



Retrograde aortic blood flow as a mechanism of stroke: MR evaluation of the prevalence in a population-based study

Andreas Harloff^{1,2} · Paul Hagenlocher^{1,2} · Thomas Lodemann^{1,2} · Anja Hennemuth³ · Cornelius Weiller^{1,2} · Jürgen Hennig^{2,4} · Werner Vach^{5,6}

Received: 15 November 2018 / Revised: 7 February 2019 / Accepted: 12 February 2019 / Published online: 15 March 2019
© European Society of Radiology 2019

Abstract

Objectives Retrograde blood flow from complex atheroma in the descending aorta (DAo) has only recently been described as a potential mechanism of stroke. However, prevalence of this mechanism in the general population and the exact factors influencing stroke risk are unclear.

Methods One hundred twenty-six consecutively recruited inhabitants of Freiburg, Germany, between 20 and 80 years of age prospectively underwent 3-T MRI. Aortic plaque location and thickness were determined by 3D T1 MRI (1 mm³). 4D flow MRI (spatial/temporal resolution 2 mm³/20 ms) and dedicated software were used to determine prevalence and extent of flow reversal and potential embolization from DAo plaques. Flow was correlated with baseline characteristics and echocardiographic and MRI parameters (aortic diameter, wall thickness, and pulse wave velocity).

Results The maximum length of retrograde blood flow connecting the DAo with the left subclavian artery (LSA) increased from 16.1 ± 8.3 mm in 20–29-year-old to 24.7 ± 11.7 mm in 70–80-year-old subjects, correlated with age ($r = 0.37$; $p < 0.001$), and was lower in females ($p = 0.003$). Age was the only independent predictor of increased flow reversal. Complex DAo plaques ≥ 4-mm thickness were found in eight subjects (6.3%) and were connected with the LSA, left common carotid artery, and brachiocephalic trunk in 8 (100%), 1 (12.5%), and 0 (0%) cases, respectively.

Conclusions Retrograde blood flow from the DAo was very frequent. However, potential retrograde embolization was rare due to the low incidence of complex DAo plaques. The magnitude of flow reversal and prevalence of complex atheroma increased with age. Thus, older patients with aortic atherosclerosis are especially vulnerable to this stroke mechanism.

Key Points

- 4D flow MRI allows in vivo visualization and quantification of individual and three-dimensional blood flow patterns within the thoracic aorta including retrograde components.
- This population-based study showed that blood flow reversal from the proximal descending aorta to the brain-supplying great arteries is very frequent and able to reach all brain territories. The extent of such flow reversal increases with age and with the extent of aortic atherosclerosis.
- The combination of blood flow reversal with plaque rupture in the proximal descending aorta constitutes a potential stroke mechanism that should be considered in future trials and in the management of stroke patients in clinical routine.

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00330-019-06104-z>) contains supplementary material, which is available to authorized users.

✉ Andreas Harloff
andreas.harloff@uniklinik-freiburg.de

¹ Department of Neurology and Neurophysiology, Medical Center, University of Freiburg, Breisacherstr. 64, 79106 Freiburg, Germany

² Faculty of Medicine, University of Freiburg, Freiburg, Germany

³ Institute for Cardiovascular Computer-Assisted Medicine, Charité - Universitätsmedizin Berlin, Berlin, Germany

⁴ Department of Diagnostic Radiology, MR Physics, Medical Center - University of Freiburg, Freiburg, Germany

⁵ Institute for Medical Biometry and Statistics, Medical Faculty and Medical Center, University of Freiburg, Freiburg, Germany

⁶ Department of Orthopaedics and Traumatology, University Hospital Basel, Basel, Switzerland

Keywords Magnetic resonance imaging · Angiography · Atherosclerosis · Embolism · Thoracic aorta

Abbreviations

AAo	Ascending aorta
BCT	Brachiocephalic trunk
LCCA	Left common carotid artery
DAo	Descending aorta
GRAPPA	Generalized autocalibrating partial parallel acquisition
LSA	Left subclavian artery
PEAK	Parallel MRI with extended and averaged GRAPPA kernels
PWV	Pulse wave velocity
TTE	Transthoracic echocardiography

Introduction

Complex plaques in the ascending aorta or proximal arch are considered to be a major source of stroke [1] and are associated with a four times higher risk for brain ischemia [2]. However, recent studies have demonstrated that plaques of the descending aorta (DAo) also constitute an important source of brain embolism due to the functional connectivity to the proximal arch by diastolic blood flow reversal (= stroke mechanism) [3–11]. Aortic blood flow reversal (or retrograde blood flow) is a change of the direction of the blood stream that starts at the aortic valve and goes downstream in the aorta in systole. In diastole, a fraction of the aortic blood volume reverses the direction and flows back towards the aortic valve in diastole. This mechanism is of special interest to the circa 30% of patients with otherwise cryptogenic stroke etiology due to its potential implications on treatment and future stroke prevention [12].

