With advancing age the central elastic arteries stiffen and the waves reflected from the periphery return faster, reach the central arteries during systole, and cause augmentation of late systolic blood pressure. Arterial stiffening explains why with advancing age systolic blood pressure rises and diastolic blood pressure falls, so that pulse pressure increases.\textsuperscript{1,2} Such systemic increase in pulse pressure has little effect on the perfusion of most organs, because constriction of arteries and arterioles regulate blood flow.\textsuperscript{3} A unique feature of the brain is that this organ is continually and passively perfused at high-volume flow throughout systole and diastole.\textsuperscript{3} The resistance of the cerebral circulation is low. Pulsations of pressure and flow originating from the periphery extend well into this organ, so that even the venous efflux from the brain shows pulsatility. Flow pulsation at cerebral arteries could be accurately measured as pulsatility index (PI) by intracranial Doppler ultrasonography, especially at the middle cerebral arteries (MCAs).

Studies in hypertensive patients\textsuperscript{4,5} and in the general population,\textsuperscript{6–8} suggest that the risk of stroke,\textsuperscript{4,6} white matter lesions\textsuperscript{5,7,8} or cognitive decline increased with aortic stiffness.\textsuperscript{4,6} However, the underlying mechanism remains to be clarified. We hypothesized that the flow pattern in the MCA would reflect the pulsatile component of systemic blood pressure, which in turn is related to arterial stiffness. Such mechanism is clinically meaningful as it might explain the association between degenerative changes in the brain and arterial stiffness in the macrocirculation. In the present study, we investigated association of flow pulsatility in the MCA with various arterial stiffness indices, including 24-h pulse pressure, central and peripheral pulse pressure, and carotid-femoral and brachial-ankle pulse wave velocities.

\textbf{BACKGROUND}

The brain is perfused at high-volume flow throughout systole and diastole. We explored the association of blood flow in the middle cerebral artery (MCA) with the pulsatile components of blood pressure in the systemic circulation and indices of arterial stiffness.

\textbf{METHODS}

We enrolled 334 untreated subjects (mean age, 50.9 years; 45.4\% women) who had been referred for ambulatory blood pressure monitoring to Ruijin Hospital, Shanghai, China. We measured the MCA pulsatility index (PI) by transcranial Doppler ultrasonography. The indices of arterial stiffness included pulse pressure (brachial (bPP) and central (cPP) measured at the office and 24-h ambulatory (24-h PP)) and carotid-femoral (cf-PWV) and brachial-ankle (ba-PWV) pulse wave velocity. Effect sizes, expressed per 1 s.d., were adjusted for sex, age, heart rate, and mean pressure.

\textbf{RESULTS}

Women had faster MCA blood flow than men (68.0 vs. 58.3 cm/s), but lower PI (75.4 vs. 82.3%; \(P < 0.001\)). The five arterial stiffness indices were intercorrelated (\(r \geq 0.37; P < 0.001\)). PI increased (\(P \leq 0.045\)) with bPP (+6.78%), cPP (+5.56%), 24-h PP (+7.58%), cf-PWV (+1.59%), and ba-PWV (+3.46%). In explaining PI variance, bPP ranked first (partial \(r^2 = 0.25\)), 24-h PP second (0.20) and cPP third (0.14). In models including both cf-PWV and ba-PWV, only the latter was significant (−0.19%; \(P = 0.84\) vs. +3.54%; \(P < 0.001\)). In models including both bPP and ba-PWV, only the former contributed to PI variance (+6.98%; \(P < 0.001\) vs. −0.24%; \(P = 0.78\)).

\textbf{CONCLUSION}

MCA blood flow is closely associated with the pulsatile pressure in the systemic circulation, which depends on arterial stiffness as measured by PWV.

\textbf{Keywords:} arterial stiffness; blood pressure; cerebral blood flow; hypertension; middle cerebral artery; transcranial Doppler ultrasound

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METHODS

Study population. From March 2009 to January 2011, we invited 791 consecutive patients who were not on antihypertensive medications for at least 2 weeks and were referred for ambulatory blood pressure monitoring to the Hypertension Clinic of Ruijin Hospital, Shanghai, China. Of those invited, 472 provided written informed consent (participation rate, 59.7%). The ethics committee of Ruijin Hospital, Shanghai Jiaotong University School of Medicine, approved the protocol. For the present analyses, we excluded 138 participants, because they had no transcranial Doppler recordings \((n = 61)\) or bilateral ultrasound window failure so that the transcranial Doppler evaluation could not be performed \((n = 42)\), or because their ambulatory blood pressure recording included <10 readings during the awakening period or five readings during sleep \((n = 4)\), or because they did not have central arterial pressure \((n = 13)\), carotid-femoral pulse wave velocity \((cf-PWV; n = 6)\) or brachial-ankle PWV \((ba-PWV; n = 12)\) measured. Thus, data from 334 subjects were analyzed.

