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The Association of Arterial Pulse Wave Velocity with Internal Carotid Artery Blood Flow in Healthy Subjects: A Pilot Study

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Abstract

Background Arteriosclerosis significantly impacts cardiovascular health. Pulse wave velocity has emerged as a valuable non-invasive method for assessing arterial stiffness. A negative association between carotid-femoral pulse wave velocity (cfPWV) and cerebral blood flow has been reported, suggesting a link between arterial stiffness and reduced cerebral blood flow. We aimed to determine whether a correlation exists between cfPWV and blood flow in the internal carotid artery (ICA) and to assess the influence of age and body mass index (BMI) on cfPWV in healthy individuals.

Methods Thirty-six healthy subjects (23 males and 13 females) with no underlying medical conditions and who were not on regular medications were enrolled in the study. Arterial stiffness was assessed by measuring the cfPWV using Vicorder® software. ICA blood flow parameters were measured using high-resolution ultrasound. ICA diameter was measured using automated edge-detection software.

Results Significant positive correlations were found between cfPWV and age (Spearman's rho coefficient 0.33, $p=0.04$), BMI (Spearman's rho coefficient 0.32, $p=0.05$), and ICA diameter (Pearson's coefficient 0.35, $p=0.03$). No significant correlations were observed between cfPWV and ICA peak systolic velocities (PSV; $p=0.22$), or resistive index (RI; $p=0.76$), nor between age and ICA diameter ($p=0.42$), PSV ($p=0.09$), or RI ($p=0.89$).

Conclusion Our findings demonstrate a positive correlation between arterial stiffness, age, and BMI in a healthy population, along with an association between increased ICA diameter and arterial stiffness. The lack of correlation between cfPWV and ICA blood flow parameters suggests that the ICA may dilate as a compensatory mechanism to mitigate the effects of increased arterial stiffness, ensuring optimal cerebral blood flow in healthy individuals.

Keywords Arterial stiffness, Pulse wave velocity, PWV, Internal carotid artery, Blood flow

1 Introduction

Arteriosclerosis is characterized by arterial wall thickening and hardening, which has significant impacts on cardiovascular health and is associated with various diseases, such as atherosclerosis, chronic kidney disease, vascular dementia, and Alzheimer's disease [1–3]. The condition primarily affects the elastic arteries, leading to a loss of elastic fibers and increased fibrosis in arterial walls due to repetitive cyclic stress [4].

Cardiovascular function gradually declines with age, due to age-related changes within the cardiovascular system. Atherosclerosis, congenital and rheumatic heart diseases, and hypertension are major contributors to disability and mortality among middle-aged and elderly individuals, accounting for over 40% of deaths in those aged 65 years and over [5]. Vascular age, determined by

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measuring arterial stiffness, provides valuable insights into cardiovascular disease (CVD) risk [6]. Obesity and related factors such as dyslipidemia, hepatic steatosis, and insulin resistance, have been proposed as potential mechanisms contributing to the higher incidence of CVD in overweight individuals, and are associated with increased arterial stiffness [7–9].

Pulse wave velocity (PWV) has emerged as a valuable non-invasive method for evaluating arterial stiffness, whereby increased arterial stiffness leads to higher PWV values [10]. Its simplicity, affordability, and reproducibility have contributed to its widespread use in epidemiological research, enabling the evaluation of arterial stiffness and estimation of CVD risk [11]. PWV has been clinically associated with adverse cardiovascular outcomes, independent of conventional risk factors such as aging, hypertension, diabetes, dyslipidemia, obesity, and smoking [12].

