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## Relationship between bleeding risk and arterial stiffness in patients with cerebral aneurysms

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**Background/aim:** A comprehensive risk factor assessment evaluating the susceptibility of cerebral aneurysms (CAs) to rupture has not yet been established. Therefore, the clinical management of unruptured CAs remains uncertain. This study aimed to assess whether arterial stiffness was associated with rupture risk in patients with CAs.

**Materials and methods:** Following magnetic resonance angiography, 49 patients with CAs and subarachnoid haemorrhage and ruptured CAs (confirmed via digital subtraction angiography) were included in the study. Arterial stiffness was measured using the VaSera VS-1000 vascular scanning system and expressed as cardio-ankle vascular index (CAVI) values. The CAVI values were compared between the patient groups.

**Results:** The mean age of the cerebrovascular aneurysm group was  $51 \pm 11$  years, while that of the cerebrovascular aneurysmal haemorrhage group was  $58 \pm 12$  ( $p = 0.308$ ) years. Left and right CAVI values were significantly higher in the cerebrovascular aneurysm group ( $p < 0.05$  for both). The CAVI values were positively correlated with haemorrhagic CA ( $p < 0.05$ ).

**Conclusion:** This study revealed that increased arterial stiffness was associated with an increased risk of haemorrhage in patients with CAs. This result demonstrates the importance of evaluating arterial stiffness as an informative parameter for treatment and follow-up decisions in patients with CAs.

**Key words:** Arterial stiffness, cardio-ankle vascular index, cerebral aneurysm, subarachnoid haemorrhage

### 1. Introduction

The most common cause of spontaneous subarachnoid haemorrhage (SAH) is intracranial aneurysms (IAs). These aneurysms are defined as irreversible, pathological focal enlargements of the vessel wall, with a prevalence of 1%–2% in the population [1]. With the widespread use of cross-sectional imaging methods, the detection rate of unruptured aneurysms has increased, altering the approach to managing these patients. The annual risk of rupture in IAs is 1.4%, and the five-year risk of rupture is 3.4%. Independent risk factors for rupture include the patient's age, aneurysm size, arterial hypertension, aneurysm localisation, and a previous history of SAH [2].

The mortality rate of aneurysmal SAH remains between 30% and 40%, despite advancements in intensive care, and morbidity among survivors is approximately 30% [3]. Therefore, treating IAs before rupture is crucial. In patients with aneurysms smaller than 7 mm and no

risk factors, the rupture risk is low, and these patients are typically followed-up conservatively. However, there is no consensus on the treatment of unruptured IAs larger than 7 mm [4].

Cumulative arterial wall disruption due to degeneration and remodelling, accompanied by inflammatory cell infiltration, has been associated with the development of cerebral aneurysm (CA) rupture in several studies [5,6]. Altered arterial wall elastic properties and hypertrophic remodelling may predispose CAs to rupture [7,8]. The cardio-ankle vascular index (CAVI), a parameter used to assess arterial stiffness, is a reliable and practical index of blood pressure-independent arterial stiffness and encompasses both organic and functional stiffness [9,10]. Compared to other methods for assessing arterial stiffness, CAVI measurement is notable for being easily applicable, reproducible, operator-independent, and less affected by blood pressure variations [11].

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This study aimed to investigate the hypothesis that arterial stiffness, as measured by the CAVI, may predict the risk of CA rupture in patients with CAs. The study design addressed a novel aspect that has not been previously reported in the literature.

## 2. Materials and methods

### 2.1. Study population

Two separate groups diagnosed with CAs and ruptured CAs between September 2023 and September 2024 were evaluated consecutively. The CA group was selected based on inclusion and exclusion criteria from patients presenting to the neurosurgery outpatient clinic with headaches, whose diagnoses were confirmed via digital subtraction angiography (DSA) following detection of a CA on magnetic resonance angiography. Patients with ruptured CAs were consecutively selected according to the inclusion and exclusion criteria from those referred from the emergency department with a diagnosis of subarachnoid haemorrhage, confirmed by DSA imaging. Patients with aneurysms in the anterior circulation were included, while those with aneurysms in the posterior circulation were excluded. Only patients with aneurysm sizes of 10 mm or less were included.

The exclusion criteria were a history of atherosclerotic heart disease and/or myocardial infarction, neurological deficits, diabetes mellitus, heart failure (left ventricular ejection fraction <50%), renal failure (estimated glomerular filtration rate <60 mL/min/1.73 m<sup>2</sup>), peripheral arterial disease, ankle-brachial index (ABI) <0.9, and severe comorbid conditions. After applying these criteria, 49 patients were prospectively included in the study. Of the patients included, 29 were treated micro surgically, and 20 underwent endovascular treatment. The patients with CAs were divided into two groups: the cerebrovascular aneurysm group and the cerebrovascular aneurysmal haemorrhage group. Baseline demographic data, biochemical parameters, and CAVI values were compared between the groups.

