Original Paper

Cerebrovascular Diseases

Cerebrovasc Dis 2014;38:410–417
DOI: 10.1159/000369001

Received: August 5, 2014
Accepted: October 13, 2014
Published online: December 3, 2014

Prevalence of Potential Retrograde Embolization Pathways in the Proximal Descending Aorta in Stroke Patients and Controls

Thomas Wehrum[a] Miriam Kams[a] Christoph Strecker[a] Iulius Dragonu[d]
Felix Günther[b] Annette Geibel[b] Johann Drexl[f] Anja Hennemuth[f]
Martin Schumacher[c] Bernd Jung[d, e] Andreas Harloff[a]

Departments of [a]Neurology, [b]Cardiology and Angiology, [c]Neuroradiology and [d]Diagnostic Radiology – Medical Physics, University Medical Center Freiburg, Freiburg, Germany; [e]Institute of Diagnostic, Interventional and Pediatric Radiology University Medical Center Bern, Bern, Switzerland; [f]Fraunhofer MEVIS, Bremen, Germany

Key Words
Aorta · Atherosclerosis · 4D flow MRI · Retrograde embolization

Abstract
Background: Retrograde diastolic blood flow in the proximal descending aorta (DAo) connecting complex plaques (≥4 mm thick) with brain-supplying supra-aortic arteries may constitute a source of stroke. Yet, data only from high-risk populations (cryptogenic stroke patients with aortic atheroma ≥3 mm) regarding the prevalence of this potential stroke mechanism are available. We aimed to quantify the frequency of this mechanism in unselected patients with cryptogenic stroke after routine diagnostics and controls without a history of stroke. ***Methods:*** 88 patients (67 stroke patients, 21 cardiac controls) were prospectively included. 3D T1-weighted bright blood MRI of the aorta was applied for the detection of complex DAo atheroma. ECG-triggered and navigator-gated 4D flow MRI allowed measuring time-resolved 3D blood flow in vivo. Potential retrograde embolization pathways were defined as the co-occurrence of complex plaques and retrograde blood flow in the DAo reaching the outlet of (a) the left subclavian artery, (b) the left common carotid artery, or/and (c) the brachiocephalic trunk. The frequency of these pathways was analyzed by importing 2D plaque images into 3D blood flow visualization software. ***Results:*** Complex DAo plaques were more frequent in stroke patients (44 in 31/67 patients (46.3%) vs. 5 in 4/21 controls (19.1%); p = 0.039), especially in older patients (29/46 (63.04%) patients ≥60 years of age with 41 plaques vs. 2/21 (9.14%) patients <60 years of age with 3 plaques; p < 0.001). Contrary to our assumption, retrograde diastolic blood flow at the DAo occurred in every patient irrespective of the existence of plaques with a similar extent in both groups (26 ± 14 vs. 32 ± 18 mm; p = 0.114). Therefore, only the higher prevalence of complex DAo plaques in stroke patients resulted in a three times higher frequency of potential retrograde embolization pathways compared to controls (22/67 (32.8%) vs. 2/21 (9.5%) controls; p = 0.048). ***Conclusions:*** This study revealed that retrograde flow in the descending aorta is a common phenomenon not only in stroke patients. The

E-Mail karger@karger.com
www.karger.com/ced

Thomas Wehrum, MD
Department of Neurology
University Medical Center Freiburg
Breisacher Straße 64, DE–79106 Freiburg (Germany)
E-Mail thomas.wehrum@uniklinik-freiburg.de

existence of potential retrograde embolization pathways depends mainly on the occurrence of complex plaques in the area 0 to ~30 mm behind the outlet of the left subclavian artery, which is exposed to flow reversal. In conclusion, we have shown that the frequency of potential retrograde embolization pathways was significantly higher in stroke patients suggesting that this mechanism may play a role in retrograde brain embolism.

Introduction

Complex atheromatous plaques (i.e., ≥4 mm thick, ulcerated or containing thrombi) of the ascending aorta and aortic arch are considered a major source of stroke, while atheromas of the descending aorta (DAo) are thought to be a marker of atherosclerosis [1, 2]. However, data from an echocardiographic study have shown that the probability of stroke was higher when ≥4 mm thick plaques were located in the proximal compared to the distal straight DAo (odds ratio 5.5 vs. 1.5) [3]. A likely explanation is the presence of diastolic aortic flow reversal originating at such plaques and entering the outlet of a brain-supplying artery of the arch. Early studies assigned this phenomenon only to patients with coincident aortic valve insufficiency [1], but later studies revealed that it was also common in stroke patients with normal aortic valves [4–7]. Indirect evidence for retrograde embolization from DAo plaques was further provided by transesophageal echocardiography (TEE) demonstrating oscillating thrombus motility [4], retrograde blood flow in Doppler flow curves [5], and by the description of right-left propensity of cerebral lesion patterns in patients with cardiogenic versus aortogenic stroke etiology [8]. However, only 4D flow MRI enables the direct in vivo visualization of retrograde embolization pathways and thus aids in differentiating between complex aortic plaques with or without the risk of stroke [6, 7].

