Complex Plaques in the Proximal Descending Aorta
An Underestimated Embolic Source of Stroke

Andreas Harloff, MD; Jan Simon; Stefanie Brendecke; Dawit Assefa, MD; Thomas Helbing, MD; Alex Frydrychowicz, MD; Johannes Weber, MD; Manfred Olschewski, MS; Christoph Strecker, MD; Jürgen Hennig, PhD; Cornelius Weiller, MD; Michael Markl, PhD

Background and Purpose—To investigate the incidence of retrograde flow from complex plaques (≥4-mm-thick, ulcerated, or superimposed thrombi) of the descending aorta (DAo) and its potential role in embolic stroke.

Methods—Ninety-four consecutive acute stroke patients with aortic plaques ≥3-mm-thick in transesophageal echocardiography were prospectively included. MRI was performed to localize complex plaques and to measure time-resolved 3-dimensional blood flow within the aorta. Three-dimensional visualization was used to evaluate if diastolic retrograde flow connected plaque location with the outlet of the left subclavian artery, left common carotid artery, or brachiocephalic trunk. Complex DAo plaques were considered an embolic source if retrograde flow reached a supra-aortic vessel that supplied the territory of visible acute and embolic retinal or cerebral infarction.

Results—Only decreasing heart rate was correlated (P<0.02) with increasing flow reversal to the aortic arch. Retrograde flow from complex DAo plaques reached the left subclavian artery in 55 (58.5%), the left common carotid artery in 23 (24.5%), and the brachiocephalic trunk in 13 patients (13.8%). Based on routine diagnostics and MRI of the ascending aorta/aortic arch, stroke etiology was determined in 57 and cryptogenic in 37 patients. Potential embolization from DAo plaques was then identified in 19 of 57 patients (33.3%) with determined and in 9 of 37 patients (24.3%) with cryptogenic stroke.

Conclusions—Retrograde flow from complex DAo plaques was frequent in both determined and cryptogenic stroke and could explain embolism to all brain territories. These findings suggest that complex DAo plaques should be considered a new source of stroke. (Stroke. 2010;41:1145-1150.)

Key Words: acute stroke ■ aorta ■ atherosclerosis ■ magnetic resonance ■ pathogenesis

Complex aortic plaques defined as ≥4-mm-thick, ulcerated or containing mobile thrombi are considered a major source of stroke. 1 Although their incidence is highest in the proximal descending aorta (DAo), such plaques are only considered an embolic source of stroke in the unlikely coincidence of severe aortic valve insufficiency causing retrograde flow and embolization in case of plaque rupture.1,2 However, there is growing evidence that diastolic retrograde flow in the DAo may be a frequent phenomenon in the presence of atherosclerosis and thus an overlooked mechanism of retrograde embolization in stroke patients. Oscillating thrombus mobility3 and Doppler flow curves in the DAo in transesophageal echocardiography (TEE) indirectly proved the existence of flow reversal.4 In contrast to TEE, flow-sensitive 4-dimensional MRI permits the precise analysis of individual 3-dimensional flow patterns at the site of complex DAo plaques.5-7 Moreover, it allows for a more reliable detection and characterization of aortic plaques compared to TEE.8,9 In this context, retrograde embolization from complex DAo plaques was recently described as a proof-of-principle and constituted the only probable source of ischemia in the posterior circulation in individual stroke patients of this cohort.10

Because of the incomplete coverage of late diastolic retrograde flow by MRI in this study,10 we hypothesized that its true frequency and the potential to reach all supra-aortic arteries was still underestimated. Therefore, in a newly and consecutively recruited patient cohort we applied both an MRI protocol providing complete temporal coverage and a visualization strategy coregistering plaque location with 3-dimensional blood flow. This allowed analyzing potential embolization pathways from DAo plaques to all brain-supplying arteries. The frequency of this mechanism was systematically evaluated in acute stroke patients with advanced aortic atherosclerosis and determined or cryptogenic stroke etiology.

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Study Population
Between June 19, 2008 and March 24, 2009, a total of 734 consecutive and unselected patients were admitted to our institution because of acute retinal/cerebral ischemia. Three hundred fourteen of them underwent TEE following a previously recommended algorithm if stroke etiology was cryptogenic after routine diagnostics. Subjects with atrial fibrillation/flutter or symptomatic high-grade ICA stenosis undergoing TEE were excluded because of the known stroke etiology, incompatibility with the ECG trigger in MRI, or both. One hundred seventy-two consecutive patients fulfilled the inclusion criteria of acute retinal/cerebral ischemia, age 18 years or older, and aortic plaque thickness ≥3 mm in TEE.

Thirty-two patients declined participation and 20 patients had contraindications against MRI at 3 T. Fourteen patients were excluded because of unstable clinical conditions (n=2), incomplete compliance (n=4), body mass index exceeding 42 (n=2), transfer to hospital for inpatient treatment (n=4), and incomplete plaque images (n=2), or because of severe back pain or infectious diarrhea (n=2).

Twelve of the remaining 106 patients interrupted MRI examination before completion or MRI data quality was insufficient. Thus, our prospective analyses focused on the remaining 94 patients. Written informed consent was obtained from each participant. The study was approved by the local ethics committee.