Interestingly, flow reversal has been demonstrated on average in the first 20–30 mm of the proximal DAo, i.e., distal to the outlet of the left subclavian artery, with the potential to reach all brain territories. In some individuals, however, flow reversal occurred 50–60 mm distal to the left subclavian artery (LSA) and was still able to reach the aortic arch [4–9]. The extent of retrograde blood flow was similar in stroke and cardiac patients, but potential embolization was more frequent in stroke patients due to the higher prevalence of complex plaques in the DAo [6, 7]. Independent predictors of enhanced flow reversal were heterogeneous between studies and included age [4], lower heart rate [5], as well as the presence of complex aortic plaques and larger aortic diameter [6]. Another study, using ultrasound for the assessment of retrograde diastolic flow, identified increased aortic stiffness as another reason for increased flow reversal [10].

The limitation of these previous studies is the lack of normal data, as a general population has not yet been examined

for this purpose. Accordingly, it is unclear to what extent diastolic retrograde flow and the observed stroke mechanism occur in the general population. In addition, influencing factors including age- and gender-related flow conditions have not yet been systematically studied.

Therefore, we prospectively conducted a population-based study, allowing the investigation of both the magnitude of retrograde blood flow and the frequency of complex aortic atheroma in the DAo using modern 3D MRI technology in a larger and representative cohort. In addition, we aimed to comprehensively study independent predictors of enhanced flow reversal increasing the probability of retrograde brain embolization in order to identify subjects at risk of this stroke mechanism.

Methods

Study population

We performed a cross-sectional observational study of the population of the city of Freiburg, Germany, based on data obtained from the local residents' registration office. Circa 20 subjects per decade (~ 10 females and ~ 10 males) between 20 and 80 years of age were consecutively and prospectively recruited. From October 2012 to August 2014, 3500 age-stratified and randomly selected residents were contacted by mail and asked to participate in our study (for more details, please see [9]). Because of insufficient response in the group of 20–29- and 30–39-year-old males, the study was also advertised on the intranet of our institution for men of that age. Finally, complete MRI and transthoracic echocardiography (TTE) datasets of 126 subjects (111 were recruited by the registration office and 15 by additional advertising in our institution) were available for analysis. The study was approved by the local ethics committee and written informed consent was obtained from all participants.

Baseline characteristics

We performed an interview on site to determine cardiovascular risk factors and demographics and measured blood pressure at the left upper arm in a supine position after 5-min rest before and after MRI examination. The heart rate was measured every 5 min during blood flow measurements in MRI.

Transthoracic echocardiography

Performance of TTE examinations was apportioned between two physicians who were experienced in echocardiography.

They used a Toshiba Artida system (4.8–2-MHz transducer; Toshiba Medical Systems Corporation) based on the recommendations and standards of the American Society of Echocardiography [13] and in the majority on the same day as MRI (median = 1).

Measurement of aortic atherosclerosis

MRI examinations were executed on a routine 3-T MRI (TIM Trio, Siemens), using a standard 12-element body coil. T1-weighted bright-blood (3D gradient echo sequence, echo time/repetition time (TE/TR) = 1.89 ms/152.53, flip angle = 20°, acceleration = GRAPPA ($R = 2$, 32 ref. lines) with a spatial resolution of $1.1 \times 0.9 \times 1.1 \text{ mm}^3$ was applied to measure the maximum diameter of the ascending aorta (AAo) and DAo at the level of the pulmonary artery. The aortic arch was defined as the segment between the outlet of the brachiocephalic trunk and the left subclavian artery. The diameter of the arch was measured at the summit and between the brachiocephalic trunk (BCT) and the left common carotid artery (LCCA). The maximum plaque thickness was determined manually in each of these three aortic segments in an orthogonal plane using electronic calipers and a routine picture archiving and communication system (PACS) (IMPAX EE, Agfa HealthCare). Plaques ≥ 4 -mm thickness were considered complex plaques [1, 14].

Measurement of aortic blood flow

Time-resolved and 3D blood flow information was obtained in each individual by 4D flow MRI using prospective ECG- and navigator-gating to allow free breathing and minimize motion artifacts [15]: TE/TR = 2.54/5 ms, flip angle = 7°, temporal resolution = 20 ms, matrix size = $340 \times 255 \times 75 \text{ mm}^3$, bandwidth = 450 Hz/pixel, spatial resolution = $2.5 \times 2.1 \times 2.5 \text{ mm}^3$, velocity sensitivity along all three directions = 1.5 m/s, and parallel imaging (PEAK-GRAPPA) along the phase encoding direction (ψ) with an acceleration factor of $R = 5$ (20 reference lines). Depending on individual heart rate and respiration, the overall acquisition time for the 4D flow sequence was ca. 15–20 min.