Currently, only data from high-risk populations (cryptogenic stroke patients with aortic atheroma ≥3 mm) regarding the prevalence of this potential stroke mechanism are available [6, 7]. Therefore, it is unclear how potential embolization pathways (i.e., co-occurrence of complex plaques and flow reversal) are distributed in unselected stroke patients and subjects without previous stroke. We hypothesized that the proposed mechanism is rare in patients without a history of brain ischemia, which would emphasize its role as a stroke mechanism.

Methods

We conducted a cross-sectional case-control study with prospective data acquisition (aortic MRI) on patients with ischemic stroke with cryptogenic etiology after routine diagnostics (before TEE) and on cardiac controls.

Study Cohort

Over a 9-month period in 2011, 715 consecutive stroke patients were admitted to our institution. Out of the 715, 365 of them underwent TEE and transthoracic echocardiography (TTE) as part of an acute ischemic stroke workup if stroke etiology was cryptogenic after routine diagnostics. Inclusion criteria were: acute transient ischemic attack (TIA) or ischemic stroke, >18 years of age, and suitability for 3-Tesla MRI examination. Cardiac patients without a history of TIA or stroke (information obtained by interview and patient's medical history) who underwent TEE and/or TTE for the assessment of cardiac conditions at our institution were chosen as controls in order to account for cardiac parameters (systolic ejection fraction and aortic valve abnormalities). Controls were frequency matched to cases in terms of age, sex, and hypertension. Patients were excluded from the study due to MRI contraindications, cardiac arrhythmias such as atrial fibrillation disturbing ECG-triggering, and impaired general condition (for recruitment details see online suppl. material; for all online suppl. material, see www.karger.com/doi/10.1159/000369001). Finally, 88 patients (67 stroke and 21 cardiac patients) were successfully included and examined.

Cardiovascular risk factors were prospectively documented. Etiology and severity of stroke on admission was assessed as described previously [7]. All stroke patients underwent a complete diagnostic workup during their hospital stay (i.e., brain CT and/or MRI, extra-/intracranial angiography (MRA or CTA) if indicated, ultrasound of extra-/intracranial arteries, TEE and TTE, 12 lead- and Holter-ECG, and routine laboratory tests).

The study was approved by the University of Freiburg Ethics Committee and informed consent was obtained from all participants.

MRI of the Aorta

All MRI examinations were conducted using a 3-Tesla MRI system (TIM Trio, Siemens Healthcare AG, Erlangen, Germany). 4D flow MRI (echo time/repetition time (TE/TR) = 2.6 ms/5 ms, flip angle = 7°, temporal resolution = 40 ms, spatial resolution = $2.0 \times 1.7 \times 2.2$ mm^3) was acquired to obtain time-resolved and three-dimensional blood flow parameters of the thoracic aorta with a velocity sensitivity (venc) of 150 cm/s in all 3 spatial directions. A T1-weighted, fat-saturated, three-dimensional bright-blood gradient echo sequence (3DT1) ((TE/TR) = 2.53 ms/5.5 ms, flip angle = 20°, spatial resolution = $0.9 \times 1.1 \times 1.1$ mm^3) was used for the assessment of DAo plaques and aortic geometry [7]. Experiments were ECG-synchronized and respiration-controlled using navigator-gating [9].

Detection of Plaques of the Descending Aorta

Complex plaques (defined as ≥4 mm thick) of the thoracic aorta were detected based on 3DT1 bright blood MRI (J-Vision; Tiani Medgraph AG, Vienna, Austria), which proved to be reliable for the identification of high-risk plaques in comparison with TEE [10]. The DAo was defined as the part of the aorta located distal to