Routine Diagnostics
Cardiovascular risk factors and severity of stroke on admission were assessed according to the National Institute of Health stroke severity scale.12

Brain MRI was performed in 88 patients (93.6%). In 6 patients (6.4%) brain MRI could not be realized before discharge and these patients received only brain CT. MRI and CT were performed in 41 patients (6.4%). Eighty-four patients (89.4%) underwent intracranial and extracranial Doppler TCD, 12 lead ECG, and Holter ECG. One patient with persistent monocular visual loss interrupted MRI examina-

MRI of the Aorta
MRI of the aorta (n=94) was performed using a 3-T MRI (TRIO; Siemens). Patients with a glomerular filtration rate ≥40 mL/min underwent time-resolved contrast-enhanced 3-dimensional MR angiography (0.1 mL/kg gadobenate dimeglumine at 3.5 mL/sec) of the aorta. High-resolution MRI (0.9×1.1×1.1 mm3) covering the entire upper thoracic aorta was performed for plaque detection (ECG-gated T1-weighted fat-saturated 3-dimensional gradient echo imaging; diastolic acquisition window=157 ms; time to echo [TE]/time to repeat [TR]=2.3 ms/5.5 ms; flip angle=20°).8 At the site of Aao plaques ≥4 mm, additional ECG-gated T2-weighted 2-dimensional turbo spin-echo imaging (TE=78 ms) was performed (TR=2 cardiac cycles; spatial resolution=1.1×1.2×3 mm3). The 3-dimensional T1 ciné imaging (CINE) imaging (TE/TR=1.8 ms/3.3 ms; temporal/spatial resolution=53 ms/1.3×1.5×1.3 mm3) was used to detect mobile plaque components. Finally, ECG-synchronized flow-sensitive 4-dimensional MRI was executed (TE/TR=2.6 to 3.5 ms/5.1–6.1 ms; flip angle=7°–15°; temporal/spatial resolution=40.8 ms/1.7×2.0×2.2 mm3). Data were acquired with 3-directional velocity encoding (velocity sensitivity=150 cm/sec) and complete coverage of the thoracic aorta. Respiratory gating was used for both 3-dimensional T1 and flow-sensitive 4-dimensional MRI.13 Blood pressure levels of the upper arm were recorded before and after MRI examination. Heart rate was documented every 4 minutes during flow measurement.

Multiplane reformating (J-Vision; Tiani Medgraph AG) was used to localize complex plaques in analysis planes normal to the aortic lumen and to determine maximum wall thickness.8 Aortic thrombi were defined as plaques with eccentric protrusion into the lumen, hypointense signal in T1, and motion of plaque components in 3-dimensional T1-CINE images. The definition of plaque ulceration was identical to that in echocardiography. Two readers blinded to patients’ data and the results of other diagnostics evaluated MR plaque images in consensus reading and involved a third blinded reader in case of disagreement for final decision.

On a case-by-case basis, 2-dimensional analysis planes of complex Aao plaques were coregistered with flow-sensitive proximal to the BCT and distal to the LSA outlet were defined ascending aorta and Aa, respectively. Maximum aortic wall thickness was measured manually in magnification using electronic calipers. Ulcerated plaques showed an indentation of the luminal surface with base width and maximum depth of at least 2 mm.

Brain Imaging
One neuroradiologist who had only access to brain imaging data determined the existence of acute brain ischemia or vessel occlusion, the brain territory affected, stroke pattern,10 and calculated narrowing of intracranial and vertebral arteries based on criteria of a former study.14

Materials and Methods

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4-dimensional MRI data via image fusion (EnSight; CEI). An emitter plane was positioned exactly at the site of the plaque and used to generate time-resolved 3-dimensional particle traces. The calculated traces resembled time-resolved 3-dimensional blood flow and could thus visualize diastolic retrograde flow originating from the atheroma as shown in Figure 1.

Stroke Subtyping
Based on modified TOAST criteria, stroke etiology was classified by 1 neurologist blinded to patients identity and to MRI results regarding the DAo (Table 2). On a visual basis, 1 reader assessed the presence of individual embolic pathways from complex plaques located in predefined 10-mm sections of the DAo as illustrated in Figure 2. Retrograde embolization was defined present if: (1) retrograde flow originating at the site of a complex DAo plaque reached the outlet of a supra-aortic great artery; (2) that artery matched with the territory affected by acute ischemia; and (3) it was clearly documented by an embolic pattern of infarction in funduscopy or brain imaging. In patients with flow reaching all 3 brain-feeding arteries, retrograde embolization was judged existent even if acute infarction or vessel occlusion was not visible in brain imaging.

Retrograde Embolization
Maximum retrograde flow and location of complex DAo plaques was assessed as described previously. On a visual basis, 1 reader assessed the presence of individual embolic pathways from complex plaques located in predefined 10-mm sections of the DAo as illustrated in Figure 2. Retrograde embolization was defined present if: (1) retrograde flow originating at the site of a complex DAo plaque reached the outlet of a supra-aortic great artery; (2) that artery matched with the territory affected by acute ischemia; and (3) it was clearly documented by an embolic pattern of infarction in funduscopy or brain imaging. In patients with flow reaching all 3 brain-feeding arteries, retrograde embolization was judged existent even if acute infarction or vessel occlusion was not visible in brain imaging.

Statistical Analysis
Data are presented as mean ± standard deviation for continuous and absolute and relative frequencies for categorical variables. Univariate logistic regression analysis was performed to detect a correlation of the extent of retrograde flow with patients’ baseline characteristics, MRI (maximum wall thickness, aortic lumen diameter), or echocardiographic data (ejection fraction, grade of aortic valve insufficiency); 25 mm was the median of retrograde flow of all patients and was chosen as the cut-off. Results are presented as odds ratios (OR) with 95% confidence intervals (CI). All tests performed were 2-sided and used 0.05 as level of statistical significance (SAS statistical package, version 8.2; SAS).