Determination of retrograde blood flow

Datasets of 4D flow MRI measurements were analyzed offline using MevisFlow software (Fraunhofer MEVIS) [16]. After corrections for Eddy currents and phase wraps, the aorta was semi-automatically segmented. A centerline was automatically positioned along the DAo from the aortic root to the level of the diaphragm. Then, MRI analysis planes were automatically distributed along the first 60 mm of the proximal DAo and along the centerline by manually setting start and end points within the aortic lumen. Analysis planes were orientated normal to the aorta, and inter-plane distance was

5 mm. A contour surrounding the lumen was defined automatically and adapted to all time points of the cardiac cycle [17]. Individual 3D blood was visualized using streamlines [18]. The strategy to assess individual maximum flow reversal was described and illustrated in detail in a previous study (figure 2 in [4]). In brief, on a visual basis, one reader assessed individual embolic pathways. The maximum retrograde blood flow was determined by identifying the most remote analysis plane that was connected with the LSA by diastolic retrograde blood flow. Examples of such flow reversal are given in Fig. 1 and in movies 1 and 2. Pulse wave velocity of the thoracic aorta was calculated using 4D flow MRI data as described previously [19].

Statistical analysis

Data are presented as mean (\pm standard deviations) or median (interquartile range) for continuous, absolute, and relative frequencies of categorical variables. Differences between the three calculation algorithms of pulse wave velocity (PWV) were analyzed using a Wilcoxon test.

Regression analysis was performed to quantify the effect of age and gender. The residuals from this regression were then correlated with the residuals of regression of other factors on age and gender in order to assess the association beyond the general aging and gender effects. The factors considered were baseline characteristics (males, or females 5 years after menopause, body mass index, hypertension, hypercholesterinemia, smoking habit), vital signs (systolic, diastolic, and mean blood pressure before and after MRI examination, mean heart rate during MRI), echocardiographic (ejection fraction), and MRI parameters (maximum plaque thickness and diameter of the ascending and descending aorta and the aortic arch). 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 and Stata 14.1.

The corresponding author had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Patients' characteristics

Baseline characteristics and cardiovascular risk factors are given in Table 1. All participants were Caucasian. Hypertension and hypercholesterolemia were more frequent in older subjects; no other differences of cardiovascular risk factors were found