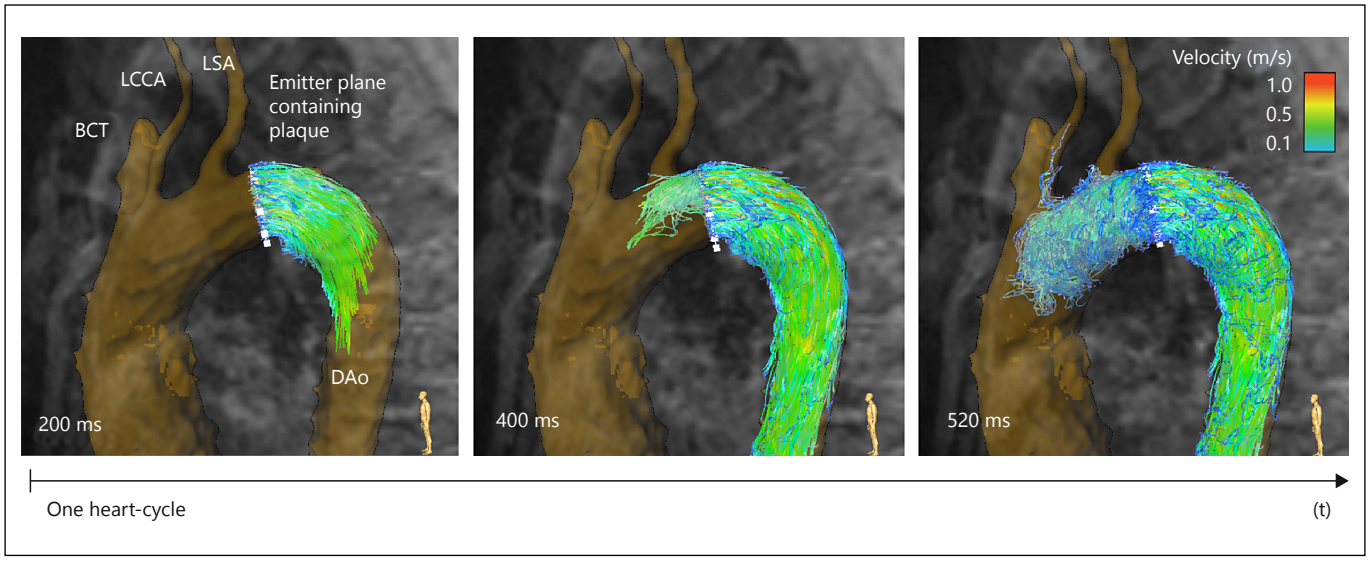


Fig. 1. Visualization of flow reversal from a DAo plaque over one average heart-cycle using particle tracing. Color coding represents absolute velocities in m/s. LSA = Left subclavian artery; LCCA = left common carotid artery; BCT = brachiocephalic trunk.

the outlet of the left subclavian artery (LSA). Two readers with experience in MRI reading of four and one year(s), respectively, identified maximum plaque thickness by manual measurements using electronic calipers and plaque location in consensus reading. A third reader with an experience of twelve years in MRI reading was involved for final decision in case of disagreement. All readers were blinded to patient data and results from TEE and TTE.

Post-Processing of Acquired MRI Data

4D-flow MRI datasets were processed and analyzed using MEVISFlow software (Fraunhofer MEVIS, Bremen, Germany) [11]. The processing workflow consisted of (a) correction of velocity offset errors due to eddy currents and concomitant gradient fields, (b) phase unwrapping (i.e., correction of velocity aliasing artifacts), (c) semi-automatic 3D segmentation, and (d) particle tracking within the time-resolved and three-dimensional flow data (for technical details see online suppl. material).

Quantification of Retrograde Blood Flow

Maximum retrograde flow based on particle traces and emitted from analysis planes with positions of 0–60 mm from the LSA (with a distance of 10 mm between the centers of each plane) was assessed by one observer on a visual basis [7].

Potential Retrograde Embolization Pathways

Two-dimensional planes of complex DAo plaques imported from 3DT1 data were co-registered with 4D flow MRI data in each patient. An emitter plane was positioned at the site of the plaque and time-resolved, three-dimensional particle traces resembling blood flow originating at this site were generated [7].

A possible retrograde embolization pathway was defined present in case of co-occurrence of a complex DAo plaque and retrograde blood flow connecting this plaque with the outlet of a brain-supplying artery of the arch. Possible retrograde embolization pathways reaching the outlet of (a) the LSA, (b) the left common carotid artery (CCA), and (c) the brachiocephalic trunk (BCT) were identified (see fig. 1 and online suppl. video 1 + 2).

Statistical Analysis

Data are presented as mean (± standard deviations) or median (interquartile range) for continuous, absolute, and relative frequencies for categorical variables. Departures from normality were detected with the Shapiro-Wilk statistic. Differences between patient groups were evaluated using the Fisher's exact test, one-way between-subjects random-effects ANOVA, and the Kruskal-Wallis test (with the post-hoc Wilcoxon rank sum test for multiple comparison adjustment), respectively. Subgroup analyses regarding age and stroke etiology were performed.

All tests were two-sided with 0.05 as the level of statistical significance. Statistical analyses were performed using IBM-SPSS Statistics version 19.0.1.

Results

Baseline Characteristics

Demographics, cardiovascular risk factors, and the results of echocardiography in stroke and cardiac patients are given in table 1.

The median stroke severity according to the National Institute of Health Stroke Scale (NIHSS) was 2 (interquartile range = 0–4). Stroke etiology according to the TOAST classification was determined (including multiple probable sources) in 38/67 (56.8%) patients (large-artery atherosclerosis in 29/67 (43.3%), cardioembolism

