ORIGINAL ARTICLE

Assessment of the Willis circle flow changes and the severity of degenerative aortic stenosis and cognitive impairment

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KEY WORDS
arterial stiffness, cardiovascular comorbidities, cognitive status, degenerative aortic stenosis, transcranial color-coded Doppler ultrasonography

ABSTRACT

BACKGROUND Degenerative aortic stenosis (DAS) and cognitive function deterioration frequently coexist in elderly patients, which affects the prognosis.

AIMS We aimed to evaluate the Willis circle intracranial blood flow parameters and cognitive status in patients with DAS.

METHODS Ultrasonography of the Willis circle and the assessment of cerebral blood flow (CBF) volume, acceleration time (AT), pulsatile and resistive indexes (PI, RI), as well as cognition tests (Mini-Mental State Examination [MMSE] and Montreal Cognitive Assessment [MoCA]) were performed in group 1—41 patients with severe DAS (aortic valve area indexed to the body surface area [AVAi] <0.5 cm^2/m^2) and group 2—41 patients with moderate DAS (AVAi [range], 0.51–0.99 cm^2/m^2). The control group comprised 52 patients without DAS.

RESULTS Compared with controls, mean (SD) CBF volume in groups 1 and 2 was lower (1.37 [0.32] l/min vs 1.5 [0.44] l/min vs 1.71 [0.21] l/min, respectively; P <0.001), while AT (212 [20] ms vs 161 [33] ms vs 86 [21] ms, respectively; P <0.001), RI (0.64 [0.07] vs 0.65 [0.06] vs 0.59 [0.05], respectively; P <0.001), and PI (1.13 [0.21] vs 1.16 [0.17] vs 0.99 [0.12]; P <0.001) were higher. Both MMSE and MoCA scores did not differ according to CBF, RI, PI, and AT. In multivariable regression analysis, age, renal failure, left ventricular ejection fraction, and diabetes, yet not CBF parameters, were independently associated with cognitive function.

CONCLUSIONS Patients with DAS had significantly reduced CBF volume and increased arterial stiffness. However, cognitive impairment may be attributed to concomitant comorbidities rather than CBF parameters.

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INTRODUCTION The incidence of degenerative aortic stenosis (DAS) increases with age, and the coincidence of advanced age, severe DAS, and cardiovascular comorbidities such as hypertension, atherosclerosis, arrhythmia, or diabetes is a common observation.[1-4] Degenerative aortic stenosis is not only a valvular disease, as it also leads to extravalvular cardiac complications such as left ventricular hypertrophy, remodeling, fibrosis, and myocardial dysfunction.[5]

Degenerative aortic stenosis remains asymptomatic for a few years, but it eventually leads to symptom occurrence resulting from the high resistance of the aortic valve, elevated left ventricular end-diastolic pressure, and increasing pressure in pulmonary capillaries. Increasing systemic vascular resistance and stiffness may also contribute to the vicious circle of DAS.[6] Once symptoms of DAS develop, life expectancy is shortened to around 3 years, unless

WHAT'S NEW?

In the rapidly aging population, degenerative aortic stenosis (DAS) as well as cognitive function impairment frequently coexist in elderly patients and affect their prognosis. Whether cognitive decline is due to decreased cardiac output and altered cerebral blood flow in response to DAS or results from atherosclerosis risk factors remains unclear. The present study addresses this issue through the analysis of cerebral blood flow volume, cerebral arterial stiffness, and cardiovascular comorbidities in patients with an aortic valve area indexed to the body surface area less than 0.99 cm^2/m^2. Our findings indicate that: 1) patients with DAS have a significantly decreased cerebral blood flow volume and increased arterial stiffness; and 2) cognitive impairment is attributed to comorbidities rather than cerebral blood flow parameters in this subset of patients.

the mechanical obstruction to left ventricular outflow is relieved by aortic valve replacement.[7-10]

The symptoms of DAS (angina, dyspnea, and syncope) often overlap with those of other common diseases such as ischemic heart disease, anemia, hypertension, or cerebral ischemia.[11-14] While cardiac output becomes gradually reduced, cerebral and peripheral flow volume also putatively decrease, resulting in syncope or cerebral hypoperfusion. It remains unclear whether the reduced cerebral blood flow (CBF) may cause cognitive decline in patients with DAS.[15,16] Furthermore, identifying a hemodynamic threshold for cognitive decline using a simple, noninvasive method may influence decision-making in otherwise "asymptomatic" DAS.[10]

The potential relationship between the arterial flow changes in the Willis circle (WC) and cognitive function status in patients with symptomatic DAS has not been studied yet. Therefore, the present study aimed to assess the CBF parameters of the WC and the cognitive status of patients with moderate-to-severe DAS as well as to determine which parameters may be associated with cognitive decline.