PWV is determined by measuring the transit time of the arterial waveform between two points along a known distance [13]. The pathway between the carotid and femoral arteries, known as the carotid-femoral PWV (cfPWV), is a referent measure of arterial stiffness and vascular aging. The path from carotid to femoral sites consists of approximately 60% aorta and 40% femoral artery, thus being sensitive to aging in both central and peripheral arteries [14]. For cfPWV assessments, the transit time is recorded as the time between the carotid and femoral pressure waveforms [15]. Due to the importance of cfPWV as a robust predictor of cardiovascular events, international reference standards have been established to enable meaningful comparisons across different populations, age groups, and risk factor categories [9, 16]. Previous studies have demonstrated an association between increased cfPWV and cerebral small vessel disease, encompassing conditions like cerebral microbleeds, white matter hyperintensity, and lacunar infarction. Cerebral small vessel disease is frequently observed in elderly individuals and is a significant vascular contributor to stroke, cognitive impairment, and geriatric syndrome [17–20]. Previous studies have suggested that PWV is associated with cognitive dysfunction and the progression of cognitive decline in elderly individuals [21, 22]. In addition, PWV has been linked to calcification, stenosis, and the occlusion of large cerebral arteries. Elevated cfPWV has been associated with cerebral artery calcification or stenosis in individuals with hypertension [23] and patients experiencing acute ischemic stroke [24]. Furthermore, carotid intima-media thickness serves as an indicator of atherosclerosis and is linked to coronary artery disease and stroke [25, 26], with studies demonstrating a positive linear correlation between carotid intima-media thickness and cfPWV [27–29].

A recent study by Liu et al. (2021) evaluated the association between vascular dysfunction and intracranial vascular health, showing a significant negative association between cfPWV and cerebral blood flow in hypertensive males, suggesting a link between arterial stiffness and cerebral blood flow decline [30]. However, there is a lack of studies that specifically investigated the association between cfPWV and internal carotid artery (ICA) blood flow. Therefore, this study aims to determine the correlation between cfPWV and ICA blood flow, as well as the influence of age and body mass index (BMI) on cfPWV in healthy individuals.

2 Methods

2.1 Study Design and Assessment

This pilot trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice. The study was approved by the Ethics Research Committee at the University of Nottingham (Reference No: E1411201). Healthy individuals without underlying medical conditions and not taking regular medication were recruited. Participants were instructed to abstain from taking any vitamin supplements for 72 h and to avoid exercise, medications, caffeine, alcohol, and cigarette/e-cigarette smoking for 24 h prior to measurement. cfPWV and ICA blood flow measurements were taken in a room maintained at 22–24 °C, after a minimum rest period of 10 min in the supine position following an overnight fast [31, 32].

2.2 Measurements of cfPWV and ICA Blood Flow

Arterial stiffness was assessed by measuring the PWV between the carotid and femoral anatomical sites using Vicorder® software [33, 34]. cfPWV measurements were obtained using inflated cuffs placed around the neck and the right upper thigh to detect the carotid and femoral pulses. The cuffs were automatically inflated to 65 mmHg, and pulse waveforms were recorded for 3.5 s while the participant was in a supine position. The display screen was then frozen, and the cfPWV measurement was obtained. Consistency of waveforms was ensured by recording during a stable period, without participant movements; if inconsistencies were detected, the assessment was repeated. ICA diameter and blood flow parameters, including maximum systolic and diastolic velocities and downstream flow resistance (resistive index; RI), were measured using a high-frequency linear probe (L15-4 MHz) of a high-resolution ultrasound system (Terason 3200T). The ICA diameter was determined as the average of three cardiac cycles using automated edge-detection software (Cardiovascular Suite Quipu) from B-mode ultrasound images. ICA peak

systolic velocity was measured by placing a caliper over the maximum systole of three spectral waveforms, with the average considered for analysis. The cursor angle was set at 60˚ along the direction of the flow, and this angle was used for all participants. Control settings for carotid ultrasound imaging, including depth, focal point, pulse repetition frequency, color box position, and gain in the spectral display, were optimized to ensure accurate vessel wall detection and clear Doppler signals, minimizing background noise for precise caliper placement. ICA blood flow parameters and diameters were assessed at 1–2 cm distal to the carotid bulb, where the ICA lumen is uniform [35, 36].