Table 1. Baseline Characteristics of the 94 Stroke Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>67.5 ± 8.6</td>
</tr>
<tr>
<td>Female, N (%)</td>
<td>32 (34.0)</td>
</tr>
<tr>
<td>Hypertension, N (%)</td>
<td>81 (86.2)</td>
</tr>
<tr>
<td>Hyperlipidemia, N (%)</td>
<td>33 (35.1)</td>
</tr>
<tr>
<td>Diabetes, N (%)</td>
<td>26 (27.7)</td>
</tr>
<tr>
<td>Smokers, N (%)</td>
<td>25 (26.6)</td>
</tr>
<tr>
<td>Obesity, N (%)</td>
<td>24 (25.5)</td>
</tr>
<tr>
<td>Previous stroke/TIA, N (%)</td>
<td>18 (19.1)</td>
</tr>
<tr>
<td>Coronary heart disease, N (%)</td>
<td>12 (12.8)</td>
</tr>
<tr>
<td>Peripheral arterial disease, N (%)</td>
<td>9 (9.6)</td>
</tr>
<tr>
<td>NIH stroke scale</td>
<td></td>
</tr>
<tr>
<td>0, N (%)</td>
<td>21 (22.3)</td>
</tr>
<tr>
<td>1, N (%)</td>
<td>15 (16.0)</td>
</tr>
<tr>
<td>2–4, N (%)</td>
<td>35 (37.2)</td>
</tr>
<tr>
<td>5–10, N (%)</td>
<td>19 (20.2)</td>
</tr>
<tr>
<td>≥11, N (%)</td>
<td>4 (4.3)</td>
</tr>
</tbody>
</table>

Values are given as mean ± SD or as absolute numbers (%).

Results

Baseline Findings
Patients’ characteristics and stroke subtypes according to the modified TOAST classification are summarized in Tables 1 and 2. All patients underwent TEE and MRI of the aorta within a median of 6 days after admission. The median for the time between TEE and aortic MRI was 3 days. MRI scan duration was 64 ± 16 minutes (range, 37–120 minutes).
Table 2. Stroke Subtypes of the 94 Stroke Patients

<table>
<thead>
<tr>
<th>TOAST Classification</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I, Determined etiology</td>
<td>57 (60.6%)</td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>11 (11.7%)</td>
</tr>
<tr>
<td>Large artery atherosclerosis</td>
<td>42 (44.7%)</td>
</tr>
<tr>
<td>Small vessel disease</td>
<td>3 (3.2%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>Group II, Cryptogenic stroke</td>
<td>37 (39.4%)</td>
</tr>
</tbody>
</table>

Classification of stroke etiology is based on the findings of routine diagnostics including TEE and on MRI of the ascending aorta/aortic arch. Accordingly, the proposed stroke mechanism of retrograde embolization was not considered. Values are given as absolute numbers (%).

Retrograde Embolization: Analysis on a Plaque Level

In Figure 2, the distribution of the 97 complex plaques of all patients is displayed along the predefined sections of the DAo. Furthermore, the frequency of flow reversal able to connect plaque location with the outlet of the LSA, left CCA, or BCT is given. As an example, retrograde flow originating in the most proximal 10 mm of the DAo (section I) reached the LSA from 19 of 21 (90.5%) and the CCA from 10 of 21 (47.6%) plaques. Flow reversal to the BCT was least likely but still present in 5 of 21 plaques (23.8%). The probability that retrograde flow reached the LSA, CCA, or even the BCT steadily decreased with the distance of plaque location from the LSA (compare flow reversal from segment I vs V).

Summarizing all potential embolic pathways, retrograde flow reached the LSA from 65 (67.0%), reached the CCA from 24 (24.7%), and reached the BCT from 14 (14.4%) complex plaques.

Analysis on a Patient Level

Some patients showed multiple complex DAo plaques. Therefore, analysis of potential retrograde embolization on a patient level (Figure 3) is different from findings on a plaque level (Figure 2). Reverse flow connected complex DAo atheroma with the LSA in 55 (58.5%), the CCA in 23 (24.5%), and BCT in 13 patients (13.8%; Figure 3). When results of all routine diagnostics, including TEE and MRI of the ascending aorta/aortic arch, were considered, 57 patients (60.6%) were classified as having determined stroke and 37 patients (39.4%) were classified as having cryptogenic stroke. In these 2 subgroups the proposed mechanism (retrograde embolization from DAo plaques) was found in 19 of 57 patients (33.3%) with determined and in 9 of 37 patients (24.3%) with cryptogenic stroke. Brain infarction affected the posterior circulation in 6, the left hemisphere in 2, and the right hemisphere in 1 of the patients with cryptogenic stroke.

Plaque and Retroflow Characteristics

The 97 complex DAo plaques detected by MRI in 71 patients (Figure 2) were located 21.9±15.3 mm (range, 0–72.7 mm) distal to the LSA outlet; 67 of 97 plaques (69.1%) were located in the first 3 cm and 30 of 71 patients also had complex plaques in the ascending aorta/aortic arch. In the 94 patients of this study, MRI detected the following number of complex plaques/thrombi: ascending aorta, 13/0; aortic arch, 34/2; and DAo, 97/7.

