Original Paper

Cerebrovascular Diseases

Cerebrovasc Dis 2012;33:322–328
DOI: 10.1159/000335828

Received: July 15, 2011
Accepted: December 12, 2011
Published online: February 15, 2012

CT Angiography of the Aorta Is Superior to Transesophageal Echocardiography for Determining Stroke Subtypes in Patients with Cryptogenic Ischemic Stroke

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Key Words

Acute ischemic stroke · Cryptogenic stroke · CT angiography · Transesophageal echocardiography · Aorta · Aortic atherosclerosis

Abstract

Background: The etiology of ischemic strokes remains cryptogenic in about one third of patients, even after extensive workup in specialized centers. Atherosclerotic plaques in the aorta can cause thromboembolic events but are often overlooked. They can elude standard identification by transesophageal echocardiography (TEE), which is invasive or at best uncomfortable for many patients. CT angiography (CTA) can be used as an alternative or in addition to TEE if this technique fails to visualize every part of the aorta and in particular the aortic arch. ***Methods:*** We prospectively studied 64 patients (47 men, age 60 ± 13 years) classified as having cryptogenic stroke after standard and full workup [including brain MRI and 24-hour electrocardiogram (ECG)] with ECG-triggered CTA of the aorta in search of plaques and compared the results with those of TEE. Investigators were blinded to the results of both techniques. Plaques were graded on CTA according to their presence (0 = not present; 1 = mild; 2 = severe) and degree of calcification (1a or 2a = noncalcified; 1b or 2b = calcified). Associations with risk factors and infarct localization were also assessed. ***Results:*** Only 21 of 64 patients (32.8%) had aortic plaques identified by TEE, compared to 43 of 64 (67.2%) with CTA ($p < 0.05$). The plaque localization was as follows (TEE vs. CTA): ascending aorta, 10 vs. 20 ($p < 0.05$); aortic arch, 10 vs. 40 ($p < 0.05$), and descending aorta, 20 vs. 34 ($p < 0.05$). Grade 1 plaques were most commonly found in the aortic arch (25; 39%), while grade 2 plaques were most often detected in the aortic arch (15; 23.4%) and the descending aorta (14; 21.9%). There was no significant correlation between plaque location, infarct territory or vascular risk profile, except for hypertension ($p = 0.003$), which was significantly associated with the presence of plaques. ***Conclusions:*** CTA identifies more plaques throughout the aortic arch and around the origins of the major cerebral arteries in particular compared to TEE. These may represent potential embolic sources of acute ischemic

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stroke. Better plaque detection may have an impact on the best available secondary prevention regimen in individual patients if proximal embolic sources are suspected.

Introduction

Ischemic stroke is a common disease with different etiologies. While in many cases a thorough workup performed in a specialized center leads to identification of the cause of ischemia, there is still a significant number of strokes, estimated at between one fourth to one third of cases, for which a definite stroke subtype cannot be identified [1]. In these cases, strokes are classified as being of undetermined or unknown cause and are often referred to as 'cryptogenic'. Apart from being frustrating for both patients and physicians, this diagnosis renders selective secondary stroke prevention impossible if stroke patterns on neuroimaging suggest a proximal source of embolism affecting both the anterior and the posterior circulation or both cerebral hemispheres. Intermittent atrial fibrillation would result in anticoagulation if eventually identified versus antiplatelet agents in those patients with severe atherosclerosis of the aorta, as used in atherosclerosis of other vessels.

Although many studies have demonstrated an association between atherosclerotic plaques of the aorta and recurrent ischemic strokes [2–7], these still remain an underestimated factor in the stroke workup in many centers, while intensive searches for intermittent atrial fibrillation, a patent foramen ovale or large- and small-vessel atherosclerosis of the cerebral arteries are regularly performed. Data on aortic plaques and their association with cerebrovascular events mainly originate from studies with transesophageal echocardiography (TEE), which is the most frequently used method to visualize the heart and the aorta [2, 8–11]. Because TEE is fairly invasive, not always well tolerated by patients and in many cases unable to visualize the aortic arch properly [12], other methods for aortic plaque detection have been evaluated. CT angiography (CTA) has been shown to have a high sensitivity and specificity for the detection of atherosclerotic aortic plaques in a few small studies involving heterogeneous stroke subtypes [6, 13, 14]. Kaya and Yildiz [15] recently demonstrated that half of stroke cases (in diverse stroke groups) had atherosclerotic plaques in the ascending aorta or the aortic arch, but there was only a small group (n = 39) with cryptogenic stroke.