METHODS

We initially screened 139 individuals with DAS who were referred for elective coronary angiography and in whom aortic valve intervention was considered. Patients were divided into groups based on the echocardiographic aortic valve area indexed to the body surface area (AVAi).

Out of 139 patients with DAS, 57 were excluded from the study owing to ultrasonographic or clinical conditions that could bias data interpretation, including a significant stenosis of any carotid or vertebral artery (exceeding 50% lumen reduction [n = 5]), suboptimal acoustic temporal window (n = 7), permanent atrial fibrillation or other severe rhythm disturbances (n = 6), significant concomitant valvular diseases (n = 14), recent myocardial infarction (<3 months) (n = 3), ischemic stroke or transient ischemic attack (n = 6), hemodynamic instability: New York Heart Association class IV or acute heart failure (n = 5), left ventricular ejection fraction (LVEF) <40% (n = 7), aortic dissection (n = 1), neurodegenerative disease or diagnosed Alzheimer dementia (n = 2), and lack of the signed informed consent form (n = 1).

Eventually, a study cohort included 82 patients with DAS: group 1—41 patients with severe DAS (AVAi <0.5 cm^2/m^2) and group 2—41 patients with moderate DAS (AVAi [range], 0.51–0.99 cm^2/m^2). The control group comprised 52 patients with a normal aortic valve.

All study patients underwent clinical evaluation including the New York Heart Association classification and the Canadian Cardiovascular Society grading system for exertion-induced angina, body mass index, and the assessment of major cardiovascular risk factors (sex, age, hypertension, diabetes, hyperlipidemia, and smoking status) and comorbidities (eg, chronic renal failure). All patients with a history of syncope had head computed tomography or magnetic resonance imaging performed, as recommended by the consulting neurologist.

In all study patients, an adequate acoustic temporal window was obtained, which allowed us to assess the WC cerebral arteries using transcranial color-coded Doppler (TCCD) ultrasonography. Patients' cognitive status was assessed with the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) tests. Transthoracic echocardiography, carotid and vertebral artery ultrasonography, TCCD ultrasonography of the WC, along with cognitive status tests were also carried out.

The study protocol complied with the Declaration of Helsinki and was approved by the local institutional ethics committee (1072.6120.148.2018). All patients provided informed consent to participate in the study.

Echocardiographic examination

All patients underwent a complete echocardiographic examination in line with the guidelines of the European Association of Cardiovascular Imaging.[12] The peak and mean gradients through the aortic valve, AVA, AVAi, and LVEF were assessed in the entire study cohort.

Carotid and vertebral artery ultrasonography

High-resolution B-mode, color Doppler, and pulsed Doppler ultrasonography of both carotid and vertebral arteries were performed using an ultrasound machine (Aplio 450, Toshiba, Canon Medical Systems GmbH, Neuss, Germany) equipped with a 5–10-MHz linear-array transducer in a patient in supine position with the head tilted slightly backward. The examination was conducted by experienced sonographers who had no prior knowledge of the individual's clinical, echocardiographic, and angiographic characteristics.

Ultrasonographic data comprised the bilateral recording of the peak systolic velocity (PSV) and the end-diastolic velocity (EDV), as well as a vessel diameter measured within the 1–1.5-cm proximal segment of the internal carotid artery and the proximal V2 segment of the vertebral artery.

The luminal diameter was determined on the enlarged B-mode image of the vessel and regarded as the distance between the internal layers of the parallel walls. At the same site, a Doppler sample volume was positioned to cover the entire luminal width with an angle correction of 60 degrees. Angle-corrected PSV, EDV, time-averaged velocity (TAV) of blood flow, and mean TAV were averaged from 3 complete cardiac cycles.

The total CBF volume was determined as the sum of the individual flow volumes calculated for both internal carotid and vertebral arteries. Flow volume was calculated as the product of mean TAV and the vessel diameter according to the following equation: $CBF = TAV \times (\pi \times [d/2]^2)$, where CBF is cerebral flow volume, TAV is the time-averaged blood flow velocity estimated by the ultrasound system, and d is the vessel diameter.