Table 1. Patients' demographics and cardiovascular risk factors

Characteristics of patients	Case group (n = 67)	Control group (n = 21)	p value
Age, years (mean ± SD)	63.75±15.0	63.5±18.5	0.95
Female, n (%)	28 (41.2)	5 (22.7)	0.19
Hypertension, n (%)	49 (72.1)	16 (72.7)	1.00
Hyperlipidemia, n (%)	17 (25.0)	8 (36.4)	0.28
Diabetes, n (%)	16 (23.5)	3 (13.6)	0.54
Smokers, n (%)	13 (19.1)	9 (42.9)	0.04
Obesity, n (%)	8 (11.9)	4 (18.2)	0.47
Previous stroke/TIA, n (%)	12 (17.7)	0 (0)	0.06
Coronary heart disease, n (%)	9 (13.2)	9 (40.9)	0.01
Peripheral arterial disease, n (%)	7 (10.3)	1 (4.6)	0.67
Mean systolic BP*, mm Hg (mean ± SD)	136.8±29.9	130.0±14.6	0.07
Mean diastolic BP*, mm Hg (mean ± SD)	77.6±16.8	82.3±10.7	0.38
Heart rate*, bpm (mean ± SD)	68.5±3.0	64.2±2.8	0.36
EF, % (mean ± SD)	55.2±6.7	51.8±7.4	0.07
AI grade I or II, n (%)	23 (34.3)	9 (42.9)	0.81
AI grade III or IV, n (%)	0 (0.0)	0 (0.0)	1.00
AS (mild), n (%)	0 (0.0)	2 (9.5)	0.06
AS (moderate), n (%)	0 (0.0)	2 (9.5)	0.06
AS (severe and critical), n (%)	0 (0.0)	0 (0.0)	1.00

TIA = Transient ischemic attack; BP = blood pressure; EF = ejection fraction; AI = aortic insufficiency; AS = aortic valve stenosis.
* Measured during 4D flow MRI.

in 12/67 (17.9%), small-vessel disease in 3/67 (4.5%), and stroke of other determined etiology in 0/67 (0%) cases). Stroke etiology was cryptogenic in 29/67 (43.3%) patients.

Cardiac controls were hospitalized due to valvular heart disease in 6/21 (28.6%), myocardial infarction in 5/21 (23.8%), acute hypertensive crises in 3/21 (14.3%), thoracic aortic aneurysm in 2/21 (9.5%), endocarditis (1/21, 4.8%), atrial septal defect repair (1/21, 4.8%), Takotsubo apical ballooning (1/21, 4.8%), pulmonary embolism (1/21, 4.8%), and palpitations (1/21, 4.8%).

Prevalence of Complex Plaques of the Thoracic Aorta

Mean thickness of all aortic plaques (ascending + descending aorta and aortic arch) as measured by 3DT1 MRI was 5.1 ± 1.3 mm in stroke and 4.5 ± 0.5 mm in cardiac patients (p = 0.372). 9 and 3 complex plaques were found in the ascending aorta and 17 and 4 in the aortic arch in stroke patients and controls, respectively. The highest prevalence of complex plaques was found in the DAo and plaques were more frequent in stroke patients (44 in 31/67 patients (46.3%) vs. 5 in 4/21 cardiac patients (19.1%); p = 0.017). Besides group affiliation, age was the only factor differing significantly between patients with and without DAo plaques, whereas it was irrelevant if patients had one or multiple complex plaques. The relative frequency of DAo plaque occurrence in stroke patients increased with age from 0/11 (0%) <50 years, to 2/10 (20%) 50–59 years, 9/19 (47.4%) 60–69 years, 13/19 (68.4%) 70–79 years, and 7/8 (87.5%) in patients ≥80 years of age (F = 4.21 at p = 0.002). Hence, the prevalence of complex DAo plaques was 4.4-fold higher in patients ≥60 compared to <60 years of age (29/46 patients with 41 plaques vs. 2/21 patients with 3 plaques; p < 0.001), resulting in an odds ratio of 16.21 (95% CI = 3.35–78.31).

There was no significant difference regarding DAo plaque frequency between patients with determined and undetermined stroke etiology. No significant differences regarding the frequency of atheroma in other parts of the vascular system was observed in patients with complex plaques in the DAo compared to patients without DAo plaques (coronary artery disease: 5/31 vs. 4/36, p = 0.72; peripheral arterial disease: 5/31 vs. 2/36, p = 0.24, and large-artery atherosclerosis: 12/31 vs. 11/36, p = 0.61). The 4 control patients with DAo plaques (mean age 78.5 ± 7.33 years) were older than control patients without plaques (62.0 ± 17.5 years; p = 0.085), 3/4 (75.0%) had coronary artery disease compared to 6/17 (35.3%; p =

0.272), 0/4 and 1/17 (p = 1.0) had peripheral artery disease, and no large-artery atherosclerosis was present in control patients.

Prevalence of Retrograde Blood Flow in the Descending Aorta

Retrograde blood flow originating at the proximal DAo and reaching at least the LSA outlet occurred in every stroke and cardiac patient. On average, diastolic blood flow (i.e., length of pathlines) connected the LSA with a plane located 26 ± 14 mm distal to the LSA outlet in stroke and 32 ± 18 mm in cardiac patients (p = 0.114) (see fig. 2). Accordingly, plaques in the first ~30 mm of the DAo (i.e., the proximal DAo) constituted an area of potential retrograde embolization to the brain. The probability of flow reversal reaching the LSA, CCA, or the BCT steadily decreased when analysis planes were located further downstream along the DAo.