In this study, we focused on patients with cryptogenic stroke and used CTA to detect arteriosclerotic plaques in the aorta as possible sources of embolic stroke and compared the results with those of TEE, which was also performed to search for proximal embolic sources including aortic plaques, in order to see which technique better detects aortic plaques. Plaque burden and calcification were also analyzed.

Patients and Methods

Patients

Sixty-four consecutive patients (47 men, 17 women; mean age 60 ± 13 years) admitted to our Stroke Competence Center for acute ischemic stroke were studied. Table 1 shows the baseline characteristics of the population. All patients underwent a thorough stroke workup in accordance with international standards, including clinical neurological examination, brain MRI (diffusion-weighted, T1-, T2- and T2*-weighted imaging, as well as time-of-flight angiography), vascular imaging (Doppler/duplex), monitoring of blood pressure and electrocardiogram (ECG), both for at least 24 h, and TEE.

The diagnosis of cryptogenic stroke was made after all of the above examinations were completed and no certain cause of stroke was found. At this point, the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification [16] for these patients was 'undetermined origin', and the atherosclerosis, small vessel disease, cardiac source, other cause (ASCO) classification [17] delivered no grade 1 pathology. In these cases, the next step according to our stroke workup protocol is to perform a CTA of the aorta. All patients were informed about the procedure in detail and gave their written informed consent. Risk factors [arterial hypertension (history/treatment or hypertensive blood pressure on admission), hyperlipidemia (history/treatment or high fasting cholesterol levels), diabetes (history/treatment or high fasting glucose levels and elevated glycated hemoglobin), history of previous stroke and history of coronary artery disease] were analyzed. Infarct localization and ischemic patterns were recorded according to the corresponding MRI findings (anterior, posterior or both circulations; bilateral infarcts, emboligenic infarct distribution).

Transesophageal Echocardiography

The ultrasound system GE Vivid (Vivid i and Vivid 7; GE Healthcare, UK) with a 5-MHz transducer was used for TEE examinations. The examination included a search for right-to-left shunt (patent foramen ovale), atrial septal aneurysm and intracardial thrombi. The aorta was examined with respect to aortic plaques, defined as irregular thickening of the intima with increased echogenicity. TEE was performed and analyzed by an experienced investigator. The location of aortic plaques was documented by dividing the aorta into three parts, i.e. the ascending aorta, aortic arch and descending aorta.

Computed Tomography

All examinations were performed on a first-generation 64-channel dual-source CT system (Somatom Definition; Siemens

Table 1. Patients' characteristics, risk factors and infarct distribution

	All patients (n = 64)	Plaque detection by CTA		
		patients without plaques	patients with plaques	p
Age, years[1]	60 ± 13			
Men	47 (73.4%)			
Risk factors				
Diabetes	14 (21.9%)	3 (21.4%)	11 (78.6%)	0.305
Hypertension	48 (75%)	11 (22.9%)	37 (77.1%)	0.003
Hyperlipidemia	30 (46.9%)	7 (23.3%)	23 (76.7%)	0.129
Coronary heart disease	10 (15.6%)	3 (30%)	7 (70%)	0.837
Previous stroke	11 (17.2%)	1 (9.1%)	10 (90.9%)	0.066
Infarct distribution				
Anterior circulation only	36 (56.3%)	14 (38.9%)	22 (61.1%)	0.240
Posterior circulation only	20 (31.3%)	6 (30%)	14 (70%)	0.747
Both circulations	8 (12.5%)	1 (12.5%)	7 (87.5%)	0.191
Bilateral infarcts	16 (25%)	5 (31.2%)	11 (68.8%)	0.878
Emboligenic distribution	31 (48.4%)	8 (25.8%)	23 (74.2%)	0.247

Percentages in columns 3 and 4 refer to the total number in column 2.
[1] Mean ± SD.