Table 1 Participant characteristics

Characteristics	Descriptive statistics (mean ± SD) Healthy subject ($n = 36$)
Age (years)	28.5 ± 5.9
Weight (kg)	73.2 ± 13.6
Height (m)	1.72 ± 0.09
BMI	24.4 ± 3.3
SBP (mmHg)	116.4 ± 11.2
DBP (mmHg)	71.1 ± 7
cfPWV (m/s)	6.4 ± 0.8
ICA-D (mm)	4.86 ± 0.6
ICA-PSV (m/s)	0.81 ± 0.1
ICA-RI	0.62 ± 0.06

BMI body mass index, *cfPSV* carotid-femoral peak systolic velocity, *DBP* diastolic blood pressure, *ICA* internal carotid artery, *mmHg* millimeter of mercury, *PSV* peak systolic velocity, *RI* resistive index, *SBP* systolic blood pressure, *SD* standard deviation

2.3 Statistical Analysis

Pearson's correlation coefficient was used for parametric variables and Spearman's rank correlation coefficient for non-parametric variables. A significance level of 0.05 was set for all tests. Statistical analysis was performed using IBM SPSS Statistics version 21 (Armonk, NY: IBM Corp).

3 Results

Thirty-six healthy subjects (23 males and 13 females) were recruited for this study. Participant characteristics are summarized in Table 1.

3.1 Correlations Between cfPWV, Age, and BMI

Significant positive correlations were found between cfPWV and age (Spearman's rho coefficient 0.33, $p = 0.04$; Fig. 1A), and cfPWV and BMI (Spearman's rho coefficient 0.32, $p = 0.05$; Fig. 1B).

3.2 Correlation Between cfPWV and ICA Blood Flow

There was a significant positive correlation between cfPWV and ICA diameter (Pearson's coefficient 0.35, $p = 0.03$; Fig. 2A). No significant correlations were observed between cfPWV and ICA-PSV (Spearman's rho coefficient − 0.20, $p = 0.22$; Fig. 2B), or ICA-RI (Spearman's rho coefficient 0.05, $p = 0.76$; Fig. 2C).

3.3 Correlation Between Age and ICA Blood Flow

There were no significant correlations between age and ICA diameter (Spearman's rho coefficient 0.13, $p = 0.42$; Fig. 3A), ICA-PSV (Spearman's rho coefficient − 0.28, $p = 0.09$; Fig. 3B), or ICA-RI (Spearman's rho coefficient -0.02, $p = 0.89$; Fig. 3C).

