Retrograde Embolism From the Descending Aorta
Visualization by Multidirectional 3D Velocity Mapping in Cryptogenic Stroke

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Background and Purpose—The purpose of this study was to determine the role of plaques ≥4 mm and thrombi (complex plaques) in the descending aorta (DAo) as an embolic high-risk source for stroke.

Methods—In 63 acute stroke patients scheduled for TEE, territory and embolic pattern of brain ischemia were prospectively assessed. Multidirectional 3D MRI velocity mapping of the aorta was performed to correlate the extent of retrograde diastolic blood flow with the distance of complex DAo plaques from the left subclavian artery (LSA). Embolic risk from the DAo was present for (1) retrograde flow connecting complex DAo plaques with the LSA, (2) embolic pattern of brain ischemia in a territory supplied by the left vertebral artery, and (3) stroke that could not be explained by other means.

Results—33 of 63 patients had complex DAo plaques (distance to LSA 28.1 ± 29.9 mm). Mean retrograde flow in these subjects was 26.2 ± 12.3 mm. In 20 of 63 patients (31.7%) retrograde flow connected complex DAo plaques with the LSA. In 4 of these 20 patients (20%) with an embolic stroke in the territory of the brain stem, cerebellum or posterior cerebral artery, etiology could not be explained by other means.

Conclusions—Substantial diastolic retrograde flow originating from complex plaques in the descending aorta was detected by multidirectional 3D MRI velocity mapping and constitutes a stroke mechanism that was previously not demonstrable.

Keywords: atherosclerosis ■ acute stroke ■ embolic stroke ■ MRI ■ TEE

Complex plaques of the aortic arch with thickness ≥4 mm or containing mobile elements (most often thrombi) or both are considered high-risk sources of brain ischemia. The incidence and thickness of such plaques is highest in the descending aorta (DAo). However, distal to the left subclavian artery they are usually not considered a potential source of stroke because retrograde embolization seems unlikely. A previous transesophageal echocardiography (TEE) study analyzing the mobility of aortic thrombi in the DAo hypothesized that retrograde cerebral embolism would be theoretically possible especially in case of concomitant aortic valve insufficiency. However, TEE is not able to demonstrate the direct correlation of plaque location and 3D blood flow patterns within the aorta. Accordingly, this stroke mechanism has not yet been systematically investigated.

Multidirectional 3D velocity mapping allows the detailed visualization of physiological and pathological 3D blood flow characteristics and the analysis of the continuation of flow from the distal aortic arch into the supra-aortic vessels. Specifically, in combination with a novel MRI protocol for 3D aortic plaque detection, the direct interrelation of complex DAo plaques and individual retrograde flow channels was recently demonstrated in 2 patients with embolic stroke.

It was the aim of this study to apply this technique in a larger cohort of stroke patients and to investigate the potential role of complex DAo plaques as an embolic source in patients with cryptogenic brain infarction.

Materials and Methods

Study Population
Between January 1, 2006 and January 15, 2007, 63 patients with acute retinal or cerebral ischemia who were examined by TEE were prospectively included. Following a previous study, TEE was scheduled if stroke etiology was undetermined after routine diagnostics (brain MRI including MR angiography or CT, transthoracic echocardiography, ECG, extra-/intracranial ultrasound, laboratory testing). Additionally, TEE was individually performed in younger patients to screen for other cardiac sources, in patients with carotid artery stenosis to exclude additional embolic sources such as complex aortic plaques, and in patients with a history of atrial
fibrillation but sinus rhythm in the current Holter-ECG. Furthermore, patients had to be 18 to 85 years of age and suitable for MRI examination at 3 Tesla. Finally, because of the limited MRI measurement capacities, 2 patients per week matching the inclusion criteria were randomly chosen. The study was approved by the local ethics committee (vote 141/05), and written informed consent was obtained from all participants.