Medical Solutions, Forchheim, Germany). Retrospectively ECG-gated CTA was performed with the following scan parameters: detector collimation 0.6 mm, gantry rotation time 330 ms, tube current time product 320 mAs and a pitch of 0.2–0.5 adapted to the heart rate. Low tube voltage (100 kV), automatic tube current modulation (CARE Dose 4D) and automatic ECG pulsing were used for radiation dose reduction in all patients [18–20]. For vascular enhancement, 120 ml of iomeprol 400 (Iomeron 400; Bracco Imaging S.p.A., Milan, Italy) were injected using a power injector (Stellant® D CT Injection System; Medrad Inc., Warrendale, Pa., USA) with an injection rate of 4 ml/s, followed by a saline chaser of 40 ml using the same flow rate. The craniocaudal scan was started using automatic bolus triggering and scanned at 2-second intervals in the ascending aorta (trigger level 100 Hounsfield Units) with a delay of 5 s. The patients were instructed to hold their breath at a mild inspiratory position. Transversal images of the entire scan range were reconstructed with a slice thickness of 1 mm and increments of 0.8 mm using a standard B30f soft tissue kernel. The volume CT dose index and dose length product were recorded. The effective dose of the CTA was estimated from the product of the DLP using a conversion coefficient of 0.017 mSv/mGy/cm as reported in the European Guidelines [21] for chest examinations.

Image Analysis

The CTA datasets were evaluated by consensus by two radiologists, a board-certified radiologist with 10 years of experience in CT imaging and a third-year resident. The thoracic aorta was divided into three segments, namely the ascending aorta, aortic arch (beginning with the brachiocephalic artery and ending distal to the left subclavian artery) and descending aorta. For each segment, the presence of atherosclerotic plaques was documented and assessed on a 3-point scale [grade 0 = not present; grade 1 = mild (rare, small plaques); grade 2 = severe (frequent, large plaques)]. The atherosclerotic plaques found to be present were classified as noncalcified (grade 1a or 2a) or calcified (grade 1b or 2b) on a segmental basis.

Statistical Analysis

The 2-tailed Fisher's exact test and χ^2 test were used to compare TEE and CTA plaque findings as well as associations with risk factors and infarct localization. The kappa statistic was additionally used to calculate agreement between the two techniques. A p value <0.05 was considered to indicate a statistically significant difference. Statistical analysis was performed using the Statistical Package for the Social Sciences, version 19.0 (IBM, USA).

Results

Table 1 shows patients' characteristics, risk factors and infarct localization and their associations with plaques detected by TEE and CTA. There was no significant correlation between diabetes (11/14; 78.6% with plaques), hyperlipidemia (23/30; 76.7% with plaques) and coronary heart disease (7/10; 70% with plaques) and the atherosclerotic changes in the aorta. Thirty-seven out of 48 patients (77.1%) with hypertension had aortic plaques, which was shown to be statistically significant (p = 0.003). All but one patient with a history of a previous stroke (10/11; 90.9%) had plaques detected by CTA, but statistical significance was missed by a small margin (p = 0.066).

Table 2. Plaque detection results with TEE and CTA

	n	%	p value
Patients with plaques on TEE	21	32.8	
Patients with plaques on CTA	43	67.2	<0.001
Patients with plaques on TEE and CTA	21	32.8	
Plaque localization			
Ascending aorta			
TEE	10	15.6	
CTA	20	31.2	0.004
Aortic arch			
TEE	10	15.6	
CTA	40	62.5	0.008
Descending aorta			
TEE	20	31.2	
CTA	34	52.3	<0.001

Table 3. Localization and grading of aortic plaques in 64 patients as detected by CTA

	Ascending aorta	Aortic arch	Descending aorta	Overall
No plaques	44 (68.8)	24 (37.5)	30 (46.9)	21 (32.8)
Grade 1a	3 (4.7)	9 (14.1)	9 (14.1)	14 (21.9)
Grade 1b	15 (23.4)	16 (25.0)	10 (15.6)	29 (45.3)
Grade 2a	0	3 (4.7)	6 (9.4)	7 (10.9)
Grade 2b	2 (3.1)	12 (18.8)	8 (12.5)	14 (21.9)
Total patients with plaques	20 (31.2)	40 (62.5)	34 (53.1)	43 (67.2)

Data are presented as n (%). Grade 1: mild; grade 2: severe; a: noncalcified plaques; b: calcified plaques.