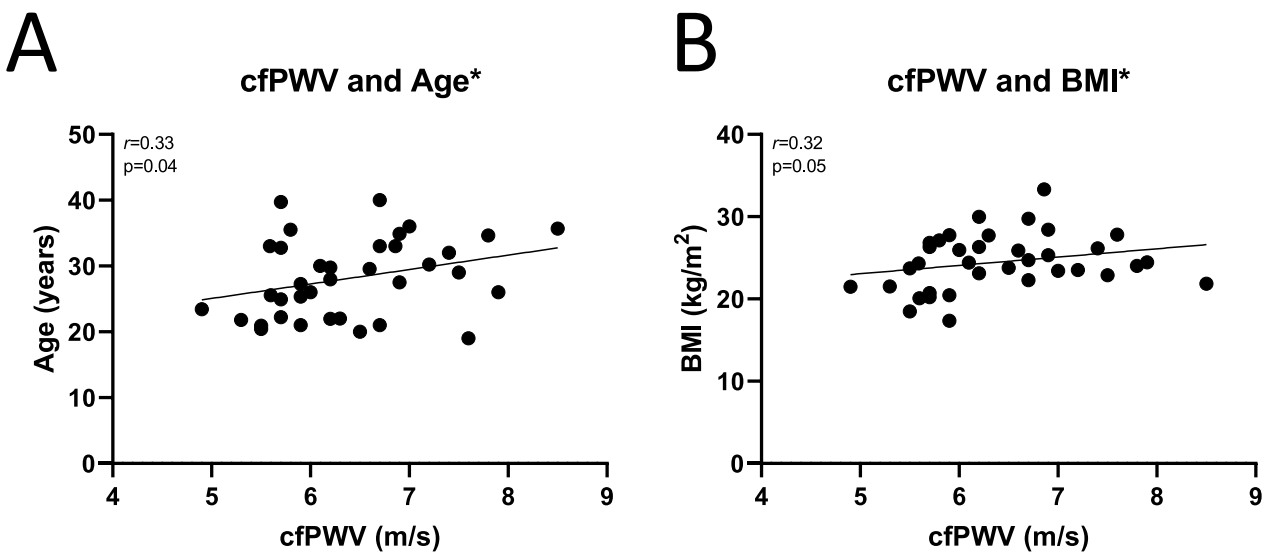

Fig. 1 Correlation of aortic stiffness, measured through carotid-femoral pulse wave velocity (cfPWV), with **A** age and **B** body mass index (BMI). *$p \leq 0.05$ using Spearman's rank correlation