Blood flow in the MCA. As described elsewhere, \(^9\) a single skilled observer \((J.X.)\) performed all transcranial Doppler examinations by means of a Pioneer TC8080 ultrasound device \((Nicolet Vascular Division; VIASYS Healthcare, Madison, WI)\) equipped with a 2.5 MHz probe. This observer was blinded to the information of other arterial measurements, and vice versa. With the patient in the supine position, the ultrasonographer recorded end-diastolic \((V_d)\), peak systolic \((V_s)\), and mean \((V_m)\) blood flow velocities in both MCAs at a depth of 50 mm \((45–55 \text{ mm})\). The intraobserver intrasession variability of blood flow velocity measurements was <15%. \(^{10}\) The mean cerebral blood flow velocity was defined as: \(1/3 \times (V_s + 2 \times V_d)\). \(^{10}\) The PI was calculated as: \(\text{PI} = (V_s - V_d)/V_m \times 100\). \(^{10}\) If data were available for both arteries, the average value was used for analysis.

Central pulse pressure. Within 2 h after the transcranial Doppler assessment, one trained observer \((W.X.F)\) measured the radial arterial waveform at the dominant arm of the patient. He recorded the waveform during a 8-s period by applanation tonometry by means of a high-fidelity SPC-301 micromanometer \((Millar Instruments, Houston, TX)\) interfaced with a laptop computer, running the SphygmoCor software version 7.1 \((AtCor Medical, West Ryde, Australia)\). The radial pulse wave was calibrated by the supine brachial systolic and diastolic blood pressures, which were obtained immediately before the tonometric recordings. From the radial signal, the SphygmoCor software calculates the aortic pulse wave by means of a validated generalized transfer function. \(^{11,12}\)

Carotid-femoral PWV. Using the SphygmoCor device, cf-PWV was measured by sequential electrocardiogram-gated recordings of the arterial pressure waveform at the carotid and femoral arteries. Distances from the suprasternal notch to the carotid sampling site \((\text{distance } A)\) and from the suprasternal notch to the femoral sampling site \((\text{distance } B)\) were measured. Pulse wave travel distance was calculated as distance \(B\) minus distance \(A\). Pulse transit time was the average of 10 consecutive beats. PWV was the distance in meters divided by the transit time in seconds.

Brachial-ankle PWV. Using the Omron Colin BP-203RPEIII VP-1000 device \((\text{Omron Health Care, Kyoto, Japan})\) ba-PWV was measured as described previously. \(^{13}\) The Omron Colin device extrapolates the travel path from body height and automatically computes ba-PWV by dividing time difference between the pulse waves that were transmitted to the brachial and ankle arteries by the travel path. \(^{13}\)

Office blood pressure and pulse pressure. For the present analysis, office blood pressure was the average of three oscillometric blood pressure readings \((\text{Omron HEM 705IT device; Omron Health Care})\) \(^{14}\) obtained at the brachial artery for calibration of the radial pressure waves with the subjects in the supine position. Hypertension was a blood pressure of 140 mm Hg systolic or 90 mm Hg diastolic or higher.

24-h blood pressure and pulse pressure. Within 1 week before the arterial examinations, the patients underwent 24-h ambulatory blood pressure monitoring. Validated oscillometric \((\text{SpaceLabs 90217 monitors (SpaceLabs, Redmont, WA)})\) were programmed to obtain blood pressure readings at 20-min intervals from 6:00 AM until 10:00 PM and at 30-min intervals from 10:00 PM to 6:00 AM. \(^{15}\) All recordings covered >20 h and included at least 10 readings during the awakening period and five readings during sleep. The 24-h blood pressure means were weighted for the time interval between consecutive readings to account for the difference between these time intervals. \(^{16}\) Pulse pressure was the difference between systolic and diastolic blood pressures.

Other measurements. A physician administered a standardized questionnaire, inquiring into each subject's medical history, intake of medications, and smoking and drinking habits. Nurses measured body height to the nearest 0.5 cm. Participants wore light indoor clothing without shoes for body weight measurement. Body mass index was weight in kilograms divided by the height in m\(^2\). After subjects had fasted overnight, venous blood samples were obtained and analyzed by automated enzymatic methods for serum total cholesterol and blood glucose. Diabetes mellitus was a plasma glucose level of 126 mg/dl or higher or the use of antidiabetic drugs. \(^{17}\)