Embolic Stroke

Embolic origin of ischemia was defined present in patients with one or multiple acute lesions in brain imaging, ie, disturbed diffusion weighted MRI or delineated hypodense region indicating acute or subacute ischemia in CT, with involvement of the cortex (both supratentorial and infratentorial) or the striato-capsular territory.\textsuperscript{11} Patients without such a lesion but with acute occlusion or intraluminal thrombus of the retinal or ophthalmic arteries or the distal part of brain supplying arteries as detected by digital subtraction angiography, CT- or MR-angiography, or Duplex sonography were also classified embolic stroke.

MR Imaging

The MR imaging protocol (3T MR system TRIO) for aortic plaque localization and multidirectional 3D velocity mapping was described recently.\textsuperscript{10,13} Briefly, plaque localization was based on T1-weighted fat-saturated 3D gradient echo MRI (T1 3D-GRE, spatial resolution $0.8 \times 1.1 \times 1.1$ mm$^3$). Further, time-resolved contrast-enhanced MR angiography (CE-MRA) covering the entire thoracic aorta and supra-aortic branches was performed (0.05 mL/kg gadobenate dimeglumine at 3.5 mL/s). For the assessment of blood flow in the thoracic aorta ECG synchronized and respiration controlled time resolved multidirectional 3D velocity mapping was employed (spatial resolution=$2.1 \times 3.2 \times 3.5$ mm$^3$, temporal resolution=48.8 ms).

Data Analysis

T1 3D-GRE data were used to locate high-risk plaques in the descending aorta and to measure maximum plaque thickness. The distance of complex DAo plaques to the outlet of the left subclavian artery (LSA) was determined using the CE-MRA data (Figure 1). The extent of retrograde flow originating in the descending aorta was evaluated using 3D visualization (EnSight, CEI, Apex, NC, USA). To measure maximum retrograde flow length for all patients, a series of emitter planes (interplane distance $=10$ mm) were positioned distal to the LSA outlet and 3D particle traces were successively evaluated.

Figure 1. A, Detection of a DAo plaque with a maximum thickness $\geq 4$ mm (yellow arrows) by T1 3D gradient echo imaging (T1 3D-GRE). Calculation of the distance from the LSA outlet by contrast enhanced MR angiography (CE-MRA). AAo indicates ascending aorta; DAo, descending aorta.

Figure 2. Data evaluation strategy for the assessment of maximum retrograde flow. For emitter plane locations 1 to 5, marked retrograde flow reaching at least as far as the left subclavian artery (LSA) can be identified (open white arrows). The maximum length of retrograde flow (40 mm) connecting emitter plane 5 and the LSA clearly exceeds the distance between plaque and LSA (10 mm, red marker).
calculated and displayed (Figure 2). Based on the interplane distance, a systematic error of ±5 mm was assumed.

Role of Plaques in the Descending Aorta

Following modified TOAST criteria,12 the term "cryptogenic stroke" was reserved for patients with no explanation for stroke in routine diagnostics including TEE (eg, no atrial fibrillation in ECG or left atrial thrombus in TEE). In addition, high risk pathology (complex plaques or dissection) of the ascending aorta and aortic arch had to be excluded by 3D MRI. Embolic risk from the Dao was present in patients with (1) retrograde flow connecting complex DAo plaques with the LSA in MRI, (2) embolic pattern of brain ischemia in a territory supplied by the left vertebral artery, and (3) stroke that could not be explained by other means.

Statistical Analysis

Multivariate logistic regression analysis was performed to evaluate independent predictors for an increased extent of retrograde flow using patients' baseline characteristics, echocardiographic, or MRI data. All tests were 2-sided and used 0.05 as level of statistical significance (SAS statistical package, version 8.2).

Results

In 32 patients, embolic stroke pattern was identified by brain imaging. In 5 other subjects an intraluminal thrombus or distal occlusion of eye of brain supplying arteries was detected by angiography or Duplex sonography.