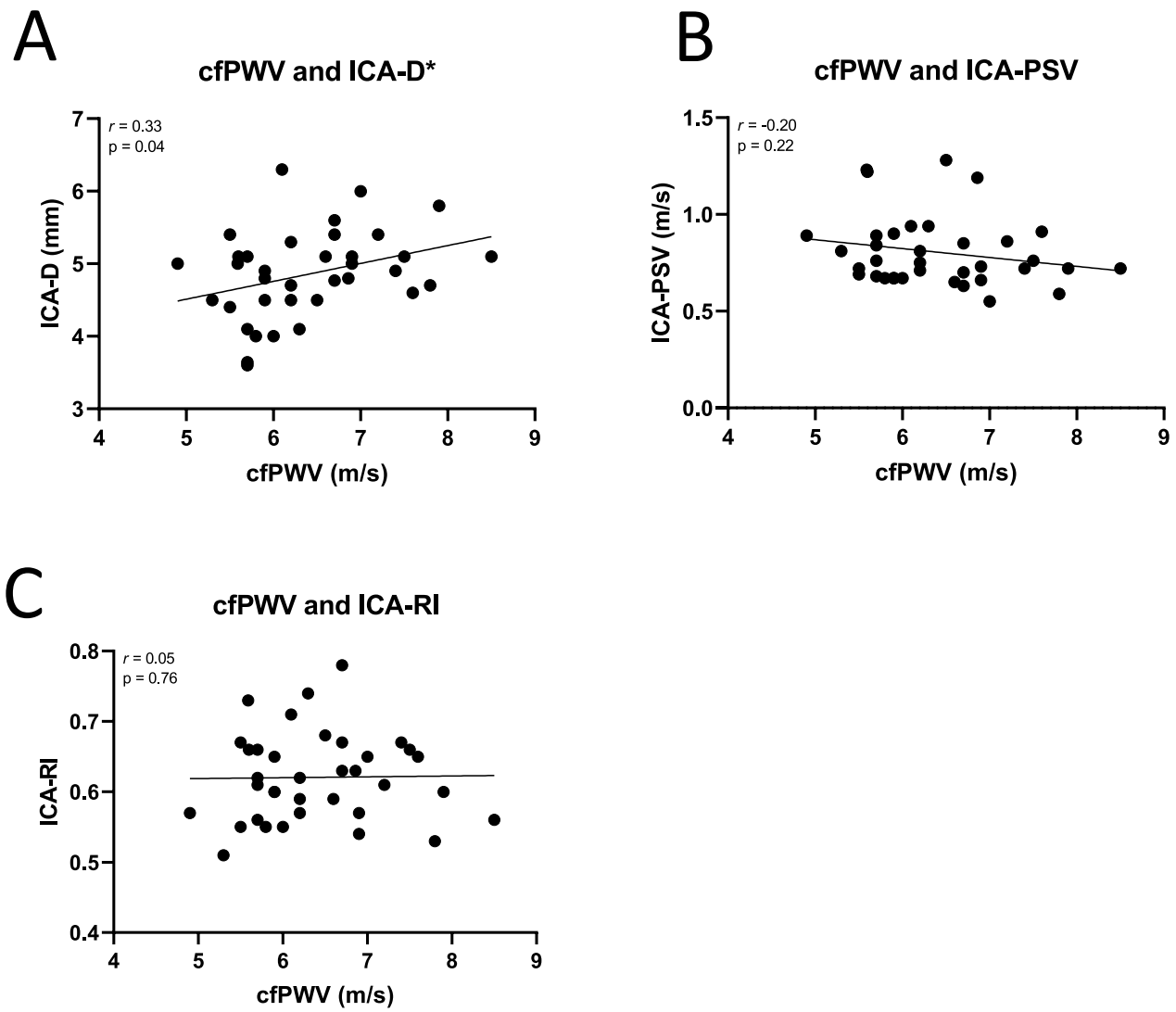

Fig. 2 Correlation of aortic stiffness, measured through carotid-femoral pulse wave velocity (cfPWV), with **A** internal carotid artery diameter (ICA-D), **B** peak systolic velocity (ICA-PSV), and (C) resistive index (ICA-RI). *$p \leq 0.05$ using Pearson's correlation

4 Discussion

In this study, we observed a positive correlation between arterial stiffness, estimated using cfPWV, and both age and BMI in healthy young adults. Participants had a mean age of 28.5 years and a mean BMI of 24.4. These findings align with previous research indicating that cfPWV increases with age [37–40]—a factor that should be considered when establishing reference values in elderly populations [16]. The well-established age-related increase in arterial stiffness is attributed to gradual cardiovascular function decline, and is one of the earliest pathophysiological processes, constituting an independent risk factor for CVD [16, 41]. The arterial walls undergo mechanical degradation with aging, characterized by the fraying of elastin structures and the formation of crosslinked collagen fibers due to advanced glycation end-products, ultimately leading to a gradual increase in arterial stiffness [42, 43]. Obesity is well-reported to negatively impact the function of large arteries—a process that may be attributed to metabolic dysregulation and inflammatory processes [44]. Several indicators of vascular function, including the stiffness index, central and peripheral augmentation index, and central and peripheral pulse pressure, have been found to correlate with body fat, suggesting that obesity contributes to arterial remodeling and hemodynamic changes [45, 46]. Positive associations between adiposity measures, such as BMI, waist circumference, waist-height ratio, and PWV have been reported