We were particularly interested in patients with cerebral infarctions affecting both the anterior and the posterior circulation or both hemispheres. Indeed, 7 of 8 patients (87.5%) with infarcts in both circulations and 11 of 16 patients (68.8%) with bihemispheric infarcts had plaques detected by CTA. However, these results were not statistically significant, probably because of the small sample size. The emboligenic distribution of infarcts, even if they are located only in one brain region, is (as the name suggests) also an indication of an embolic stroke source. Twenty-three of 31 patients (74.2%; $p = 0.247$) with such an infarct pattern had plaques on CTA.

Table 2 summarizes the results of plaque detection with TEE and CTA. Overall, atherosclerotic plaques were identified in 21 patients (32.8%) by TEE. CTA confirmed plaques in all of them plus an additional 22 patients (43; 67.2%; $p < 0.001$, $\chi^2 = 15.26$, $\Phi = 0.488$, $\kappa = 0.385$). In the ascending aorta, plaques were identified in 10 patients (15.6%) by TEE and in 20 (31.2%) by CTA ($p = 0.004$, $\chi^2 = 8.28$, $\Phi = 0.360$, $\kappa = 0.326$). In the aortic arch, CTA detected plaques in 4 times as many patients as TEE [40 (62.5%) vs. 10 (15.6%); $p = 0.008$, $\chi^2 = 7.11$, $\Phi = 0.333$, $\kappa = 0.200$]. Results were similar for the descending aorta; plaques were found in 20 patients by means of TEE (31.2%) compared to 34 patients with CTA (52.3%; $p < 0.001$, $\chi^2 = 15.88$, $\Phi = 0.498$, $\kappa = 0.450$). Divergent results were shown in only 3 cases (4.7%) with plaques in the ascending aorta detected by TEE but not by CTA and in 2 cases (3.1%) with plaques in the descending aorta. In the aortic arch, there were no plaques detected solely by TEE and not by CTA. The sensitivity of TEE for detecting aortic plaques, when compared to CTA, was 48.8%. The average radiation dose (± SD) was 15.23 ± 9.72 mSv.

Table 3 summarizes the grading of plaques in the three different parts of the aorta as detected by CTA. Most of the plaques were found in the aortic arch (40; 62.5%) and the descending part of the aorta (34; 53.1%). In the ascending aorta, only 20 patients (31.2%) had detectable plaques. Grade 1 plaques were most commonly found in the aortic arch (n = 25), while grade 2 plaques were most frequently found in the aortic arch (n = 15) and the descending aorta (n = 14). Figure 1 shows examples of CTA plaque detection with different grades of plaques.

Discussion

We found that 67.2% of our patients had atherosclerotic aortic plaques. CTA was able to detect them significantly more frequently than TEE, while it also detected almost all positive TEE findings. Differences were highly significant with regard to the total and each of the three aortic segments separately. Tenenbaum et al. [14] compared dual-slice CT with TEE for detecting aortic plaques in 32 patients with recent ischemic (but not otherwise specified) stroke and/or systemic emboli and came to the conclusion that CT showed high accuracy in detecting aortic atheroma, especially in areas not clearly depicted by TEE. Hussain et al. [13] also conducted a similar investigation comparing CT with TEE in a general population of 32 ischemic stroke patients and concluded that CT is similar to TEE in detecting aortic plaques and may even be better than TEE in detecting smaller atheromas or defining their morphology. Thus, our results not only confirm

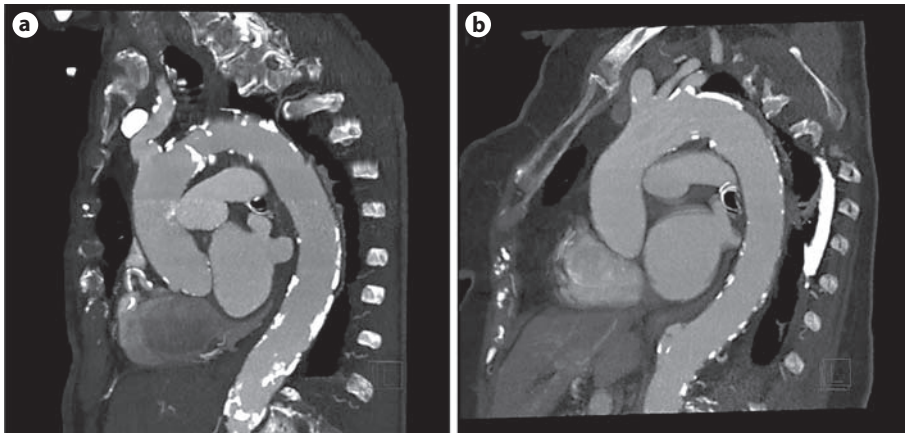

Fig. 1. Examples of aortic plaque detection by ECG-triggered CTA in sagittal oblique maximum-intensity projection of the aorta. **a** Multiple calcified plaques can be seen in the aortic arch and in the descending aorta (grade 2b). **b** Some calcified plaques can be seen in the descending aorta (grade 1b).

