi), the association between plaque size and HITS remained statistically significant (Figure). Among the 27 patients without other possible cardiac sources, HITS were detected in 7 (70%) of 10 patients with large AAs versus 3 (18%) of 17 patients with small AAs (OR 10.9, 95% CI 1.7 to 68.5; P=0.013).

**Discussion**

The present study demonstrates that TCD-detected HITS are significantly associated with large AAs in elderly acute IS patients. To our knowledge, this is the first reported systematic TCD study of HITS in IS patients with AAs. Previous studies have included a smaller number of patients with AAs, mainly referred for echocardiography to rule out a cardiac source of embolization, and most of them had atrial fibrillation, prosthetic cardiac valves, or cardiac thrombus.1,3,7–12,18,23,24

The clinical relevance of HITS in the cerebral circulation in patients with cardiac and carotid artery disease is still uncertain. However, several studies have found an association between HITS and increased risk of stroke.14,17–19,25–29 Tong et al19 found an association of HITS with known cardioembolic risk factors and history of prior stroke. In patients with carotid stenosis, HITS have been related to the degree of stenosis and associated with an increased risk of subsequent stroke or transient ischemic attack.17,27–29 Early finding of HITS after carotid endarterectomy has also been related to early postoperative stroke recurrence.29

Association between AA size and presence of HITS. The significant association observed in the entire group was also observed after exclusion of 19 patients with atrial fibrillation (7 patients), PFO (7 patients), SPEC (9 patients), and thrombus (2 patients).
We found the association between HITS and large AAs to exist even after exclusion of patients with other possible TEE findings that may cause HITS (atrial fibrillation, PFO, SPEC, and thrombi). Additionally, we found HITS in all patients with complex AAs, which are known to be associated with the greatest increase in stroke risk. Although the clinical relevance of such finding is still uncertain, it may support the causal role of large AAs in IS in elderly patients.

The present study has some limitations. Although we reported a statistically significant association between large AAs and HITS, definitive conclusions cannot be drawn from the presented results. Data were obtained in a selected population of elderly patients with IS and with no evidence of significant extracranial or intracranial carotid artery disease. Furthermore, the number of patients analyzed in the study was small. A significant proportion of the patients (26%) was excluded because of an inadequate acoustical window. This was related to the higher proportion of African Americans and women in our study in whom we were unable to insonate intracranial vessels. This situation has also been previously reported. Also, results apply only to elderly patients. However, the reported prevalence of large atheromas in patients aged <60 years is low. Finally, the lack of a control group precludes the assessment of the association between HITS and AAs in stroke-free subjects. The presence of HITS and their association with large AAs in stroke-free subjects could make the relation between this finding and the risk of stroke less strong. However, this would not necessarily detract from the potential clinical relevance of HITS, because HITS could also be related to silent infarcts and increased future risk of stroke or other vascular events. Prospective follow-up studies are necessary to further determine the clinical significance of HITS.

The examination of AAs by TEE and the potential for cerebral microembolism by TCD-HITS monitoring might have a role in the management of patients with acute stroke. HITS monitoring in patients with large AAs may be important for determining the risk of stroke recurrence and may be important in stratifying patients into groups that may benefit from different stroke prevention medications. Larger prospective studies are required to confirm the clinical relevance of the association between HITS and AAs and to determine the predictive value of HITS detection.

Acknowledgments

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References

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