Patients' characteristics, cardiovascular risk factors, stroke etiology, plaque occurrence, and echocardiographic parameters were not associated significantly with increasing blood flow at the proximal DAo.

Frequency of Potential Embolization Pathways

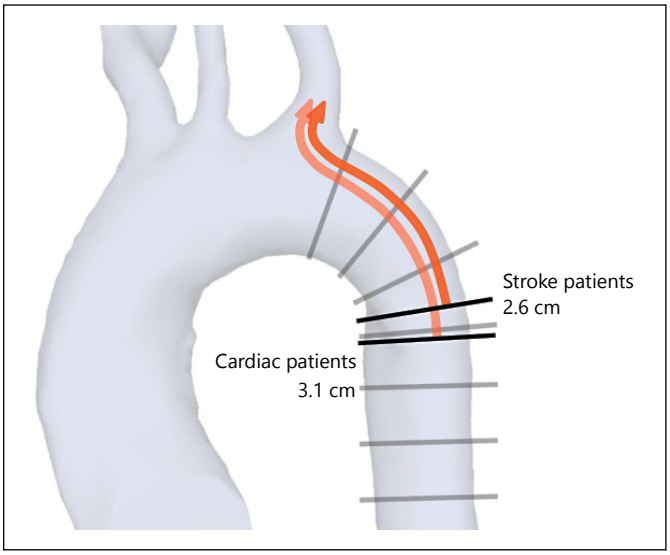
Potential embolization pathways were identified by demonstrating a connection of individual complex DAo plaque locations with one or multiple supra-aortic, brain-supplying arteries (i.e., BCT, CCA, and LSA) by flow reversal (see fig. 3). During one single average cardiac cycle, potential embolization pathways were identified in 22/67 (32.8%) stroke and 2/21 (9.5%) cardiac patients (p = 0.048; OR = 4.64, 95% CI = 0.99–21.75) (fig. 4). The mechanism was more frequent in stroke patients ≥60 compared to <60 years of age (3/21 vs. 18/46; p = 0.037; OR = 4.07, 95% CI = 1.05–15.76) but not significantly different between etiology groups.

Location of Ischemic Lesions on Cerebral Imaging

All stroke patients underwent cerebral imaging (MRI with diffusion weighted imaging in 50/67 (74.6%) and CT in 17/67 (25.4%) cases) after admittance. 47/67 (70.2%) patients had a detectable lesion. No significant difference concerning lesion patterns and location of brain infarction was found between patients with determined and undetermined stroke.

Discussion

Our study examined unselected patients with cryptogenic stroke etiology scheduled for TEE and compared them with cardiac controls regarding the prevalence of complex DAo plaques, maximum extent of retrograde blood flow, and potential embolization pathways. The methods used (3DT1 and 4D flow MRI) have been applied and proven for accuracy for the identification of aortic plaques, flow quantification, and visualization [12, 13]. Cardio-aortic MRI may even be superior to TEE in detecting high-risk embolic source [14].



Color version available online

Fig. 2. Mean extent of flow reversal reaching the LSA in stroke (orange) and cardiac (red) patients. Colors refer to online version.

In agreement with former studies [3, 6, 7], we were able to confirm that the prevalence of complex aortic plaques is the highest in the proximal DAo (especially in older patients [15]). Furthermore, plaques ≥4 mm thick in the DAo were more frequent in stroke patients compared to controls despite a similar distribution of age and cardiovascular risk factors. This finding could be explained by differences in aortic hemodynamics such as critical wall shear stress (WSS) [16], which may predispose some stroke patients to plaque development in the thoracic aorta.

Moreover, we demonstrated that retrograde blood flow originating in the proximal DAo and reaching at least one of the supra-aortic arteries (i.e., the LSA outlet) occurred in every stroke and cardiac patient. In contrast to previous findings, patients' demographics, cardiovascular risk factors (especially age and heart frequency), and echocardiographic parameters did not correlate with the retrograde flow [3, 6, 7]. Thus, our findings suggest that flow reversal in the proximal DAo may be a common finding. However, population-based data investigating this phenomenon are missing [4–7].