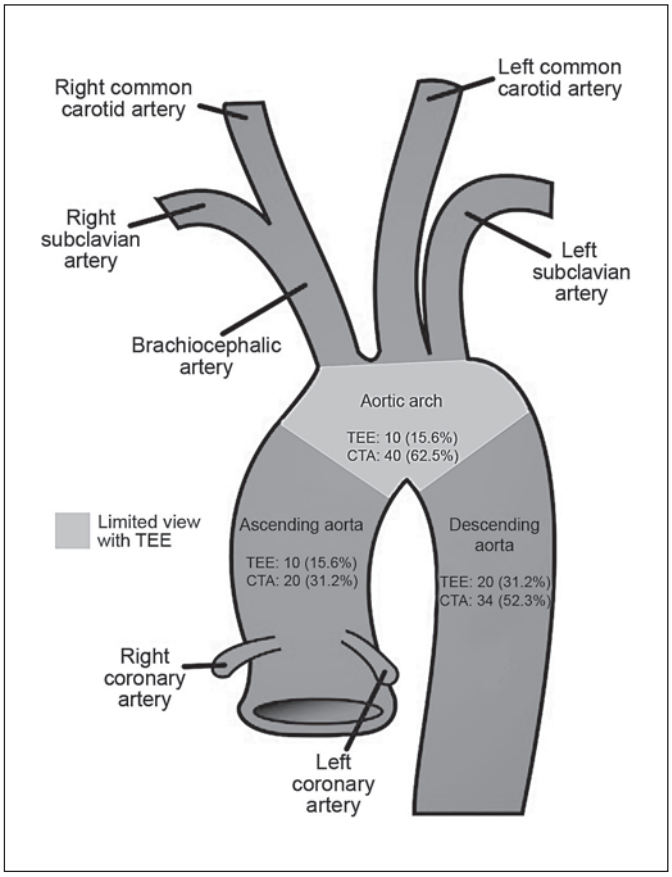

Fig. 2. Approximate illustration of the aortic area in which only limited visualization is possible by TEE. Figures refer to numbers and percentages of patients with detected plaques. This figure is based on a public domain reproduction of a lithograph plate from *Gray's Anatomy*.

the accuracy of CTA reported in previous smaller series but also support the hypothesis that CTA is capable of detecting plaques where TEE fails to do so and in the most important patient groups for diagnostic purposes (i.e. those with cryptogenic strokes) and therapeutic decisions (antiplatelet agents vs. anticoagulation). Kaya and Yildiz [15] examined a group of 195 patients with ischemic stroke of various classifications, 39 of whom presented with cryptogenic stroke. Their patients with cryptogenic stroke showed a lower percentage of plaques than in our study (20% in the ascending aorta or in the aortic arch and 59% in the descending aorta in contrast to a total of 67.2% in our patient group). This could be explained by the different definition of cryptogenic stroke; our patients had no otherwise detectable possible stroke cause, as opposed to the study performed by Kaya and Yildiz [15], in which the group of cryptogenic stroke patients also included patients in whom more than one potential cause was found (including a cardiac source of embolism).

In our study, most plaques were found in the aortic arch (62.5%), followed by the descending part of the aorta (53.1%). In the aortic arch, CTA detected plaques in four times as many patients as TEE (40 vs. 10). In this part of the aorta, the disagreement between the two techniques was the strongest ($\kappa = 0.200$), which can probably be explained by the fact that anatomic conditions do not always allow complete visualization of the aortic arch with TEE. It is well known that the distal part of the ascending aorta, as well as the proximal/right part of the aortic arch, are often poorly visualized in TEE due to the juxtaposition of the trachea and the right main bronchus between the esophagus and the aorta (fig. 2). While visualization of this area has improved with the aid of newer techniques and technology, false-negative results are still

probable [22, 23]. A high frequency of plaques in the descending aorta was described in previous CTA studies [15] and is confirmed by our data. However, until recently, plaques in this part of the aorta were not considered embolic sources of ischemic stroke [8, 15]. Recent MRI studies using advanced techniques with multidirectional velocity mapping have demonstrated that substantial diastolic retrograde flow in the descending aorta is possible; therefore, plaques in this region also constitute a potential embolic source [24].