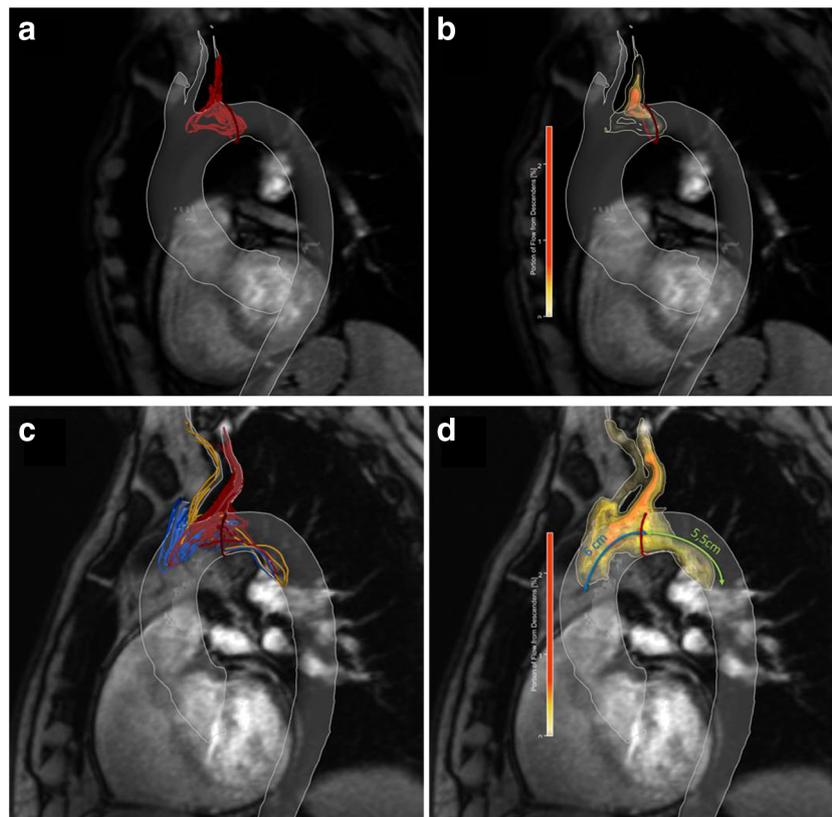


Fig. 1 Maximum retrograde blood flow from the descending aorta (DAo) and its connection with the brain-supplying arteries is illustrated in two subjects by considering two cardiac cycles based on streamlines (**a, c**) and connectivity mapping (20) (**b, d**). Streamlines are color-coded in dependency of their connectivity to the DAo with the brachiocephalic trunk (BCT, blue), with the left common carotid artery (LCCA, orange), or with the left subclavian artery (LSA, red). Connectivity mapping shows the proportion of reverse flow in relation to the blood flow volume passing the analysis plane in the very proximal DAo. In subject no. 1, a 67-year-old female (**a, b**), maximum flow reversal is minor and only reaches the LSA (red) from 10 mm downstream of the proximal DAo. Color-coded tracking of streamlines indicates that there is no connection to the LCCA and BCT. Accordingly, connectivity mapping shows that the majority of

backward flow enters the LSA whereas the residual blood volume remains within the aortic lumen in the transition between aortic arch and DAo. In subject no. 2, a 67-year-old male (**c, d**), there is extensive blood flow reversal in diastole, reaching back to the left subclavian artery from 55 mm downstream of the DAo. In addition, streamlines also reach the LCCA and BCT from a distance of 45 mm (**c**). Connectivity mapping (**d**) illustrates that the majority of flow reversal reaches the LSA (orange and red coding), whereas the residual blood volume enters the BCT and LCCA or remains in the aorta. Blood flow in diastole follows the inner curvature of the DAo and then heads to the outlet of the supra-aortic arteries at the outer curvature. Maximum flow reversal into the aortic arch/ascending aorta from the analysis plane was 60 mm.

between groups. Few subjects had diabetes ($n = 2$), prior stroke ($n = 2$), and coronary artery disease ($n = 2$), and none had peripheral vascular disease. TTE was normal in all but two individuals, with one having a mildly reduced left ventricular function (ejection fraction = 45%) and one having an enlarged left atrium (diameter = 49 mm).

Incidence of complex aortic atheroma

Based on 3D T1 MRI, 15 complex plaques (≥ 4 -mm thickness) were found in the thoracic aorta of our cohort. One atheroma was located in the ascending aorta (AAo), 6 were found in the aortic arch, and 8 were found in the DAo. The complex DAo plaques were isolated, i.e. these eight subjects neither had another complex atheroma in the AAo nor in the aortic arch.

Determination of maximum retrograde blood flow

The increase of maximum flow reversal in the proximal DAo to the LSA outlet with increasing age is illustrated in Fig. 2. In addition, age- and gender-related values per decade are given in Table 2. Only 3/126 (2.4%) of the participants showed no flow reversal to the LSA outlet. Accordingly, retrograde flow was present in 123/126 (97.6%) and reached back from even very remote levels of the distal DAo (maximum, 50 mm downstream). On average, retrograde flow originated in the first 22 ± 11.2 mm of the DAo.

Prevalence of potential retrograde embolization

We observed a connectivity of the DAo with the outlet of the left subclavian artery (LSA) by diastolic blood flow reversal in

Table 1 Baseline characteristics and cardiovascular risk factors of study participants

Characteristics	<i>N</i> = 126
Age, years (\pm SD)	49.2 (\pm 16.6)
Female, <i>n</i> (%)	64 (50.8)
Hypertension, <i>n</i> (%)	21 (16.7)
Hypercholesterolemia, <i>n</i> (%)	21 (16.7)
Diabetes, <i>n</i> (%)	2 (1.6)
Smoker, <i>n</i> (%)	22 (17.5)
BMI, kg/m ² (\pm SD)	24.8 (\pm 4.1)
Prior stroke, <i>n</i> (%)	2 (1.6)
Coronary heart disease, <i>n</i> (%)	2 (1.6)
Peripheral arterial disease, <i>n</i> (%)	0 (0.0)
Mean systolic BP, mmHg (\pm SD)	126.6 (\pm 16.3)
Mean diastolic BP, mmHg (\pm SD)	79.8 (\pm 9.2)
Heart rate, bpm (\pm SD)	66.3 (\pm 8.2)

BMI body mass index, *SD* standard deviation, *BP* blood pressure, *bpm* heart rate

123/126 (98.0%), with the left common carotid artery (LCCA) in 53/126 (42.1%) and the brachiocephalic trunk (BCT) in 39/126 subjects (31.0%) (Fig. 3).