In the 20 complex DAo plaques of the 19 patients with determined stroke etiology and the proposed stroke mechanism, plaque thickness was 6.6±2.4 mm (range, 4.2–14.0 mm), 3 of them contained superimposed thrombi, and 1 was ulcerated. Analogously, in the 11 complex DAo plaques of the 9 patients with cryptogenic stroke, plaque thickness was 5.0±1.2 mm (range, 4.1–8.0 mm), 1 plaque had a superimposed thrombus, and 1 was ulcerated.

The average distance covered by reverse flow in the proximal DAo that reached the LSA outlet was 26.6±12.1 mm (range, 0–50 mm). Only decreasing heart rate correlated with increasing retrograde flow length in the proximal DAo (r=−0.24; P=0.018), whereas cardiovascular risk factors, age, aortic valve insufficiency, or aortic wall thickness did not. The OR for increasing retrograde flow per decreasing 10 heartbeats per minute was 0.63 (95% CI, 0.42–0.93).

Figure 3. Upper row, Diffusion-weighted cranial MR imaging. Lower row, Time-resolved 3-dimensional particle traces visualize potential embolization pathways from complex plaques in the proximal descending aorta (2-dimensional plane, yellow arrow) to the outlet of the brain-supplying arteries (red arrows). Flow reversal to the LSA potentially causes stroke (red circles) in the posterior circulation (A) or to the CCA, or brachiocephalic trunk potentially causes stroke in the left (B) or right hemisphere (C). The number of patients with potential retrograde embolization into the particular supra-aortic great artery is given in absolute values and in percentages in relation to the 94 patients.
Discussion

Complete coverage of late diastolic flow, improved data analysis, and inclusion of stroke patients with advanced aortic atherosclerosis revealed that flow reversal from complex DAo plaques potentially reaches all supra-aortic arteries. This was previously not demonstrable\(^{10}\) and extends the hazard of this potential stroke mechanism to all brain territories. In addition, retrograde embolization was frequent. It constituted the only probable source of retinal or cerebral infarction in 24% of the patients with cryptogenic stroke etiology. None of these had stenoses of the internal carotid or vertebral arteries of \(\geq 30\%\). Moreover, retrograde embolization was an alternative source in 33% of the patients with determined stroke etiology. Based on these findings and the high incidence of complex DAo plaques of 8% in determined and 28% in cryptogenic stroke,\(^{17}\) one could speculate that retrograde embolization may be found in up to 5% (one-third of 8%) and 7% (one-fourth of 28%) in serial unselected patients with determined and cryptogenic stroke.

The association of complex plaques and cerebral embolization was demonstrated in previous stroke cohorts\(^ {17-21}\) but questioned in 2 population-based studies.\(^ {22,23}\) In the present study, plaque rupture in the DAo and subsequent thromboembolism to the brain was not proven. However, the following factors suggest a causal link: the mechanism of retrograde embolization was directly visualized, constituted the only embolic source in a number of patients with cryptogenic stroke despite a detailed diagnostic work-up, and was associated with a visible embolic pattern of retinal or cerebral infarction. Moreover, flow reversal reached the adjacent outlet of the left subclavian artery more frequently than the distant brachiocephalic trunk. Accordingly, the posterior circulation was affected more often compared to the right and left hemisphere in the 9 patients with otherwise cryptogenic stroke. Finally, the mechanism is biologically plausible because incidence, thickness of plaques, and thus the risk of rupture is highest in the proximal DAo.\(^ {10,17}\) The proposed stroke mechanism may be confirmed using emboli detection in Doppler ultrasound.\(^ {24}\) Thus, a synchronous examination of both middle cerebral arteries and of the basilar artery should be performed in future studies.

Our results are supported by the large, case-control study by Amarenco et al\(^ {17}\) demonstrating a crude OR of 13.8 for complex plaques in the ascending aorta/aortic arch and stroke. In this study, the OR for stroke was still 5.5 for the proximal but only 1.5 for the distal straight segment of the descending aorta.\(^ {17}\) Our study provides 1 pathophysiological explanation for these findings: there is a higher likelihood of retrograde cerebral embolization originating from complex plaques of the proximal but not of the distal DAo.

In the current cohort, aortic valve insufficiency did not correlate with retrograde flow. This confirms our previous findings\(^ {10}\) and contradicts current beliefs that flow reversal is rare and only present in coincidence with aortic valve insufficiency.\(^ {1,2}\) An increase of retrograde flow with age\(^ {10}\) as a result of the decrease of the Windkessel function of the aorta was not reproduced and could be attributable to the limited number or different characteristics of the patients. Currently, only decreasing heart rate correlated with increasing flow reversal. Future examinations of larger cohorts are thus necessary to identify robust predictors for retrograde flow.

The best medical treatment of aortic plaques has not yet been determined.\(^ {1,25,26}\) This is the aim of the ongoing first prospective, randomized, controlled Aortic Arch-Related Cerebral Hazard trial comparing aspirin plus clopidogrel with warfarin in aortic high-risk plaques. However, this trial and 2 other large but retrospective studies\(^ {25,26}\) do not consider plaques in the DAo as a source of stroke. This fact may significantly limit the results with respect to the true embolic relevance and best medical treatment of complex aortic atheroma.