Transcranial color-coded Doppler ultrasonography

The TCCD ultrasonography examination of the intracranial arteries was performed in all patients in supine position, through the temporal window, using the Toshiba Aplio machine equipped with a 1.6–2-MHz sector-array transducer. Both PSV and EDV in the WC proximal segments of the middle, anterior, and posterior cerebral arteries were recorded on admission, and the acceleration time (AT), pulsatile index (PI), and resistive index (RI) were calculated in each evaluated segment from the following equations:

$$RI = PSV - EDV / PSV$$

$$PI = PSV - EDV / ([PSV + 2 \times EDV] / 3)$$

Acceleration time was defined as the time from the minimum EDV to PSV. The averaged values of AT, RI, and PI from all cerebral arteries were subjected to further statistical analysis.

Cognitive status assessment Before coronary angiography, the cognitive function of the study participants was assessed with the MoCA[17] and MMSE[18] scales by a neuropsychologist who was blinded to clinical data. The exclusion criteria were the cutoff score values equal to or below 20 and 14 for MMSE and MoCA, respectively, which suggested severe dementia.

Statistical analysis Continuous variables were presented as mean (SD), and categorical variables, as number (percentage). Differences between the analyzed parameters were tested by the Mann–Whitney test. The Spearman correlation coefficient was calculated for CBF parameters and cognitive function scores. The normal distribution of the variables was determined by the Shapiro–Wilk test.

Univariable and multivariable regression analyses were performed for the MMSE and MoCA tests to identify independent clinical parameters associated with cognitive status. Multivariable logistic regression analysis was carried out for variables significant in univariate analyses at $P < 0.1$. The results were expressed as odds ratios (ORs) and 95% CIs.

The Statistica 13.0 software (StatSoft Polska, Kraków, Poland) was used for statistical analysis. A P value less than 0.05 was considered significant.

RESULTS Patients in groups 1 and 2 were similar with respect to age, sex, and all major atherosclerosis risk factors, except previous cardiac interventions (TABLE 1). Control subjects more frequently had hypertension, hyperlipidemia, and a history of coronary artery disease and coronary interventions (TABLE 1).

Groups 1 and 2 had lower mean (SD) CBF than controls (1.37 [0.32] l/min vs 1.5 [0.44] l/min vs 1.71 [0.21] l/min; $P < 0.001$). Compared with controls, the mean (SD) values of AT (212 [20] ms vs 161 [33] ms vs 86 [21] ms; $P < 0.001$), RI (0.64 [0.07] vs 0.65 [0.06] vs 0.59 [0.05]; $P < 0.001$), and PI (1.13 [0.21] vs 1.16 [0.17] vs 0.99 [0.12]; $P < 0.001$) were higher in groups 1 and 2 (FIGURE 1).

Both RI and PI were significantly correlated with mean ($r = -0.331$, $P = 0.003$ and $r = -0.293$, $P = 0.009$, respectively) and peak ($r = -0.316$, $P = 0.005$ and $r = -0.265$, $P = 0.02$, respectively) aortic gradients as well as AVAi ($r = 0.296$, $P = 0.009$ and $r = 0.267$, $P = 0.02$).

The mean (SD) MoCa and MMSE scores were similar in groups 1 and 2: 24.1 (3.8) vs 24.3 (4) points ($P = 0.88$) and 27.8 (2.9) vs 27.9 (2.6) points ($P = 0.98$), respectively.

Neither MoCA nor MMSE scores were predictable by AT ($r = 0.08$, $P = 0.49$ and $r = 0.15$, $P = 0.22$), RI ($r = -0.04$, $P = 0.74$ and $r = 0.12$, $P = 0.32$), PI ($r = -0.04$, $P = 0.75$ and $r = 0.09$, $P = 0.43$), or CBF ($r = -0.054$, $P = 0.64$ and $r = 0.08$, $P = 0.49$), respectively. However, the MoCA score was correlated with age ($r = -0.242$, $P = 0.04$). Both MoCA and MMSE scores were lower in patients with diabetes ($P = 0.014$ and $P = 0.011$, respectively), chronic renal failure ($P = 0.022$ and $P = 0.065$, respectively), and lower LVEF ($P = 0.018$ and $P = 0.059$, respectively).