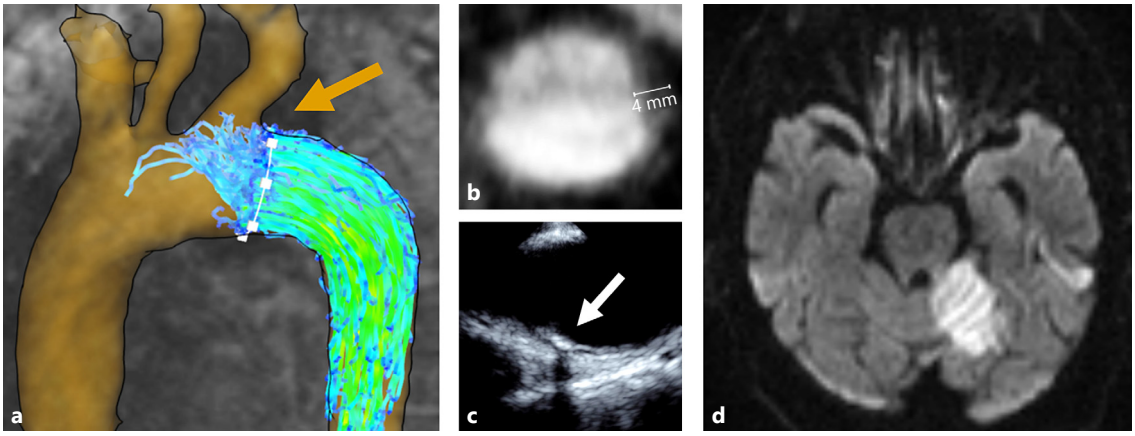


Fig. 3. Analysis of time-resolved and three-dimensional aortic blood flow in one patient with mesencephalic and cerebellar infarction and cryptogenic stroke etiology after routine diagnostics is given: a 4-mm thick plaque was located at the posterior wall of the proximal DAo directly behind the outlet of the left subclavian artery (**a**, arrow) as illustrated by 3D-T1 bright blood MRI (**b**) and TEE (**c**, arrow). Flow visualization using particle traces emitted from an analysis plane at the plaque site (**a**) demonstrated blood flow reversal in late diastole that was able to connect the atheroma with the left subclavian artery and also with the left common carotid artery and the brachiocephalic trunk. Accordingly, a potential embolization pathway exists from the DAo plaque to the infarction identified by diffusion-weighted MR imaging (**d**) via the left subclavian and left vertebral artery. As a result, this mechanism constituted the most probable source of stroke in this patient.

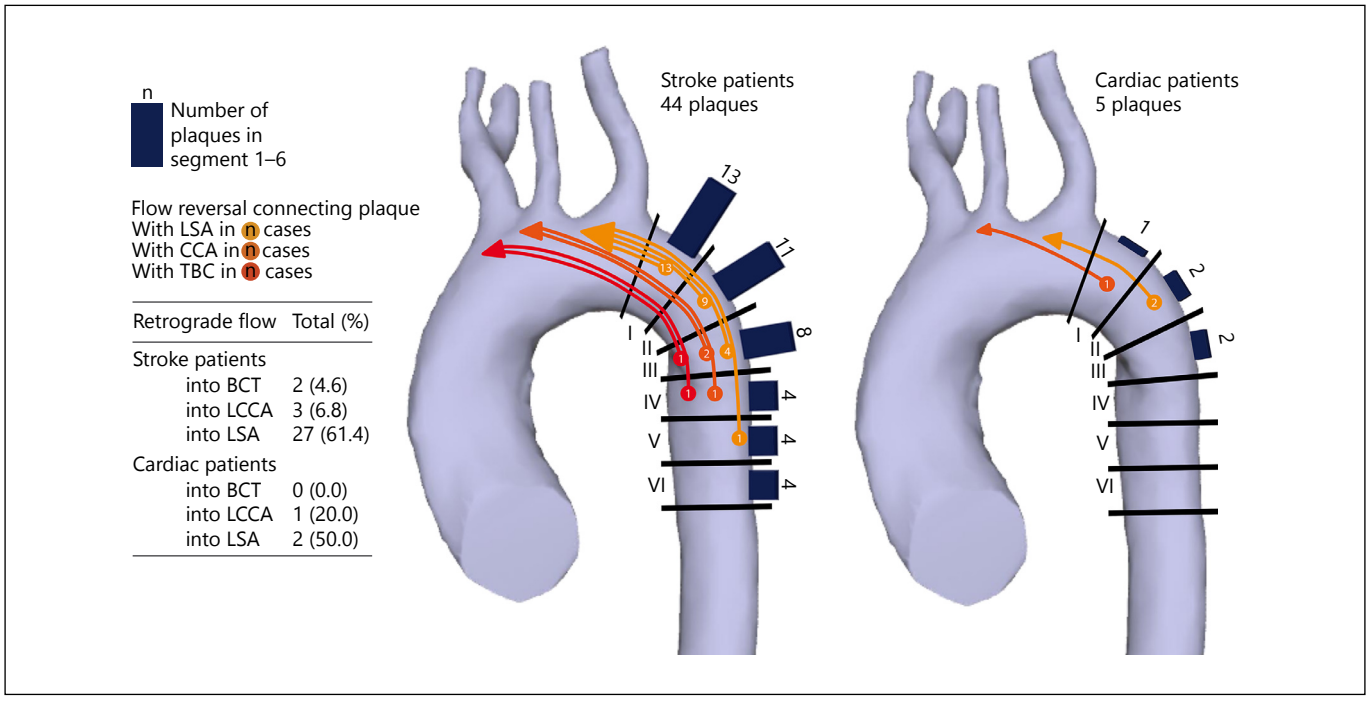


Fig. 4. Frequency of complex DAo plaques (bars) and potential retrograde embolization pathways (arrows) in 67 stroke and 21 cardiac patients are given for sections 1–6 (intersegment distance as measured from the center of each plane = 10 mm).