The study was conducted in accordance with the principles outlined in the Declaration of Helsinki, and ethical consent was obtained from the local ethics committee (number: 2024-99).

#### 2.1.1. Assessment of arterial stiffness

Arterial stiffness was assessed using the CAVI. Measurements were performed using the VaSera VS-1000 system (Fukuda-Denshi Co., Ltd., Tokyo, Japan) [12]. The CAVI is determined by recording the distance from the aortic valve to the measurement point at the ankle and the time delay between the closure of the aortic valve and the detected pressure wave change.

The patients were placed in the supine position with cuffs and clamps attached to their upper arms and ankles. After a rest period, the CAVI was calculated

automatically using electrography, phonocardiography, and measurement of the pressure and waveforms of the brachial and ankle arteries.

There are differences in blood pressure between the heart and the ankle. The CAVI blood pressure was calculated with the left CAVI (L-CAVI) value using the right upper arm and left lower leg blood pressure, and right CAVI (R-CAVI) using the left upper arm and right lower leg blood pressure values when only the left upper arm was available due to physical difficulties on the right side [13]. The ABI measurement is found by dividing the systolic pressures of the lower extremities by the value with high pressure in the upper extremities. The ABI ≤0.90 at rest is significant for the PAH, it is 99% exclusionary for >1.10 PAH of the ABI measurement [14].

### 2.2. Statistical analysis

The normality of the data distribution was evaluated using the Kolmogorov-Smirnov test. Numerical variables with a normal distribution were expressed as the mean and standard deviation. In the analysis of the categorical variables, the chi-squared test was used. The independent samples t test was used to compare numerical variables between the groups. The Pearson's correlation coefficient was used to determine correlations between cerebrovascular aneurysmal haemorrhage and the CAVI parameters.  $p < 0.05$  was considered statistically significant.

## 3. Results

The mean age of the 26 patients with cerebrovascular aneurysm was  $55 \pm 11$  years, and 57.7% ( $n = 15$ ) were female. In the cerebral aneurysmal haemorrhage group, the mean age was  $58 \pm 12$  years, and 42.3% ( $n = 11$ ) were female. No significant differences were found between the two groups in terms of the remaining demographic data, laboratory test results, systolic and diastolic blood pressure values, glomerular filtration, or mean ejection fraction ( $p > 0.05$ ).

The mean aneurysm size was  $8.3 \pm 1.1$  mm in the cerebrovascular aneurysm group and  $8.7 \pm 1.2$  mm in the cerebrovascular aneurysmal haemorrhage group. There was no statistically significant difference between the groups in terms of the aneurysm size ( $p = 0.317$ ). The laboratory results and demographic characteristics of the study patients are presented in Table 1.

The L-CAVI ( $7.89 \pm 1.29$  vs.  $9.16 \pm 2.07$ ,  $p = 0.010$ , respectively) and R-CAVI ( $7.72 \pm 1.35$  vs.  $9.45 \pm 2.20$ ,  $p = 0.020$ , respectively) measurements were significantly higher in the cerebrovascular aneurysmal haemorrhage group compared to the cerebrovascular aneurysm group (Table 2).

A positive correlation was observed between cerebral aneurysmal haemorrhage and arterial stiffness. This correlation was statistically significant in terms of the L-CAVI and R-CAVI. The R-CAVI showed a moderate correlation coefficient ( $r = 0.440$ ,  $p = 0.002$ ) (Table 3).

**Table 1.** Demographic and laboratory findings of the study group.

Variables	Cerebrovascular aneurysm (n = 26, 53.1%)	Cerebrovascular aneurysmal haemorrhage (n = 23, 46.9%)	p-value
Age (years)	55 ± 11	58 ± 12	0.308
Sex, female (%)	15 (57.7%)	11 (42.3%)	0.490
HT (%)	12 (52.2%)	11 (47.9%)	0.907
BMI (kg/m <sup>2</sup> )	28.3 ± 6.5	27.9 ± 4.9	0.751
SBP (mmHg)	137 ± 8	134 ± 7	0.172
DBP (mmHg)	83 ± 3	80 ± 2	0.138
EF (%)	59 ± 3	58 ± 2	0.358
Cerebral aneurysm size (mm)	8.3 ± 1.1	8.7 ± 1.2	0.317
Creatinine, mg/dl	0.9 ± 0.1	0.9 ± 0.3	0.543
eGFR, mL/min/1.73 m <sup>2</sup>	75 ± 5	72 ± 3	0.687
Glucose (mg/dl)	98 ± 18	93 ± 12	0.215
Haemoglobin, g/dl	13.1 ± 1.3	12.8 ± 2.1	0.546
Total cholesterol (mg/dl)	191 ± 56	185 ± 42	0.652
LDL (mg/dl)	120 ± 39	114 ± 30	0.571

Numerical data are expressed as the mean ± standard deviation. BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, EF: ejection fraction, eGFR: estimated glomerular filtration, LDL: low-density lipoprotein.