In multivariable regression analysis, the MoCA score was associated with diabetes (OR, 1.29; 95% CI, 1.09–1.52; $P = 0.002$), chronic renal failure (OR, 1.24; 95% CI, 1.19–1.29; $P = 0.05$), age (OR, 1.23; 95% CI, 1.1–1.37; $P = 0.036$), and LVEF (OR, 1.16; 95% CI, 1.02–1.32; $P = 0.002$), while the MMSE score with diabetes (OR, 1.29; 95% CI, 1.05–1.6; $P = 0.021$) and chronic renal failure (OR, 1.32; 95% CI, 1.07–1.64; $P = 0.012$) (FIGURE 2).

TABLE 1 Clinical characteristics of the study population

Variable	Group 1[a] (n = 41)	Group 2[b] (n = 41)	*P* value (group 1 vs group 2)	Control group (n = 52)	*P* value (groups 1 and 2 vs controls)
Demographic data					
Age, y, mean (SD)	68.2 (7.6)	70.5 (7.7)	0.15	67.7 (8.7)	0.25
Female sex	20 (48.7)	24 (58.5)	0.38	27 (51.9)	0.17
Clinical symptoms					
NYHA class I	7 (17.1)	23 (56.1)	<0.001	38 (73.1)	<0.001
NYHA class II / III	34 (82.9)	18 (43.9)	<0.001	14 (26.9)	<0.001
CCS ≥II	4 (9.7)	12 (29.2)	0.03	27 (51.9)	<0.001
Syncope	2 (4.9)	3 (7.3)	0.64	1 (1.9)	0.26
Comorbidities					
Hypertension	38 (92.6)	39 (95.1)	0.64	40 (76.9)	0.004
Diabetes	12 (29.3)	15 (36.6)	0.48	17 (32.7)	0.98
Dyslipidemia	40 (97.6)	37 (90.2)	0.12	43 (82.7)	0.039
Smoking status	23 (58.7)	17 (40)	0.19	24 (46.2)	0.77
BSA, m^2, mean (SD)	1.91 (0.19)	1.91 (0.2)	0.64	1.89 (0.19)	0.46
BMI, kg/m^2, mean (SD)	30.8 (5.4)	30.6 (5.3)	0.55	28.9 (5.2)	0.13
Coronary artery disease[c]	12 (29.3)	10 (24.4)	0.62	32 (61.5)	0.0001
Previous myocardial infarction	2 (4.9)	7 (17.1)	0.08	22 (42.3)	<0.001
Previous cardiac interventions	5 (12.1)	17 (41.5)	0.003	26 (50)	0.006
Renal failure (eGFR <60 ml/min/1.73 m^2)	5 (12.2)	8 (19.5)	0.36	10 (19.2)	0.61
Laboratory test results, mean (SD)					
Creatinine, µmol/l	80.8 (15.2)	79.7 (22.4)	0.3	89.4 (21.3)	0.12
eGFR, ml/min/1.73 m^2	76.7 (15.2)	76 (17.7)	0.84	74.7 (18.2)	0.79
LDL cholesterol, mmol/l	2.8 (1)	2.7 (0.9)	0.82	2.92 (1)	0.26
Selected echocardiographic data, mean (SD)					
LVEF, %	63 (7)	61 (8)	0.28	62 (8)	0.85
Mean aortic gradient, mm Hg	60.5 (18.6)	30 (11.3)	<0.001	NA	NA
Peak aortic gradient, mm Hg	98.4 (30.6)	50 (17.9)	<0.001	NA	NA
Peak aortic valve velocity, m/s	4.86 (0.7)	3.43 (0.65)	<0.001	NA	NA
AVA, cm^2	0.78 (0.15)	1.27 (0.28)	<0.001	NA	NA
AVAi, cm^2	0.4 (0.07)	0.67 (0.14)	<0.001	NA	NA

Data are presented as number (percentage) unless otherwise indicated.

a AVAi ≤0.5 cm^2/m^2
b AVAi, 0.51–0.99 cm^2/m^2
c Coronary artery disease with lumen stenosis >50% in at least one coronary artery

Abbreviations: AVA, aortic valve area; AVAi, aortic valve area indexed to the body surface area; BMI, body mass index; BSA, body surface area; CCS, Canadian Cardiac Society; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NA, not applicable

DISCUSSION Our study demonstrated that patients with DAS had reduced CBF compared with patients with normal aortic valves. Furthermore, we found higher values of PI and RI in those with moderate-to-severe DAS compared with the control group, which indicated greater arterial stiffness. Moreover, PI and RI were significantly correlated with AVAi.