Our study focused on consecutive acute patients with cryptogenic stroke and aortic wall thickness \(\geq 3 \) mm in TEE. Therefore, we cannot exclude that some individuals with complex aortic plaques were erroneously excluded because of the limited visualization of the aortic arch by TEE.\(^ {8}\) In addition, 18% of the patients suitable for the study refused to participate and \(\approx 12\%\) had contraindications against 3-T MRI, which may have biased our findings. Furthermore, future improvements of the MRI protocol are needed for robust multicontrast MR imaging\(^ {9,27}\) to optimally assess the risk of plaque rupture.

Conclusion

In conclusion, retrograde flow originating from complex plaques of the proximal DAo was frequent and has the potential, as demonstrated here for the first time to our knowledge, to cause embolic stroke in all brain territories. These findings suggest that complex DAo plaques should be considered a new source of stroke. The true incidence and clinical relevance of this mechanism in unselected patients should be evaluated in larger stroke cohorts.

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Disclosures

None.

References


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An Underestimated Embolic Source of Stroke

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背景和目的：研究降主动脉复合性斑块（厚度≥4 mm，溃疡性或叠加血栓）反流的发生情况及其在栓塞性卒中的作用。

方法：前瞻性纳入了94例经食道超声发现主动脉斑块厚度≥3 mm的急性卒中患者。MRI检查定位主动脉内复合性斑块的位置和测量时间分辨三维(3D)血流情况。3D可视化研究用来评估是否舒张期反流连接斑块的位置与左锁骨下动脉、左颈总动脉或头臂干的出口。如果反流到达主动脉以上供应血管且可见到急性视网膜或脑的梗死，就考虑降主动脉复合性斑块为栓塞的源头。

结果：仅心率降低与增加的主动脉弓反流相关（P<0.02）。从降主动脉粥样硬化斑反流到左锁骨下动脉的患者55例(58.5%)，反流到颈总动脉的患者23例(24.5%)，反流到头臂干的有13例患者(13.8%)。根据常规检查的结果及升主动脉/主动脉弓的MRI检查，57例患者为有明确病因的卒中，37例患者为隐源性卒中。降主动脉斑块作为潜在的栓子来源，明确病因组有19例患者(33.3%)而隐源性卒中组有9例患者(24.3%)发现了降主动脉斑块。

结论：降主动脉斑块反流在明确病因和隐源性卒中患者中都很常见，此机制可以解释栓塞性卒中。这些结果提示，降主动脉斑块应该作为新的可以引起卒中的原因。

关键词：急性卒中，主动脉，动脉粥样硬化，磁共振，发病机制

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复合性斑块定义为4 mm 厚的溃疡性或含有活动性栓子的斑块，其被认为是引起卒中的重要原因之一[1]。尽管这样的斑块在近端降主动脉非常常见，但其只在非常少见的情况下才考虑是卒中的栓子来源，即当严重的主动脉瓣膜功能不全引起反流，同时遇到斑块破裂才考虑可能由栓塞引起[1,2]。

然而越来越多的证据显示，在动脉粥样硬化患者中，降主动脉舒张期反流是比较常见的现象，其引起卒中的反流性栓塞机制可能被低估了。经食道超声(TEE)显示的降主动脉的振动性栓子流动[3]和多普勒血流曲线间接证明了反流现象的存在[4]。与TEE相比，血流敏感性的四维(4D)MRI 技术不仅能精确地分析个体降主动脉复合性斑块的三维(3D)血流形式[5-7]，而且还能可靠地检测和分析斑块的特征[8,9]。最近一项队列研究提出一个需要验证的理论，反流性栓子可能来源于降主动脉复合性斑块，该研究发现，这样的栓子是唯一可能引起患者后循环缺血的原因[10,11]。

而该研究没有完全评估舒张晚期反流的情况[10,11]，我们认为，反流发生的频率及其与主动脉弓以上血管的关系尚不明确。因此，我们连续纳入患者，使得MRI方案覆盖整个舒张期，同时采取了可视化研究即同时记录了斑块的位置和三维血流情况。这样可以让我们详细分析栓子从降主动脉到不同脑血管的情况。我们在伴主动脉粥样硬化同时有明确病因或不明原因急性卒中的患者中系统地评估了该机制参与卒中发生的情况。

资料与方法

研究人群

在2008年6月19日至2009年3月24日期间，
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共有734例连续性非选择的急性视网膜或脑缺血患者入往我院。其中314例患者根据先前的规定[11]，常规检查后未发现卒中的原因，因此进行了TEE检查。在接受TEE检查的患者中，如伴有房颤/房扑或严重的症状性颈内动脉狭窄的患者均被排除，原因为：病因明确、有MRI检查禁忌或者两者兼有。172例患者满足下述纳入标准：急性视网膜或脑缺血，年龄在18岁以上，TEE显示主动脉斑块厚度≥3 mm。32名患者拒绝参加本研究，20例患者有MRI检查禁忌。另外排除了14例患者，原因为：病情不稳定(n=2)，依从性不佳(n=4)，体重指数超过42(n=2)，在MRI检查前转入其他医院(n=4)，严重的背痛或感染性腹泻(n=2)。

在剩余的106例患者中，又有12例患者因为MRI检查完成前中断了检查或者数据质量欠佳被排除。因此，我们前瞻性分析了剩余的94例患者。每个患者签署了知情同意书，当地伦理委员批准了该研究。