Statistical methods. For database management and statistical analyses, we used the SAS software, version 9.1.3 \((\text{SAS Institute, Cary, NC})\). We first analyzed the characteristics of the study participants by sex. We compared means and proportions by Student’s \(t\)-test and the \(\chi^2\)-statistic, respectively. Both univariate and multivariate regression analyses were performed to search for determinants of the PI, which was used as dependent variable in the subsequent regression analyses. The \(P\) values
for explanatory variables to enter and stay in the models were set at 0.10. We considered the following covariables: sex, age, body mass index, current smoking and alcohol intake, plasma glucose, serum total cholesterol, heart rate, and mean arterial pressure. Univariate analyses between PI and each of the arterial stiffness measures were performed. The arterial measures were closely correlated and therefore analyzed in separate multivariate regression models to avoid collinearity. We tested collinearity using the variance inflation factor as implemented in the PROC REG procedure of the SAS software. We performed the Shapiro–Wilk test and Durbin–Watson test to check the normality and independence of the residuals in the linear regressions, respectively.

**RESULTS**

**Characteristics of the participants**

The 334 participants’ age ranged from 19.0 to 81.0 years. The brachial blood pressure averaged (± s.d.) 134 ± 15 mm Hg systolic and 79 ± 9 mm Hg diastolic. Of all participants, 113 (33.8%) were hypertensive, 56 (16.8%) were current smokers, and 65 (19.5%) reported regular alcohol intake. Compared to men (Table 1), women had faster mean blood flow velocity at MCA (68.0 ± 15.0 vs. 58.3 ± 14.7 cm/s; *P < 0.001*) but lower PI (75.4 ± 11.0 vs. 82.3 ± 15.0; *P < 0.001*).

**Correlates of the PI**

In single regression analysis, the PI increased with age (*r* = 0.25; *P < 0.001), but was not correlated with body mass index (*r* = 0.05; *P = 0.36). Furthermore, the PI was negatively correlated with heart rate and mean arterial pressure on 24-h ambulatory monitoring. The correlation coefficients with heart rate and mean arterial pressure were −0.22 (*P < 0.001*) and −0.15 (*P = 0.005*), respectively.

In stepwise multiple regression analyses, sex (women vs. men, −8.57 ± 1.50%; *P < 0.001*), age (0.39 ± 0.06% per year; *P < 0.001*), current smoking (smokers vs. non-smokers, 3.50 ± 2.03%; *P = 0.086*) and alcohol intake (drinkers vs. nondrinkers, −3.79 ± 1.80%; *P = 0.036*) 24-h heart rate (−0.37 ± 0.10% per heart beat; *P < 0.001*) and 24-h mean arterial pressure (−0.23 ± 0.08% per mm Hg; *P = 0.0049*) explained 24.6% of the variance of the PI.

**Association of the PI with measures of arterial stiffness**

In unadjusted analyses the PI at the MCA increased (Figure 1; *P < 0.001*) with pulse pressure on brachial or central measurement at the office and with the 24-h pulse pressure. The PI also increased (Figure 2; *P ≤ 0.036*) with cf-PWV and ba-PWV. Five measures of arterial stiffness were closely (*P < 0.001*) intercorrelated, with a correlation coefficient ranging from 0.37 between cf-PWV and 24-h pulse pressure to 0.75 between central and brachial pulse pressures (bPPs).

The multivariable-adjusted analyses with adjustments applied for significant covariables identified by stepwise regression appear in Table 2. The PI at the MCA significantly (*P ≤ 0.045*) increased with all measures of arterial stiffness after adjustment for age, sex, current smoking, alcohol intake, 24-h heart rate, and mean arterial pressure (Table 2).

When we included pulse pressure on brachial and central measurement and 24-h pulse pressure together with the covariables into the same model to determine which pulse pressure was more closely related to the PI, the variance inflation factors for pulse pressure exceeded 6, highlighting a major problem of collinearity. We therefore determined the fraction contributed by each pulse pressure to the total variance of the PI explained by each model. In explaining the PI, bPP ranked first (partial *r² = 0.25*), 24-h pulse pressure second (partial *r² = 0.20*) and central pulse pressure (cPP) third (partial *r² = 0.14*, Table 2). When cf-PWV and ba-PWV were included in the same model, the variance inflation factor was <2.24. In the latter model, ba-PWV retained significance, whereas cf-PWV...
did not. The increase in the PI for a 1 s.d. increase amounted to 3.54% (95% confidence interval (CI), 1.56–5.52; \( P < 0.001 \)) for ba-PWV and −0.19% (95% CI, −2.03–1.64; \( P = 0.84 \)) for cf-PWV after multivariate adjustment. In a further step of the analysis, we constructed a model including both bPP and ba-PWV in addition to the covariables. The increase in the PI for a 1-s.d. increase amounted to 6.92% (95% CI, 5.49–8.35; \( P < 0.001 \)) for bPP and −0.29% (95% CI, −1.96–1.38; \( P = 0.73 \)) for ba-PWV, respectively.