In the 33/63 patients with complex plaques ≥4 mm in the descending aorta the plaque-LSA distance was 28.1±29.9 mm. The extent of maximum average retrograde flow was similar (P>0.05) for patients with plaques <4 mm (n=30, 26.2±12.3 mm) and plaques ≥4 mm (n=33, 23.8±13.9 mm; Figure 3A). Comparison of plaque location and extent of retrograde flow demonstrated retrograde flow connecting plaque and LSA in 20/33 (60.6%) patients (Figure 3B). In 4 of these 20 patients, etiology of stroke could not be explained by other means. Particularly, high-resolution 3D MRI excluded an additional complex plaque in the ascending aorta or aortic arch. Furthermore, stroke occurred in a territory likely to be affected by the left vertebral artery: posterior cerebral artery territory (2 patients), brain stem and both cerebellar hemispheres (one patient), dorsolateral medulla oblongata (one patient). The latter showed a concomitant occlusion of the ipsilateral posterior inferior cerebellar artery in MR-angiography and only minimal white matter lesions in other regions of the brain despite the age of 73 years.

Age was the only independent predictor of increased retrograde flow. Logistic regression analysis revealed a step-wise increase of the risk of length of retrograde flow ≥25 mm with increasing age: adjusted OR =1.92 (95% CI 1.16 to 3.19) for each decade. In contrast, no significant correlation was found for the extent of retrograde flow and the severity of aortic valve insufficiency (Figure 3C).

Discussion

Our new MRI technique allows the detection of a previously not demonstrable stroke mechanism in patients with acute embolic brain ischemia. We were able to show the strong association between complex plaques in the descending aorta, lesions in parts of the brain that were likely to be affected by retrograde flow involving the left vertebral artery, and brain infarctions that could not be explained by other means in four patients. The definition of embolic brain ischemia based on lesion patterns in MRI is limited in case of isolated brain stem infarction as seen in 1 of these 4 subjects. However, small-vessel disease as an alternative etiology of stroke seems unlikely because of the presence of ipsilateral occlusion of the posterior inferior cerebellar artery and absence of significant white matter lesions of the brain in this patient.

The actual MR imaging protocol was limited to data acquisition in systole and early diastole. As a result, the true extent of retrograde flow may even have been underestimated. We currently calculated the distance of retrograde flow from complex DAo plaques to the LSA, which represents the first potential pathway to the brain for retrograde embolism. However, using retrospective ECG synchronization with full coverage of the cardiac cycle in future studies will also permit an evaluation of late diastolic retrograde flow.

Figure 3. A, Mean lengths of retrograde flow channels and mean plaque-LSA distance. B, Case by case comparison of plaque location and extent of retrograde flow. Results demonstrate the potential for retrograde embolization pathways, ie, data points within the lower gray shaded triangle, for the majority of patients (error bars indicate systematic errors for plaque distance [vertical bars] and retrograde flow [horizontal bars]). C, Mean extent of retrograde flow in relation to aortic valve insufficiency.
flow. This will significantly improve the demonstration of individual embolic pathways to all brain territories. Actual data analysis required the manual positioning of emitter planes, which may result in operator dependent variability. However, because both the left subclavian artery and the aortic lumen could easily be identified in all data sets, operator differences in emitter plane positioning are expected to be small.

Surprisingly, age but not aortic valve insufficiency was the only predictor for increased retrograde flow. Underlying and currently undetermined factors, such as decrease of aortic compliance, deserve further validation to define parameters identifying patients with increased risk of retrograde embolization. Our findings and the direct visualization of individual embolic pathways may be relevant for the future assessment of aortic plaques. Particularly, investigations in patients with embolic stroke of cryptogenic origin could directly prove that complex plaques in the DAo are the cause of stroke and no innocent bystander or risk marker. Future studies need to validate whether the spectrum of stroke etiologies needs to be expanded to DAo plaques. Accordingly, they will provide evidence indicating whether findings of the ongoing Aortic arch Related Cerebral Hazard (ARCH) trial evaluating the best medical treatment of complex aortic arch atheroma should by applied to the descending aorta.

Acknowledgments
We thank Adriana Komancsek and Manuela Keckeis for their help and support with respect to the MRI examinations.

Sources of Funding
M. Markl is supported by Deutsche Forschungsgemeinschaft (DFG), Grant # MA 2383/4-1 and by the Bundesministerium für Bildung und Forschung (BMBF), Grant # 01EV0706.

Disclosures
None.

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Stroke. 2009;40:1505-1508; originally published online January 29, 2009;
doi: 10.1161/STROKEAHA.108.530030
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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