Analysis of individual blood flow in the eight subjects with complex DAo plaques (\geq 4-mm thickness) revealed that it was sufficient to connect such plaques at their specific location with the LSA, common carotid artery, and brachiocephalic trunk in 8 (100%), 1 (12.5%), and 0 (0%) cases, respectively. Accordingly, the potential for retrograde embolization to the brain was found for all patients with DAo plaques which was 8/126 participants (6.3%) of the total cohort.

Determinants of retrograde blood flow

Flow reversal significantly correlated with increasing age (estimated increase per 10 years, 2.3 mm; 95% CI, 1.19, 3.40; $p < 0.001$) and gender (estimated increase in men, 5.7 mm; 95% CI 2.00, 9.31; $p = 0.003$). After adjustment for age, we observed only moderate correlations with the continuous characteristics considered (Table 3) and small differences between the levels of the binary characteristics menopausal status, hypertension, hypercholesterolemia, and smoking status (maximal absolute difference in mean values, 0.28; $p > 0.22$). Surprisingly, PWV did not correlate with retrograde flow extent after adjustment of age ($r = 0.08$, $p = 0.38$).

Discussion

In the present study, we visualized and measured three-dimensional and time-resolved aortic blood flow in a population-based study using 4D flow MRI. Dedicated software

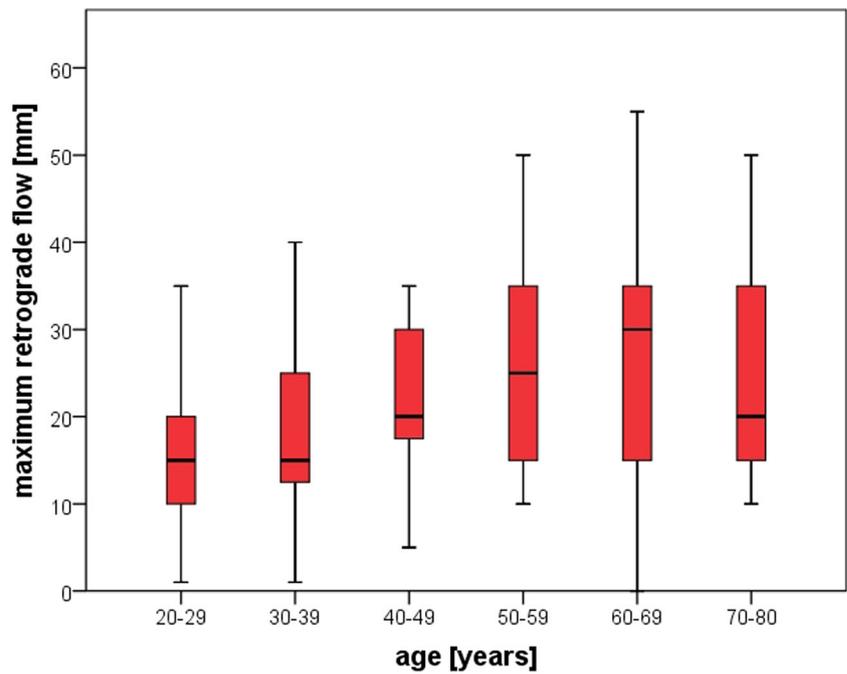
enabled us to precisely analyze both the individual extent of diastolic blood flow reversal and the potential risk of cerebral embolization that arises from such flow phenomena in case of complex plaques of the proximal DAo, detected by high-resolution 3D T1 MRI. Our study is the first to systematically investigate the prevalence of such flow phenomena and the influence of cardiovascular risk factors and echocardiographic and MRI parameter on retrograde flow in a general population.

One of our main findings is that flow reversal in the proximal DAo occurred in 98% and thus in almost all subjects between 20 and 80 years of age. Accordingly, retrograde flow must be considered physiological. On average, it originated in the first 20–30 mm and even reached back from regions that were located \geq 50 mm downstream of the DAo in individual cases. The extent of retrograde blood flow increased with increasing age whereas other predictors of previous studies such as lower heart rate were not independent factors after adjustment for age. Surprisingly, increased aortic pulse wave velocity did not predict increased flow reversal, despite being an indicator of increased aortic stiffness. We had hypothesized that stiffening of the aorta would lead to a higher grade of reflection of the blood volume and thus facilitate reversal of blood flow to the aortic arch, but apparently such findings were mainly driven by age in this cohort. However, the limited number of participants and the relatively low prevalence of cardiovascular risk factors and atherosclerosis in our population should be taken into account. Findings in acute stroke patients with more advanced aortic atherosclerosis and thus stiffer aortas could differ from the present results.