常规诊断

评估心血管病危险因素，入院时根据国立卫生院卒中严重度评分确定卒中严重程度[12]。88例患者(93.6%)接受了脑MRI检查。6例患者接受了脑CT检查。接受了MRI和CT的患者有41例(43.6%)。84例(89.4%)患者进行了颅内外血管TOF-MRA检查。3例患者还接受了CTA或DSA检查。所有患者均接受了颅内外血管超声检查、经胸心脏超声检查(TTE)、经食道超声检查(TEE)、12导联心电图检查和Holter检查。1例患者由于持续性单眼视力障碍，接受了眼底镜检查。

心脏超声检查

TEE和TEE由两名有经验的超声医生使用2-4 MHz和5-7 MHz多探头进行检查(HDI 5000；飞利浦)。一名超声科医生自下而上对超声心动图的图像结果重新评估以识别斑块的位置和形态。主动脉病变包括动脉瓣膜功能不全的程度[11][13]。

动脉弓(AA)的范围包括从头臂干(BCT)的出口至左锁骨下动脉(LSA)之间。

头臂干的近端部分和左锁骨下动脉出口至远端分别定义为升主动脉和降主动脉。动脉壁最大厚度通过人工使用电子卡尺测量。溃疡性斑块表现为宽基底的最大深度至少2 mm的凹入壁管的斑块。

脑影像学

一名仅能获取影像学数据的影像学专家决定急性脑缺血或血管病变、受累的区域、卒中的类型和评估颅内动脉和椎基底动脉狭窄的程度[14]。

主动脉MRI检查

94例患者接受了主动脉3-T磁共振(TRIO；西门子)检查。当患者肾小球滤过率≥40 mL/min时，使用时间分辨对比增强三维磁共振血管成像检查主动脉(钆贝酸二葡甲胺0.1 mL/kg体表面积，以3.5 mL/sec的速度推注)。高分辨MRI(0.9×1.1×1.1 mm³)检测整个上部胸主动脉的斑块情况(心电图定位的T1加权脂肪饱和3D梯度回波影像；舒张期获得窗=157 ms；回波时间[TE]/重复时间[TR]=2.3 ms/5.5 ms；翻转角=20°)。当降主动脉斑块≥4 mm时，再做一次心电图定位的T2加权2D快速自旋回波成像(TE=78 ms)TR=2s检测周期：空间分辨率=1.1×1.2×3 mm³。3D-T1电影摄影术影
像 (TE/TR=1.8 ms/3.3 ms；时间 / 空间分辨率 = 53 ms/1.3×1.5×1.3 mm³) 用来检查活动性斑块成分。最后执行心电图同步血流敏感性 4D 磁共振成像 (TE/TR=2.6-3.5 ms/5.1-6.1 ms；翻转角 = 7°-15°；时间 / 空间分辨率 = 40.8 ms/1.7×2.0×2.2 mm³)。使用 3D 速度编码 (速度敏感度 = 150 cm/sec) 获取数据，并获取全部胸主动脉区。呼吸门控成像用于 3D-T1 和血流敏感 4D 磁共振成像[13]。在 MRI 检查前和后记录上肢血压水平。在测量流速时每 4 分钟记录一次心率。

在平面分析正常时，使用多平面重组技术定位复合性斑块，观察动脉管腔和测定最大管壁厚度 [8]。主动脉血栓定义为异常突入管腔的斑块，T1 为低密度信号，3D T1-CINE 影像为斑块成分的运动。溃疡性斑块定义与心脏超声一致。两名不知情的研究者盲法评估患者，当出现不一致时与第三方讨论共同决定。对于每个患者来说，近端降主动脉复合性斑块二维平面影像与血流敏感性 4D MRI 数据通过影像输入共同记录。一个发射平面精确的定位于斑块的位置，用来产生时间分辨的 3D 粒子轨迹。计算的轨迹类似于时间分辨的 3D 血流 [10]，因此可以看出始源于动脉粥样斑块的舒张期反流情况（如图 1）。

卒中亚型

一名不知情的神经病学家根据改良的 TOAST 标准 [16] 进行病因分型（表 2）。可能的病因包括以下几方面：左房自发回声对比，左心耳速度 <30 cm/sec，卵圆孔开放伴房间隔动脉瘤，急性深静脉血栓形成或肺栓塞或近期长时间不动史或事件发生前的Valsalva 动作（心源性的），TEE 或 MRI 检查到升主动脉或主动脉复合性斑块（大动脉粥样硬化）[14]。有明确病因的（包括多个可能的病因）卒中归类为病因确定的；没有明确原因的归类为隐源性病因。

最大反流和降主动脉复合性斑块根据先前描述的方法进行评估 [10]。基于视觉分析，一名研究者评估了可能起源于降主动脉 10 mm 节段内复合性斑块的栓子路径（如图 2 所示）。如果出现下列情况可定义为反流性栓塞：(1) 反流起源于降主动脉复合性斑块，到达主动脉以上大动脉出口；(2)