Plaque morphology, number and size are also thought to play a role in ischemic stroke risk [6, 9, 25]. High plaque complexity was shown to be associated with increased stroke risk [7, 25, 26]. We found that grade 2 plaques (i.e. numerous, larger, more complex plaques) were more common in the aortic arch and the descending aorta. Thus, it can be postulated that plaques located in these parts of the aorta are associated with and may even be the cause of cryptogenic cerebral ischemia, although this of course also depends on several plaque characteristics like localization, size, morphology and mobility. Apart from that, large plaque burden could also be a good indicator of general atherosclerosis.

As atherosclerotic plaques could act as emboli with consecutive stroke, patterns of cerebral infarctions indicating an embolic source, such as infarcts in both the anterior and posterior circulations or bilateral infarcts, are especially interesting. Kaya and Yildiz [15] found a higher percentage of aortic plaques not in the group of patients with cardioembolic infarcts, but rather in the group with large artery atherosclerosis (according to the TOAST classification). We found a high percentage of patients with plaques in the group with acute infarcts in both the anterior and posterior circulations (87.5%) and in the group with bilateral infarcts (68.8%) using CTA. The same applies to the group of patients with emboligenic infarct patterns in one hemisphere, 74.2% of whom had aortic plaques detected by CTA. In spite of these high percentages, statistical significance was not attained. In all these cases, TEE could only detect a fraction of the plaques, significantly less than CTA. The fact that inter- and intraobserver variability was not determined may be a limitation of this study. We believe the accuracy of the findings to be very high, as the observers were experienced and a well-defined straightforward protocol was used; however, the possibility of inter- and intraobserver variability cannot be definitely eliminated.

Based on the findings provided by CTA, we examined the possibility of a correlation between the most important vascular risk factors and the presence of atherosclerotic aortic plaques. No statistical significance was found for diabetes, hyperlipidemia or coronary heart disease. However, there was a significant correlation between arterial hypertension and the presence of plaques. We also postulated that patients with atherosclerotic plaques in the aorta capable of creating emboli should probably have experienced more cerebrovascular events than patients without aortic plaques. There was indeed a clear tendency toward this assumption (1 patient with previous stroke and no plaques vs. 10 patients with previous strokes and plaques), but statistical significance was not reached ($p = 0.066$), probably due to the relatively small sample size.

In conclusion, we found CTA to be a method superior to TEE for detection of atherosclerotic aortic plaques, confirming previous studies with a smaller sample size, particularly in the important group of patients with cryptogenic stroke. In these patients, the issue of what is the best secondary prevention is unclear. If aortic plaques are not taken into consideration in the search for possible sources of embolism, the question arises as to whether these patients should receive repeated ECG monitoring for intermittent atrial fibrillation. Although there are no sufficient data at present to support evidence-based treatment and secondary stroke prevention in the presence of aortic plaques, ongoing studies like the Aortic Arch-Related Cerebral Hazard study comparing different treatment strategies will hopefully provide more information [27]. Modern stroke workup should include a search for relevant aortic plaques, and the ASCO classification includes aortic thrombi as well as aortic plaques in the definition of the atherosclerosis category [17]. Thus, a reliable method for detecting aortic plaques should probably be part of the workup of ischemic stroke patients when no clear cause is found during the course of the remaining examinations. Our data suggest that CTA, to a greater degree than TEE, is the proper method for this purpose. This, in combination with the fact that it is a comfortable, quick and safe examination, renders CTA a suitable scanning tool for aortic plaques in patients with cryptogenic ischemic stroke. For these reasons, we believe that the modest radiation burden of the examination can be justified, provided that patients are carefully selected. The aortic arch and the descending aorta should be of particular interest, as they seem to bear most of the emboligenic potential (i.e. possess more plaques) in this patient group.

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