**Table 2.** Comparison of the CAVI findings between the study groups.

Variables	Cerebrovascular aneurysm (n = 26, 53.1%)	Cerebrovascular aneurysmal haemorrhage (n = 23, 46.9%)	p value
L-CAVI	7.85 ± 1.29	9.16 ± 2.07	0.010
L-ABI	1.04 ± 0.06	0.99 ± 0.14	0.143
R-CAVI	7.72 ± 1.35	9.45 ± 2.20	0.002
R-ABI	1.03 ± 0.07	1.01 ± 0.09	0.514

L: left, R: right, CAVI: cardio-ankle vascular index, ABI: ankle-brachial index.

**Table 3.** Correlation analysis results of the cerebrovascular aneurysmal haemorrhage and CAVI.

Variables	Cerebrovascular aneurysmal haemorrhage	
	R	p-value
L-CAVI	0.366	0.010
R-CAVI	0.440	0.002

#### 4. Discussion

Arterial stiffness was higher in patients with CAs who developed SAH compared to those who did not. This finding suggests that arterial stiffness measurements in patients with ruptured CAs may provide an idea about the risk of potential SAH and guide follow-up and treatment decisions.

The incidence of CAs is higher among women, individuals with a family history of SAH, and patients with autosomal dominant polycystic kidney disease [2]. Factors such as the patient's age, aneurysm size, arterial hypertension, aneurysm localisation, and a previous history of SAH have been reported as independent risk factors for rupture [2]. In the current study, no significant differences were observed between the haemorrhage and nonhaemorrhage groups in terms of age, arterial hypertension, or sex. The lack of differences in these well-established risk factors underscores the importance of arterial stiffness as a potentially distinctive factor in assessing rupture risk.

Increased central and peripheral arterial stiffness has been previously shown in clinical studies as a marker associated with cardiovascular events and mortality [15,16]. Similarly, the CAVI assessment proposed herein may serve as a biomarker to evaluate the risk of IA rupture. Previous studies have linked increased arterial wall stiffness with a higher susceptibility to rupture in patients with CAs [17]. Stiffness is affected by the elastic properties of arterial wall tissue, and reduced elasticity has been associated with the development of SAH [17,18]. Arterial stiffness has also been linked to the degeneration of collagen, elastin, and the extracellular matrix [19]. Degeneration of vascular collagen contributes to arterial wall weakness by reducing wall elasticity, thereby increasing the likelihood of rupture [17,20]. Although the present study did not investigate the pathophysiological causes of arterial stiffness, the findings were consistent with previous studies correlating increased arterial stiffness with a heightened risk of SAH in patients with CAs.

The risk of rupture in abdominal aortic aneurysms has also been extensively investigated [21,22]. Studies have reported that vasculopathy and arterial distensibility predispose patients to the development, dissection, and rupture of abdominal aortic aneurysms [23]. In these patients, dissection occurs when wall tension exceeds the strength limit of the arterial wall [24]. Research evaluating the limit of aneurysm expansion has shown a correlation between the degree of distensibility and rupture risk [25,26]. Increased arterial wall stiffness, reduced elasticity, and decreased perivascular support may be

associated with vasculopathies caused by ageing, essential hypertension, diabetes mellitus, and vasculitis [27,29]. Although the current study focused on CAs rather than abdominal aortic aneurysms, the consistent relationship between arterial stiffness and rupture risk underscores the general applicability of this phenomenon across different anatomical regions.

Cumulative arterial wall disruption due to continuous remodelling, characterised by degeneration and inflammatory cell infiltration, has been implicated in the pathogenesis of SAH [30]. The results herein suggest that increased stiffness of the arterial vasculature may lead to higher susceptibility to haemorrhage in patients with aneurysms.

The primary limitation of the study was the small sample size. In addition, the cross-sectional design precluded the establishment of causal relationships. The exclusion of posterior circulation aneurysms and aneurysms over 10 mm further limited the generalisability of the findings to all aneurysm subtypes. Therefore, large-scale studies that include diverse aneurysm types are needed to validate the results. Another limitation was the inability to predict changes in the CAVI values due to haemodynamic changes (e.g., nitric oxide levels) in patients with SAH. Despite these limitations, we consider that arterial stiffness is an important parameter in assessing CAs, which represent an isolated disease group with significant haemorrhage and mortality risks.

#### 5. Conclusion

This study suggests that arterial stiffness evaluation in patients with CAs may provide valuable guidance in assessing the risk of SAH and may guide follow-up and treatment decisions.

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#### Conflict of interest

The authors declare that they have no conflicts of interest.

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#### Ethical approval

This study received ethical approval from the University of Health Sciences Trabzon Faculty of Medicine (Date: 2024, Number: 2024-99).

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