<table>
<thead>
<tr>
<th>表 1 94 例卒中患者基线特征</th>
<th>数值</th>
</tr>
</thead>
<tbody>
<tr>
<td>年龄 [岁]</td>
<td>67.5 ± 8.6</td>
</tr>
<tr>
<td>女性, [N (%)</td>
<td>32 (34.0)</td>
</tr>
<tr>
<td>高血压, [N (%)</td>
<td>81 (86.2)</td>
</tr>
<tr>
<td>高脂血症, [N (%)</td>
<td>33 (35.1)</td>
</tr>
<tr>
<td>糖尿病, [N (%)</td>
<td>26 (27.7)</td>
</tr>
<tr>
<td>吸烟, [N (%)</td>
<td>25 (26.6)</td>
</tr>
<tr>
<td>肥胖, [N (%)</td>
<td>24 (25.5)</td>
</tr>
<tr>
<td>先前卒中/TIA, [N (%)</td>
<td>18 (19.1)</td>
</tr>
<tr>
<td>冠心病, [N (%)</td>
<td>12 (12.8)</td>
</tr>
<tr>
<td>外周动脉疾病, [N (%)</td>
<td>9 (9.6)</td>
</tr>
<tr>
<td>NIH 卒中量表</td>
<td>0, [N (%)</td>
</tr>
<tr>
<td>1, [N (%)</td>
<td>15 (16.0)</td>
</tr>
<tr>
<td>2–4, [N (%)</td>
<td>35 (37.2)</td>
</tr>
<tr>
<td>5–10, [N (%)</td>
<td>19 (20.2)</td>
</tr>
<tr>
<td>≥11, [N (%)</td>
<td>4 (4.3)</td>
</tr>
</tbody>
</table>

数值表示为均数±标准差或绝对数 (%)。
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表 2 94 例卒中患者的卒中分型

<table>
<thead>
<tr>
<th>TOAST 分型</th>
<th>数值</th>
</tr>
</thead>
<tbody>
<tr>
<td>I 组, 病因明确</td>
<td>57 (60.6%)</td>
</tr>
<tr>
<td>心源性栓塞</td>
<td>11 (11.7%)</td>
</tr>
<tr>
<td>大动脉粥样硬化</td>
<td>42 (44.7%)</td>
</tr>
<tr>
<td>小血管病</td>
<td>3(3.2%)</td>
</tr>
<tr>
<td>其他</td>
<td>1(1.1%)</td>
</tr>
<tr>
<td>II 组, 隐源性卒中</td>
<td>37 (39.4%)</td>
</tr>
</tbody>
</table>

病因学分型基于常规检查结果，包括升主动脉 / 主动脉弓的 TEE 和 MRI 检查，因此，本研究提出的反流栓塞机制没有列出。数值表示为绝对数 (%).

受累脑缺血区域与供血动脉匹配；(3) 眼底镜或脑影像学证实梗死的形式为栓塞造成。当反流到达 3 个脑供血血管，即使脑影像学没有可见的梗死或血管堵塞也可判定为反流性栓塞。

统计学分析

连续性变量以均数 ± 标准差表示，分类变量以绝对或相对频数表示。根据反流程度不同 (反流速度 <25 mm vs. ≥ 25 mm) 比较患者基线特征，MRI( 最大管壁厚度，主动脉管腔直径) 或心脏超声的数据 (射血分数，动脉瓣膜功能不全程度 )；因为 25 mm 是中位反流速度，因此取其为截点。结果用 OR 值和其 95% 可信区间表示。所有的检验均为双侧检验，以 0.05 为检验水准 (SAS 统计软件包，8.2 版本)。

结果

基线结果

患者的特征和根据改良的 TOAST 标准划分的卒中亚型见表 1 和表 2。所有患者在入院 6 天内接受了经食道超声和主动脉 MRI 检查。TEE 和主动脉 MRI 检查间隔中位时间是 3 天。MRI 扫描时间为 64±16 分钟 (范围，37-120 分钟)。

反流性栓塞：基于斑块水平的分析

在图 2 中展示了所有患者在预先确定的降主动脉层面出现的 97 处复合性斑块分布情况。此外，还展示了解释斑块位置与左锁骨下动脉、左颈总动脉或头臂动脉开口反流的频率。比如，源于近端降主动脉 I 节段部分到左锁骨下动脉斑块反流为 90.5%(19/21)，到颈总动脉的斑块反流为 47.6%(10/21)，到头臂动脉的反流最少的，但仍有 23.8%(5/21) 的斑块反流到此处。随着复合斑块位置距左锁骨下动脉越来越远 (从节段 I 到 V)，斑块反流到左锁骨下动脉、颈总动脉或头臂动脉的可能性越来越小。总体反流性栓子数目到达左锁骨下动脉的有 65 个 (67.0%)，到达颈总动脉的有 24 个 (24.7%)，而到达头臂动脉的有 14 个 (14.4%)。

基于患者水平的分析

由于一些患者出现多个降主动脉复合性斑块，反流性栓塞从患者水平的分析和从斑块水平分析将有所不同 (见图 3)。从降主动脉粥样硬化斑块反流到左锁骨下动脉的患者 55 例 (58.5%)，反流到颈总动脉的患者 23 例 (24.5%)，反流到头臂动脉的有 13 例患者 (13.8%，见图 3)。根据常规检查的结果及升主动脉 / 主动脉弓的 TEE 和 MRI 检查，57 例患者 (60.6%) 为有明确病因的卒中，37 例患者 (39.4%) 为隐源性

图 3 上排，头颅磁共振弥散加权成像。下排，时间分辨 3D 轨迹显示的从斑块降主动脉复合性斑块 (二维平面，箭头 ) 到脑供血血管出口 (粗箭头) 的潜在栓塞途径。反流到左锁骨下动脉可能引起后循环卒中 (A, 图内 )，反流到颈总动脉可能引起左侧大脑半球卒中 (B, 图内 )，反流到头臂动脉可能引起右侧大脑半球卒中 (C, 图内 )。图下部显示有潜在反流栓塞到主动脉以上的患者数及其在 94 例患者中的百分数。