Nevertheless, such retrograde blood flow may become critical if it connects complex plaques with the brain. Plaque rupture and subsequent embolization is able to affect all brain territories as shown here and previously [6, 7], particularly the LSA and thus, the cerebral posterior circulation seem to be at high risk and was affected more often compared to the right and left hemisphere in patients with otherwise cryptogenic stroke in a previous study [7]. A potential confirmation of this mechanism may be the detection of embolic signals in the corresponding cerebral arteries by transcranial Doppler (TCD) [17] and should be performed in the future.

In our study, possible retrograde embolization pathways also occurred in controls and stroke patients with determined stroke etiology. In some of the last-mentioned patients, retrograde embolization thus constitutes an alternative source of stroke [7], whereas in many cases, DAo plaques have to be regarded as innocent bystanders that are not causally related to stroke [2]. Therefore, it only seems reasonable to establish the diagnosis of retrograde brain embolism if the following criteria are met: (1) diastolic blood flow reversal that (2) connects a complex DAo plaque with a supra-aortic great artery that (3) supplies the territory of brain infarction (4) in a patient with otherwise cryptogenic stroke etiology. While TEE and CT [18, 19] are reliable methods for the identification of complex plaques, currently, only 3DT1 MRI in combination with 4D flow MRI presents a solution to the above-mentioned requirements. However, a drawback of this method is its demanding character currently restricting this technique to smaller cohorts. Many vascular patients have comorbidities like arrhythmias, cardiac devices (i.e., cardiac pacemaker or cardioverter defibrillator), or are overweight and therefore not suitable for MRI examination. Besides, patients have to be in an adequate general condition and compliant for an examination lasting about 45 min (which, in controls, did not guide their individual treatment). This limited recruitment rates (as seen in the control group where half of the eligible patients had arrhythmias or MRI contraindications) and resulted in an imbalanced sample despite 1:1 matching between patients and controls in our study. In addition, it also shifted the proportion of patients toward younger and healthier patients as illustrated by the median NIHSS of 2 in stroke patients.

The strong heterogeneity of patients due to unselected inclusion, and the small sample size particularly in the control group resulted in a possible neglect of between-group differences. This may also explain the fact that no difference regarding locations of infarction was observed here between patients with determined and undetermined etiology of stroke. Nevertheless, this study revealed that DAo flow reversal is a common phenomenon not only in stroke patients and that the existence of potential retrograde embolization pathways depends mainly on the occurrence of complex plaques in the area 0 to ~30 mm behind the outlet of the LSA, which is exposed to flow reversal. Hence, retrograde brain embolization can be expected with a high certainty as soon as complex plaques are detected at this location by TEE, CT, or MRI even without additional analysis of aortic flow.

However, the strength of a comprehensive MRI approach is to identify individual embolization pathways even from plaques of the DAo that are located further downstream. Moreover, the extent of retrograde flow beyond the left subclavian artery (i.e., reaching the left common carotid artery or the brachiocephalic trunk) can be precisely determined. In addition, information derived from 4D flow MRI measurements can be used to calculate aortic pulse wave velocity or wall shear stress in order to assess the individual risk of plaque occurrence and progression [20, 21]. Finally, an optimized MRI protocol providing multi-contrast plaque imaging will allow to describe plaque composition and to detect vulnerable plaques.

In conclusion, we have shown that the frequency of potential retrograde embolization pathways was significantly higher in stroke patients, suggesting that this mechanism may play a role in retrograde brain embolism.

Acknowledgments

The authors thank Leonie Eisebraun, Adriana Komancsek, and Hansjörg Mast for performing MRI examinations.

Sources of Funding

Drs. Andreas Harloff, Iulius Dragonu, and Thomas Wehrum received funding from Deutsche Forschungsgemeinschaft (DFG) grant#HA5399/3–1. Johann Drexl received funding by DFG grant#FR2795/2–1.

Disclosure Statement

None of the authors has financial disclosures that are related to the performance or content of this study and to the submission of this paper.

References

1 Kronzon I, Tunick PA: Aortic atherosclerotic disease and stroke. Circulation 2006;114:63–75.

2 Katsanos AH, Giannopoulos S, Kosmidou M, Voumvourakis K, Parissis JT, Kyritsis AP, Tsivgoulis G: Complex atheromatous plaques in the descending aorta and the risk of stroke: a systematic review and meta-analysis. Stroke 2014;45:1764–1770. DOI: 10.1161/STROKEAHA.114.005190.

3 Amarenco P, Cohen A, Tzourio C, Bertrand B, Hommel M, Besson G, Chauvel C, Touboul PJ, Bousser MG: Atherosclerotic disease of the aortic arch and the risk of ischemic stroke. N Engl J Med 1994;331:1474–1479.

4 Tenenbaum A, Motro M, Feinberg MS, Schwammenthal E, Stroh CI, Vered Z, Fisman EZ: Retrograde flow in the thoracic aorta in patients with systemic emboli: a transesophageal echocardiographic evaluation of mobile plaque motion. Chest 2000;118:1703–1708.