The physiological function of diastolic flow reversal in the DAo seems to be an improvement of cerebral perfusion in diastole. Similar to the Windkessel function of the ascending aorta and of the proximal arch, it may help to convert pulsatile blood flow into a more continuous flow and to improve brain perfusion in diastole after the pulse wave has passed in systole. This phenomenon is very similar to the physiological flow reversal in diastole that was observed in other parts of the aorta, contributing substantially to supplying diastolic perfusion of internal organs such as the heart and kidneys [20]. Typically, retrograde blood flow originates in the first 20–30 mm of the proximal descending aorta and is able to reach back to all brain-supplying arteries. Thus, existing atheromas at this site have the potential to cause embolic stroke in any brain territory in case of plaque rupture as demonstrated in stroke cohorts [4–9].

The high prevalence of flow reversal occurring in the first 20–30 mm of the proximal DAo in this population is comparable with that of previous studies in stroke and cardiac and ophthalmological patients using 4D flow MRI [4, 5, 9]. However, only few subjects of our population study additionally showed complex DAo plaques. Thus, potential retrograde brain embolism from such atheroma to the brain-supplying arteries, i.e., reaching at least the left subclavian artery, was

Fig. 2 Maximum retrograde flow from the DAo in connection with the left subclavian artery (LSA) outlet in dependency with age



observed in only 6%. This is lower than observed in cardiac and equal to ophthalmological patients (9.5 and 5%, respectively) [5, 9], and much lower than found in stroke patients with determined (25%) or undetermined stroke etiology (32–33% to 50%) [4, 5, 9]. Even when considering only subjects aged 50–80 years ($n = 96$) in our population study, i.e., the age group that is similar to the above-mentioned cohorts, potential brain embolization from the DAo was found in 8/96 (8.3%), which is still much lower than that reported in stroke cohorts. Therefore, our findings underline that potential retrograde embolization is not exclusive to stroke patients, but much more likely in stroke cohorts and thus an indirect indicator of a causal relationship. It is of importance that both the extent of flow reversal and the likelihood of complex DAo plaques increase with age. As a result, the risk to suffer a stroke based on this mechanism increases with age.

Due to the prospective and consecutive inclusion of subjects between 20 and 80 years, we are able to provide representative age- and gender-related data regarding the extent of blood flow

reversal and potential retrograde embolization. Participants were relatively healthy, which is evident from the low incidence of cardiovascular risk factors, normal TTE in almost all participants, and the relatively low number of aortic plaques. The composition of our study cohort is probably related to the higher motivation of health-conscious people to participate in such a study, which potentially reveals important information for their own health care management. Accordingly, they were willing to undergo MRI and TTE without reimbursement. This could be one factor, which explains why correlations of flow reversal with PWV or plaque thickness etc. were not found. A cohort of patients with advanced atherosclerosis could thus reveal different associations. Another potential limitation is that the MR examinations of our study participants were all performed at rest and in a supine position. The extent of maximum retrograde blood flow from the DAo might change when volunteers or patients sit, stand up, or exercise. Accordingly, the potential risk of stroke might differ in dependence of the body position and physical strain and it would be interesting to systematically study such effects in future studies.

Table 2 Age- and gender-dependent values of the maximum extent of maximum retrograde flow from the descending aorta

	20–29 (years)	30–39 (years)	40–49 (years)	50–59 (years)	60–69 (years)	70–79 (years)
Females	$N = 10$	$N = 9$	$N = 11$	$N = 13$	$N = 12$	$N = 9$
Retrograde flow (mm)–range (mm)	11.1 ± 6.0 (1–20)	15.7 ± 10.6 (1–35)	19.5 ± 8.6 (5–30)	21.1 ± 8.8 (10–40)	21.3 ± 11.5 (0–35)	30.0 ± 11.2 (15–50)
Males	$N = 10$	$N = 14$	$N = 10$	$N = 10$	$N = 9$	$N = 9$
Retrograde flow (mm)–range (mm)	21.0 ± 7.4 (10–35)	20.7 ± 9.6 (5–40)	25.0 ± 7.5 (15–35)	29.1 ± 11.8 (10–50)	36.1 ± 13.2 (15–55)	19.4 ± 10.1 (10–45)