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卒中。我们假定的机制 (降主动脉斑块反流性栓塞)情况为, 明确病因组有 19 例患者 (33.3%), 而隐源性卒中组有 9 例患者 (24.3%)。在隐源性卒中的患者中, 梗死累及后循环的有 6 例, 左侧大脑半球 2 例, 右侧大脑半球 1 例。

斑块及反流特征
通过 MRI 检查, 71 例患者发现 97 处复合性降主动脉斑块, 距离左锁骨下动脉的出口 21.9±15.3 mm (范围, 0-72.7 mm); 67 个斑块 (69.1%) 位于前 3 cm 内, 30 例患者升主动脉 / 主动脉弓同样有复合性斑块。本研究中的 94 例患者, MRI 检查发现的复合性斑块 / 血栓如下: 升主动脉, 13/0; 主动脉弓, 34/2; 降主动脉, 97/7。

19 例病因明确的患者降主动脉有 20 个复合性斑块, 斑块厚度为 6.6±2.4 mm (范围, 4.2-14.0 mm), 其中 3 个斑块有叠加血栓, 1 个是溃疡性斑块。与此类似, 9 例隐源性患者有 11 个复合性斑块, 斑块厚度为 5.0±1.2 mm (范围, 4.1-8.0 mm), 1 个斑块有叠加血栓, 1 个是溃疡性斑块。近端降主动脉反流到左锁骨下动脉的平均距离为 26.6±12.1 mm (范围, 0-50 mm)。仅减慢的心率与增加的反流长度相关 (r =–0.24; P =0.018), 而心血管危险因素、年龄、主动脉瓣功能不全或动脉壁厚度不相关。每分钟心率降低 10 次, 反流增加的风险为 0.63 (95% CI, 0.42-0.93)。

讨论
本研究全面评估了舒张晚期血流, 改进了数据分析, 纳入晚期主动脉粥样硬化的患者, 结果发现降主动脉斑块的反流能够到达主动脉以上的动脉。此现象先前并未被证实 [10], 本研究增加了对这种潜在的栓塞机制在卒中发病中的认识。此外, 反流性栓子并不少见, 在隐源性卒中的患者, 24%的患者很可能因为此机制引起的卒中。尽管做了全面的检查, 降主动脉的病变可能是唯一的栓子来源; 可见的视网膜或脑梗死的栓塞形式与这些栓子相关。另外, 反流到左锁骨下动脉比到更远处的头臂干的频率更高。因此, 在 9 例隐源性卒中的患者, 后循环受累比右侧或左侧半球受累更常见。最后, 该机制有可能解释生物学依据, 近端降主动脉斑块的发生, 斑块的厚度和破裂的风险都是很高的 [10,17]。我们推测的这种机制可通过多普勒超声监测栓子信号予以证实 [24]。因此, 在将来的研究中, 应该同步监测大脑中动脉和基底动脉。

一项大的病例对照研究 [17] 显示, 对于有升主动脉 / 主动脉弓复合性斑块患者发生卒中的风险约为没有这些斑块患者的 13.8 倍。该研究的结果支持我们的结果。在该研究中, 近端降主动脉斑块引发卒中的风险为 5.5 倍, 而远端斑块的风险仅为 1.5 倍 [17]。我们的研究为这些现象提供了一个病理生理学的解释: 反流性栓塞机制是由近端降主动脉复合性斑块引起, 而不是远端降主动脉斑块引起。本研究中, 主动脉瓣功能不全与反流并不相关。此发现证实了我们先前研究的结果, 但与目前的观点相矛盾, 目前认为反流很少发生, 且反流与主动脉瓣功能不全或动脉壁厚度不相关。每分钟心率降低 10 次, 反流增加的风险为 0.63 (95% CI, 0.42-0.93)。

复合性斑块与脑栓塞的相关性在先前的研究中已有证实 [17-21], 但是在两个基于人群的研究中受到争议 [22-23]。本研究没有证明是否降主动脉斑块破裂与血栓 - 栓塞性卒中存在直接关系。然而, 据下面几方面可以推测是有因果关系的: 直接观察到的反流性栓塞; 一些隐源性卒中的患者尽管做了全面的检查, 降主动脉的斑块可能是唯一的栓子来源; 可见的视网膜或脑梗死的栓塞形式与这些栓子相关。此外, 反流到左锁骨下动脉比到更远处的头臂干的频率更高。因此, 在 9 例隐源性卒中的患者, 后循环受累比右侧或左侧半球受累更常见。最后, 该机制有可能解释生物学依据, 近端降主动脉斑块的发生, 斑块的厚度和破裂的风险都是很高的 [10,17]。我们推测的这种机制可通过多普勒超声监测栓子信号予以证实 [24]。因此, 在将来的研究中, 应该同步监测大脑中动脉和基底动脉。

本研究中, 主动脉瓣功能不全与反流并不相关。此发现证实了我们先前研究的结果, 但与目前的观点相矛盾, 目前认为反流很少发生, 且反流与主动脉瓣功能不全或动脉壁厚度不相关。每分钟心率降低 10 次, 反流增加的风险为 0.63 (95% CI, 0.42-0.93)。
MRI 方案^{9,27} 的改进能更好的评估斑块破裂的风险。

结论

总之，近端主动脉复合性斑块栓子反流并不少见，本研究第一次证实了其可能是引起栓塞性卒中的重要原因。这些结果显示，降主动脉复合性斑块应该考虑为卒中的原因之一。该机制的真实发生情况及其与临床的相关性应在更大的非选择性患者的研究中去验证。

参考文献