5 Svedlund S, Wetterholm R, Volkmann R, Caidahl K: Retrograde blood flow in the aortic arch determined by transesophageal Doppler ultrasound. Cerebrovasc Dis 2009;27:22–28.

6 Harloff A, Strecker C, Dudler P, Nussbaumer A, Frydrychowicz A, Olschewski M, Bock J, Stalder AF, Stroh AL, Weiller C, Hennig J, Markl M: Retrograde embolism from the descending aorta: visualization by multidirectional 3D velocity mapping in cryptogenic stroke. Stroke 2009;40:1505–1508.

7 Harloff A, Simon J, Brendecke S, Assefa D, Helbing T, Frydrychowicz A, Weber J, Olschewski M, Strecker C, Hennig J, Weiller C, Markl M: Complex plaques in the proximal descending aorta: an underestimated embolic source of stroke. Stroke 2010;41:1145–1150.

8 Kim HJ, Song JM, Kwon SU, Kim BJ, Kang DH, Song JK, Kim JS, Kang DW: Right-left propensity and lesion patterns between cardiogenic and aortogenic cerebral embolisms. Stroke 2011;42:2323–2325.

9 Markl M, Harloff A, Bley TA, Zaitsev M, Jung B, Weigang E, Langer M, Hennig J, Frydrychowicz A: Time-resolved 3D MR velocity mapping at 3T: improved navigator-gated assessment of vascular anatomy and blood flow. J Magn Reson Imaging 2007;25:824–831.

10 Harloff A, Dudler P, Frydrychowicz A, Strecker C, Stroh AL, Geibel A, Weiller C, Hetzel A, Hennig J, Markl M: Reliability of aortic MRI at 3 Tesla in patients with acute cryptogenic stroke. J Neurol Neurosurg Psychiatry 2008;79:540–546.

11 Wehrum T, Kams M, Schroeder L, Drexl J, Hennemuth A, Harloff A: Accelerated analysis of three-dimensional blood flow of the thoracic aorta in stroke patients. Int J Cardiovasc Imaging 2014, Epub ahead of print. DOI: 10.1007/s10554–014–0511-z.

12 Harloff A, Brendecke SM, Simon J, Assefa D, Wallis W, Helbing T, Weber J, Frydrychowicz A, Vach W, Weiller C, Markl M: 3D MRI provides improved visualization and detection of aortic arch plaques compared to transesophageal echocardiography. J Magn Reson Imaging 2012;36:604–611.

13 Rengier F, Delles M, Unterhinninghofen R, Ley S, Müller-Eschner M, Partovi S, Geisbüsch P, Dillmann R, Kauczor HU, von Tengg-Kobligk H: In vivo and in vitro validation of aortic flow quantification by time-resolved three-dimensional velocity-encoded MRI. Int J Cardiovasc Imaging 2012;28:1999–2008.

14 Baher A, Mowla A, Kodali S, Polsani VR, Nabi F, Nagueh SF, Volpi JJ, Shah DJ: Cardiac MRI improves identification of etiology of acute ischemic stroke. Cerebrovasc Dis 2014;37:277–284.

15 Shimada Y, Ueno Y, Tanaka Y, Okuzumi A, Miyamoto N, Yamashiro K, Tanaka R, Hattori N, Urabe T: Aging, aortic arch calcification, and multiple brain infarcts are associated with aortogenic brain embolism. Cerebrovasc Dis 2013;35:282–290.

16 Malek AM, Izumo S: Molecular aspects of signal transduction of shear stress in the endothelial cell. J Hypertens 1994;12:989–999.

17 King A, Markus HS: Doppler embolic signals in cerebrovascular disease and prediction of stroke risk: a systematic review and meta-analysis. Stroke 2009;40:3711–3717.

18 Chatzikonstantinou A, Krissak R, Flüchter S, Artemis D, Schaefer A, Schoenberg SO, Hennerici MG, Fink C: CT angiography of the aorta is superior to transesophageal echocardiography for determining stroke subtypes in patients with cryptogenic ischemic stroke. Cerebrovasc Dis 2012;33:322–328.

19 Sipola P, Hedman M, Onatsu J, Turpeinen A, Halinen M, Jäkälä P, Vanninen R: Computed tomography and echocardiography together reveal more high-risk findings than echocardiography alone in the diagnostics of stroke etiology. Cerebrovasc Dis 2013;35:521–530.

20 Markl M, Wallis W, Strecker C, Gladstone BP, Vach W, Harloff A: Analysis of pulse wave velocity in the thoracic aorta by flow-sensitive four-dimensional MRI: reproducibility and correlation with characteristics in patients with aortic atherosclerosis. J Magn Reson Imaging 2012;35:1162–1168.

21 Markl M, Brendecke SM, Simon J, Barker AJ, Weiller C, Harloff A: Co-registration of the distribution of wall shear stress and 140 complex plaques of the aorta. Magn Reson Imaging 2013;31:1156–1162.