± indicates standard deviation

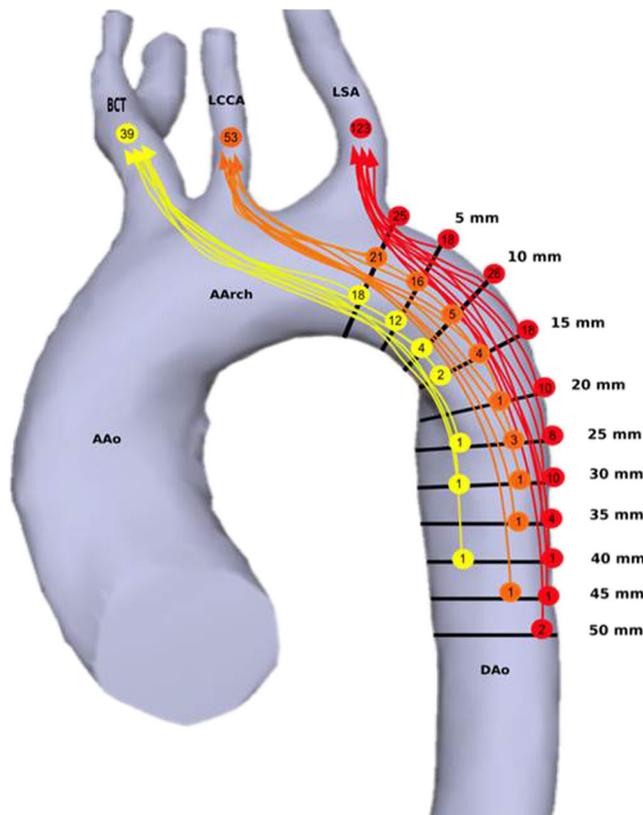


Fig. 3 The maximum flow reversal from the DAo to the outlet of the left subclavian artery (LSA), left common carotid artery (LCCA), or brachiocephalic trunk (BCT) is shown in each study participant regardless of the existence of an aortic atheroma. Such flow also reached back from very remote regions of the DAo: in single-study participants, flow reversal was powerful enough to reach the LSA outlet from 5 cm downstream or the brachiocephalic trunk from 4 cm downstream

Table 3 Correlation of baseline and MRI parameter with retrograde blood flow from the descending aorta after adjustment for age and gender

Characteristic	Correlation coefficient (<i>r</i>)	<i>p</i> value
Average systolic blood pressure (before/after MRI)	0.08	0.35
Average diastolic blood pressure (before/after MRI)	0.04	0.62
Mean arterial blood pressure (before/after MRI)	0.08	0.42
Average heart rate (during MRI)	−0.16	0.08
Body mass index	0.13	0.15
Diameter aortic root in echocardiography	−0.03	0.76
Maximum plaque thickness aorta in MRI	0.01	0.93
Diameter ascending aorta in MRI	0.05	0.61
Diameter aortic arch in MRI	−0.07	0.39
Diameter descending aorta in MRI	0.11	0.23

Conclusions

In this population-based study, we found that retrograde blood flow from the DAo is very frequent. Thus, flow reversal alone has to be considered physiological. However, it becomes a potential stroke mechanism by connecting DAo plaques with the brain arteries in diastole. This potential stroke mechanism was rare as a consequence of the low incidence of complex DAo plaques in our cohort. However, the magnitude of flow reversal and prevalence of complex atheroma increase with age. Thus, older patients with aortic atherosclerosis are especially vulnerable to this stroke mechanism. Our findings strongly emphasize that complex atheroma of the descending aorta should be considered for trials investigating stroke prevention [21] and for the optimal management of stroke patients in clinical routine.

Acknowledgements The authors thank Adriana Komancsek for performing MRI examinations and Dr. Konrad Whittaker for proof reading of the manuscript.

Funding Prof. Dr. Andreas Harloff received funding from Deutsche Forschungsgemeinschaft (DFG), Bonn, Germany, grant no. HA5399/3-1.

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Prof. Dr. Andreas Harloff.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors, Prof. Dr. Werner Vach, has significant statistical expertise and performed statistical analysis.

Informed consent Written informed consent was obtained from all subjects in this study.

Ethical approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap Data from this population-based study were analyzed and published. In these three articles, aortic pulse wave velocity, hemodynamics of the right heart, and hemodynamics of the pulmonary arteries were investigated.

Accordingly, there is only minimal overlap with the submitted paper focussing on the extent of retrograde blood flow and potential retrograde embolization from the descending aorta:

Harloff A, Mirzaee H, Lodemann T, Hagenlocher P, Wehrum T, Stuplich J, Hennemuth A, Hennig J, Grundmann S, Vach W. Determination of aortic stiffness using 4D flow cardiovascular magnetic resonance - a population-based study. *J Cardiovasc Magn Reson*. 2018 Jun 21;20(1):43.

Wehrum T, Lodemann T, Hagenlocher P, Stuplich J, Ngo BTT, Grundmann S, Hennemuth A, Hennig J, Harloff A. Age-related changes of right atrial morphology and inflow pattern assessed using 4D flow cardiovascular magnetic resonance: results of a population-based study. *J Cardiovasc Magn Reson*. 2018 Jun 14;20(1):38.

Wehrum T, Hagenlocher P, Lodemann T, Vach W, Dragonu I, Hennemuth A, von Zur Mühlen C, Stuplich J, Ngo BT, Harloff A. Age

dependence of pulmonary artery blood flow measured by 4D flow cardiovascular magnetic resonance: results of a population-based study. *J Cardiovasc Magn Reson*. 2016 May 31;18(1):31.