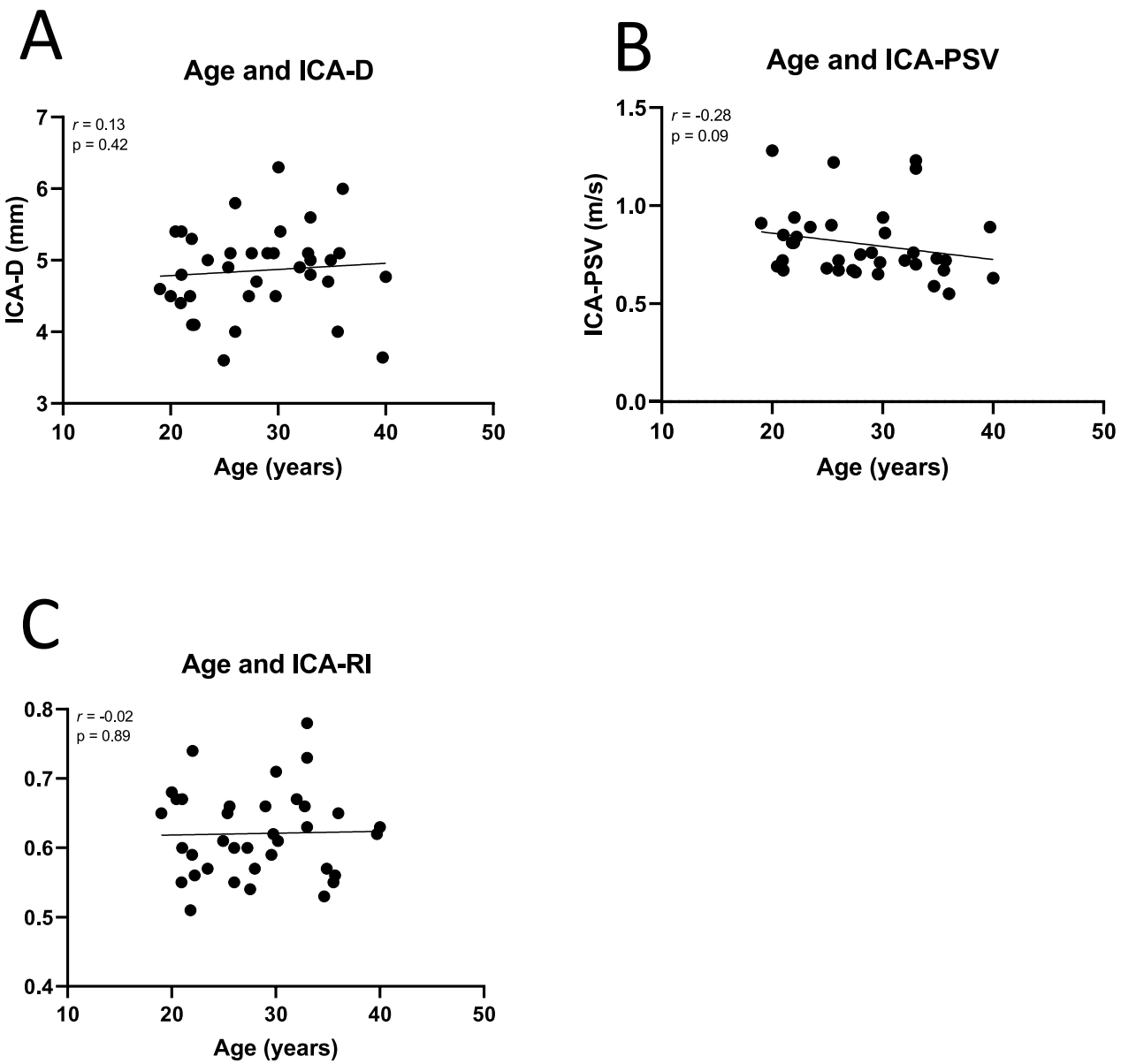

Fig. 3 Correlation of age with **A** internal carotid artery diameter (ICA-D), **B** peak systolic velocity (ICA-PSV), and **C** resistive index (ICA-RI)

in multiple studies [47–50]. Specifically, a significant association between excess body weight and increased arterial stiffness has been observed in young adults aged 20–30 years [50]. A recent study reported that obese young adults (≤ 30 years) exhibit higher PWV values and increased vascular stiffness compared to their non-obese counterparts, raising concerns about the impact of rising obesity rates on vascular aging [51]. Further research is needed to investigate the reversibility of high BMI effects on vascular stiffness.

Arterial stiffness can adversely affect cerebral blood flow and cognitive function. Associations have been demonstrated between arterial stiffness and reduced brain blood flow in adults without cardiovascular or neurological diseases, with arterial stiffness linked to decreased blood flow in the frontal and parietal white matter, which are susceptible to microvascular damage [52, 53]. Age-related arterial stiffness increases cerebrovascular impedance, resulting in excessive pressure and flow pulsatility that may result in microvascular damage [54–56]. Fico et al. (2022) investigated the association between cfPWV and the pulsatility index in cerebral arteries, including ICA, using 4D flow MRI. Participant groups were comprised of young or older adults, with