Increased arterial stiffness is a strong indicator of the increased risk of mortality and cardiovascular events.[19-21] In diabetic patients, PI may predict cerebrovascular complications, while in

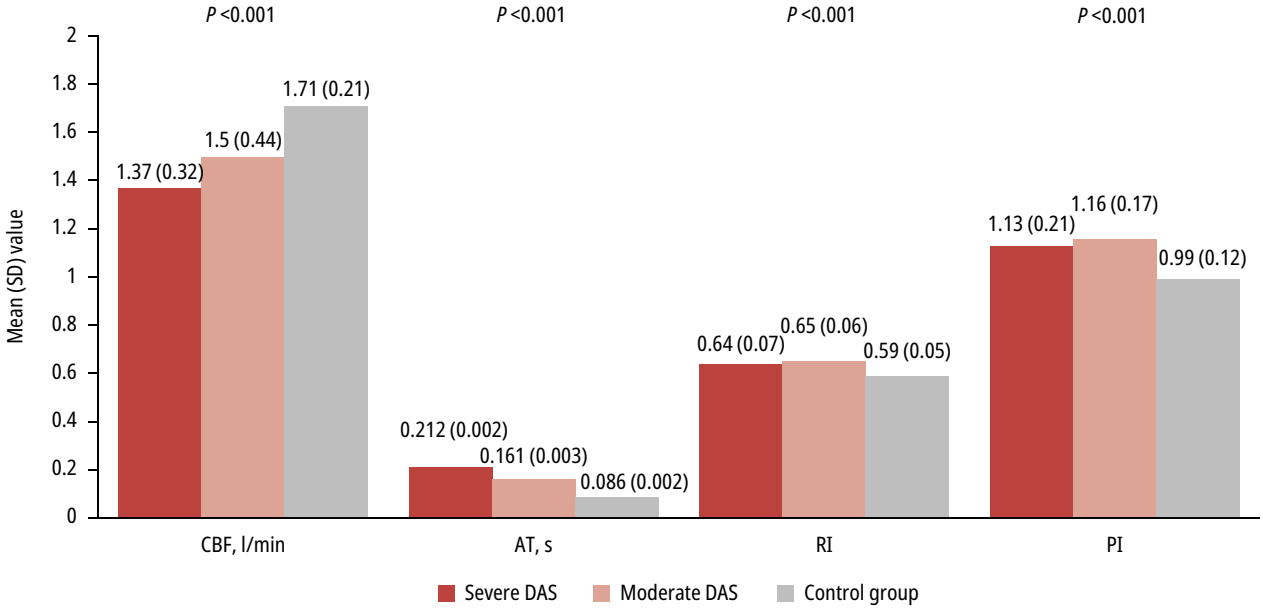

FIGURE 1 Cerebral blood flow volumes, acceleration times, and resistive and pulsatile indexes in the study patients with severe versus moderate degenerative aortic valve stenosis and controls

Abbreviations: AT, acceleration time; CBF, cerebral blood flow; PI, pulsatile index; RI, resistive index

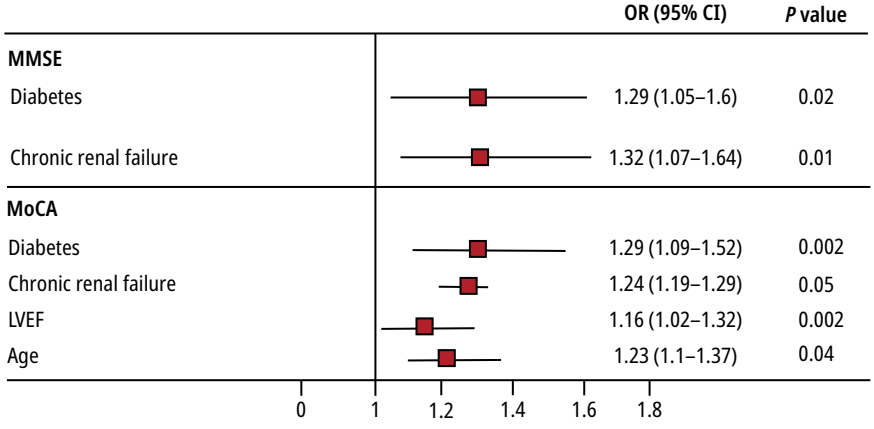

FIGURE 2 Multivariable regression analysis of the parameters independently associated with cognitive status