Methodology

- prospective
- cross-sectional study/observational
- performed at one institution

References

1. Tunick PA, Kronzon I (2000) Atheromas of the thoracic aorta: clinical and therapeutic update. *J Am Coll Cardiol* 35:545–554
2. Cui X, Li Y, Liu J, He S, Liu M (2014) Aortic arch atheroma and the risk of stroke: a meta-analysis. *J Evid Based Med* 7:185–191
3. Harloff A, Strecker C, Frydrychowicz AP et al (2007) Plaques in the descending aorta: a new risk factor for stroke? Visualization of potential embolization pathways by 4D MRI. *J Magn Reson Imaging* 26:1651–1655
4. Harloff A, Strecker C, Dudler P et al (2009) Retrograde embolism from the descending aorta: visualization by multidirectional 3D velocity mapping in cryptogenic stroke. *Stroke*. 40:1505–1508
5. Harloff A, Simon J, Brendecke S et al (2010) Complex plaques in the proximal descending aorta: an underestimated embolic source of stroke. *Stroke*. 41:1145–1150
6. Wehrum T, Kams M, Strecker C et al (2014) Prevalence of potential retrograde embolization pathways in the proximal descending aorta in stroke patients and controls. *Cerebrovasc Dis* 38:410–417
7. Wehrum T, Guenther F, Vach W et al (2017) Aortic atherosclerosis determines increased retrograde blood flow as a potential mechanism of retrograde embolic stroke. *Cerebrovasc Dis* 43:132–138
8. Markl M, Semaan E, Stromberg L, Carr J, Prabhakaran S, Collins J (2017) Importance of variants in cerebrovascular anatomy for potential retrograde embolization in cryptogenic stroke. *Eur Radiol* 27:4145–4152
9. Wehrum T, Dragonu I, Strecker C et al (2017) Aortic atheroma as a source of stroke - assessment of embolization risk using 3D CMR in stroke patients and controls. *J Cardiovasc Magn Reson* 19:67
10. Hashimoto J, Ito S (2013) Aortic stiffness determines diastolic blood flow reversal in the descending thoracic aorta: potential implication for retrograde embolic stroke in hypertension. *Hypertension*. 62:542–549
11. Shen X, Schnell S, Barker AJ et al (2018) Voxel-by-voxel 4D flow MRI-based assessment of regional reverse flow in the aorta. *J Magn Reson Imaging* 47:1276–1286
12. Yaghi S, Bernstein RA, Passman R, Okin PM, Furie KL (2017) Cryptogenic stroke: research and practice. *Circ Res* 120:527–540
13. Lang RM, Bierig M, Devereux RB et al (2005) Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 18:1440–1463
14. Macleod MR, Amarenco P, Davis SM, Donnan GA (2004) Atheroma of the aortic arch: an important and poorly recognised factor in the aetiology of stroke. *Lancet Neurol* 3:408–414
15. Markl M, Harloff A, Bley TA et al (2007) Time-resolved 3D MR velocity mapping at 3T: improved navigator-gated assessment of vascular anatomy and blood flow. *J Magn Reson Imaging* 25:824–831
16. Wehrum T, Kams M, Schroeder L, Drexler J, Hennemuth A, Harloff A (2014) Accelerated analysis of three-dimensional blood flow of the thoracic aorta in stroke patients. *Int J Cardiovasc Imaging* 30:1571–1577
17. Tautz L, Chitiboi T, Hennemuth A (2015) Automatic perfusion analysis using phase-based registration and object-based image analysis. In: Camara O, Mansi T, Pop M, Rhode K, Sermesant M, Young A (eds) *Statistical Atlases and Computational Models of the Heart - Imaging and Modelling Challenges*. STACOM 2014. Lecture Notes in Computer Science, vol 8896. Springer, Cham
18. Hennemuth A, Friman O, Schumann C et al (2011) Fast interactive exploration of 4D MRI flow data. *Proc. SPIE 7964, Medical Imaging 2011: Visualization, Image-Guided Procedures, and Modeling*, 79640E. <https://doi.org/10.1117/12.878202>
19. Harloff A, Mirzaee H, Lodemann T et al (2018) Determination of aortic stiffness using 4D flow cardiovascular magnetic resonance - a population-based study. *J Cardiovasc Magn Reson* 20:43
20. Bogren HG, Buonocore MH (1994) Blood flow measurements in the aorta and major arteries with MR velocity mapping. *J Magn Reson Imaging* 4:119–130
21. Harloff A, Schlachetzki F (2018) Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med* 379:986–987

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.