a mean age of 33 and 62 years, respectively. A positive association was reported between cfPWV and the cerebral arterial pulsatility index in the combined age group and in elderly adults (excluding ICA) but not in the young adult group [57]. These findings suggest age-dependent variations in the relationship between arterial stiffness (cfPWV) and the cerebral pulsatility index. The findings in the young adult group agreed with our study, in which no associations were observed between cfPWV and ICA blood flow or RI. We also found no significant correlation between age and ICA diameter, blood flow, or RI. However, a significant positive correlation between cfPWV and ICA diameter was observed in healthy individuals. This suggests that factors other than age-related elastin fragmentation might influence ICA diameter variations in this cohort. While arterial diameter typically increases with age due to elastin fragmentation [58, 59] and arterial elasticity and stiffness are not uniform across the arterial tree [60], the observed correlation between cfPWV and ICA diameter may reflect the ICA's elasticity in healthy young adults. This elasticity allows the artery to adapt to varying blood flow and elevated arterial stiffening, highlighting the dynamic nature of the ICA in accommodating increased pulsatility, maintaining optimal cerebral blood flow, and responding to elevated arterial stiffness in healthy young adults.

The brain is vulnerable to excessive pulsatility due to its high blood flow demand and low arteriole resistance [61, 62]. Typically, the arterial pulse travels away from the heart, but increased arterial stiffness causes greater resistance and pulse wave reflections, augmenting the pressure within the arterial system [63]. These reflected waves can travel back to the carotid artery, leading to carotid artery vasodilatation as a compensatory mechanism to maintain optimal brain blood flow [64]. It has been suggested that the elasticity of the ICA contributes to accommodating pressure changes and maintaining optimal cerebral blood flow, potentially mitigating the reduction in flow caused by increased arterial stiffness [65, 66]. This indicates that elasticity is crucial for managing vascular dynamics, underscoring its importance in conditions characterized by disrupted blood flow to the brain [65]. These highlight the importance of large conducting arteries like the carotid in buffering pulsatility before it reaches the cerebral circulation [67, 68]. Together, these findings suggest that the relationship between arterial stiffness and cerebral hemodynamics varies with age. Further research should explore the complex interplay between arterial stiffness, cerebral blood flow, and age-related vascular changes. Understanding these mechanisms could contribute to the development of targeted interventions aimed at mitigating the adverse effects of arterial stiffness on cerebral hemodynamics, ultimately promoting brain health and cognitive function.

This study has several limitations, including its relatively small sample size, which limits the ability to perform multiple regression analyses. Future research should adjust the association between cfPWV and carotid artery parameters for age and gender. Additionally, this study focused exclusively on healthy individuals, potentially limiting the applicability of the results to broader populations, including those with underlying health conditions. Furthermore, the assessment of arterial stiffness was based on cfPWV and ICA blood flow parameters, overlooking the potential impact of other arterial segments and their contributions to cerebral hemodynamics. Future studies should include larger and more diverse populations, including individuals with varying health conditions. Longitudinal designs and comprehensive assessments of multiple arterial segments and cerebral blood flow parameters would further enhance the current knowledge.

5 Conclusion

This study provides evidence of a positive correlation between arterial stiffness, measured by cfPWV, and both age and BMI in a healthy population, along with an increase in ICA diameter. However, no significant correlations were found between cfPWV and ICA blood flow, or between age and ICA diameter or blood flow. These findings suggest that the ICA may dilate as a compensatory mechanism to counteract increased arterial stiffness, thereby ensuring optimal cerebral blood flow in healthy individuals. This underscores the potential role of ICA elasticity in cerebral hemodynamics. Further research is essential in both healthy individuals and those with underlying health conditions to improve understanding of the role of arterial elasticity and stiffness in cardiovascular health.

Author Contributions
SRS: conceived and designed the experiments; collected and analysed the data; wrote and revised the manuscript.

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

Declarations

Conflict of interest
The author declare no conflicts of interest exist.

Ethics approval and consent to participate
This research is approved by the Ethics Research Committee at the University of Nottingham (Reference No.: E1411201) and written informed consent was taken from all participants.

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