Abbreviations: MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; OR, odds ratio; others, see TABLE 1

hypertensive individuals, it reflects the chronicity of the disease.[19-21]

Similar to our study, Cay et al[22] demonstrated higher aortic PI in patients with DAS compared with the control group. Moreover, as in our study, PI was significantly correlated with aortic gradients, which confirms the association between arterial stiffness and the severity of calcific DAS.[22] However, it remains unclear whether calcific DAS leads to increased arterial stiffness or increased arterial stiffness leads to the gradual development of DAS. Most probably, both mechanisms coexist.

Our finding of increased arterial stiffness is in contrast to what we would expect, because, putatively, DAS leading to the hypoperfusion of the brain structures should be associated with decreased cerebral RI and PI.[23] Reduced cerebral vascular resistance, likely through autoregulation, would compensate for decreased CBF, with the PI values in symptomatic patients typically documented as lower than 1.[24,25] Heyer et al[25] found that patients with symptomatic carotid artery stenosis who had a baseline PI below 0.8 were likely to have increased CBF and improved cognitive function after carotid endarterectomy.[25] Thus, decreased PI would be associated with improved prognosis.

These unexpectedly high values of RI and PI in patients with DAS, which obviously indicate the failure of the physiological autoregulation mechanism in response to reduced CBF, can be partially explained by the negative impact of age and comorbidities, such as diabetes, hyperlipidemia, and hypertension, resulting in the increased stiffness of the macrovasculature and small-vessel disease.[26-29]

Another common belief is that CBF or CBF velocity should be correlated with cognitive

status.[30-32] However, previous reports have only partially explained the relationship between cognition and hemodynamics.[31,32] In a study by Kidher et al,[15] which included 56 patients with severe DAS, aortic stiffness (assessed by carotid–femoral pulse wave velocity) was an indicator of preoperative cognitive dysfunction.[12] These data were supported by the results of an observational study of 42 patients with high-grade, asymptomatic carotid artery stenosis, in whom cognitive impairment was linearly correlated with mean flow velocity below a threshold of 45 cm/s in the hemisphere supplied by the stenosed internal carotid artery.[30] In line with this finding, carotid artery stenosis may be associated with mild cognitive impairment in either neurologically symptomatic or asymptomatic patients.[26,33] In a group of 60 patients with ulcerated plaque causing internal carotid artery stenosis ≥70%, Puz et al[34] showed reduced cerebrovascular reactivity, which indicated a crucial role of TCCD ultrasonography.

However, most cohort studies have not elucidated whether cognitive status is attributable to decreased CBF due to DAS or carotid stenosis or there are other coplayers that impact cognitive decline.

In the present study, we did not show a direct relationship between CBF or arterial stiffness parameters and the results of cognitive tests. Other variables such as age, diabetes, chronic renal failure, and left ventricular systolic function represented the independent determinants of cognitive status. This is in line with data from other observational studies.[35-39] Diabetes was a relevant predictor of cognitive decline in the elderly, associated with deficits in attention and executive functions in some studies, whereas the greater the severity of chronic kidney disease, the greater the progression of cognitive decline was observed.[35-38] At present, the main treatment strategy in vascular cognitive impairment is prevention by treating vascular diseases and controlling other risk factors such as hypertension and diabetes.[40]

Study limitations Admittedly, our study included relatively small groups of patients with DAS, which was due to numerous ultrasonographic and clinical exclusion criteria that could potentially bias the interpretation of results. The control group was not matched by the prevalence of risk factors; for that reason, no cognitive tests from that group were subjected to statistical analysis. Apart from patients with a history of syncope, none of the study participants underwent a routine neurological examination or neuroimaging. Diseases of the central nervous system could also influence the results.

Conclusions Our findings showed that patients with DAS have significantly decreased CBF and increased arterial stiffness. However, in this patient population, cognitive impairment may be attributed to concomitant diseases rather than cerebral flow parameters.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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