**Sensitivity analyses**

Our study population included 113 hypertensive patients who were diagnosed according to office blood pressure. In consistent with our findings in the whole study population, the PI was significantly (\( P < 0.01 \)) associated with pulse pressure measures and ba-PWV in both univariate and multivariate analyses in this hypertensive subgroup. The variance of PI was mainly explained by pulse pressure measures (39–67% of total variance), and was very little explained by ba-PWV (5%). No significant association was observed between the PI and cf-PWV (\( P > 0.47 \)).

Our results remained consistent after we excluded the seven patients with a mean flow velocity exceeding 140 cm/s at MCA, which indicates an asymptomatic artery stenosis of 50% or more.\(^\text{18}\) Similar results were also observed when heart rate and mean arterial pressure on 24-h ambulatory measurement in the multivariate models were replaced by that of office measurement (data not shown).

**DISCUSSION**

The MCA is one of the three major paired arteries that supplies close to 80% of the blood to the brain hemispheres. The present report focused on the association of the flow pattern in the MCA and various measures of arterial stiffness in the systemic arterial circulation. Our key finding was that blood flow pulsatility in the MCA as captured by the PI was closely related to pulse pressure in the systemic circulation, whereas PWV in the large arteries was also, albeit weakly associated with the flow pattern in the MCA. In models including both pulse pressure and PWV, PWV lost significance, suggesting that increasing arterial stiffness in the systemic circulation influences the flow pattern in the cerebral circulation via widening of the pulse pressure. ba-PWV was a slightly stronger correlate of the PI in the MCA than cf-PWV, probably because the travel path to compute ba-PWV involves both elastic and muscular arteries, whereas cf-PWV reflects only stiffness of the central elastic arteries.
Table 2 | Multivariable-adjusted associations of the pulsatility index at the middle cerebral artery with measures of arterial stiffness

<table>
<thead>
<tr>
<th></th>
<th>β (95% CI)</th>
<th>P</th>
<th>r²/ R²</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachial PP (+10.8 mm Hg)</td>
<td>6.78 (5.53–8.03)</td>
<td>&lt;0.001</td>
<td>0.25/0.43</td>
<td>58.1</td>
</tr>
<tr>
<td>Central PP (+10.1 mm Hg)</td>
<td>5.56 (4.01–7.11)</td>
<td>&lt;0.001</td>
<td>0.14/0.33</td>
<td>42.4</td>
</tr>
<tr>
<td>24-h PP (+8.6 mm Hg)</td>
<td>7.58 (6.29–8.87)</td>
<td>&lt;0.001</td>
<td>0.20/0.46</td>
<td>43.5</td>
</tr>
<tr>
<td>cf-PWV (+1.5 m/s)</td>
<td>1.59 (0.042–3.14)</td>
<td>0.045</td>
<td>0.0094/0.24</td>
<td>3.92</td>
</tr>
<tr>
<td>ba-PWV (+2.3 m/s)</td>
<td>3.46 (1.79–5.13)</td>
<td>0.0074</td>
<td>0.017/0.27</td>
<td>6.30</td>
</tr>
</tbody>
</table>

Covariates in the models included sex, age, current smoking and alcohol intake, 24-h heart rate and 24-h mean arterial pressure. Association sizes (β) with 95% confidence intervals (CI) were shown. They express the increase in the pulsatility index independently associated with a 1-s.d. increase in the measure of arterial stiffness (given between parentheses). P indicates the significance of the association. r² is the partial coefficient of determination and R² the coefficient of multiple determination. % expresses the relative contribution of the measure of arterial stiffness to the total amount of variance in the pulsatility index explained by the multivariate model. PP, pulse pressure; ba-PWV, brachial-ankle pulse wave velocity; cf-PWV, carotid-femoral pulse wave velocity.

Few studies addressed the relation between the flow pattern in cerebral artery and arterial stiffness in the systemic circulation. To the best of our knowledge, Kwater’s study is the only article currently available.\(^9\) This study showed that the PI at the MCA was independently related to age, bPP and cf-PWV.\(^9\) Our current observations expand Kwater’s finding by showing that the PI is also related to cPP, the 24-h pulse pressure, and cf-PWV and ba-PWV. We also demonstrated that pulse pressure is a stronger correlate of the PI than PWV. However, in the association with the PI, we did not observe any superiority of central over bPPs. On the contrary, bPP, regardless of whether it was measured at office or during 24-h ambulatory monitoring, was more closely correlated with PI than cPP. There was controversy over the accuracy of the central blood pressure estimation by the SphygmoCor device.\(^20\) However, it is not clear whether current observations were due to a specific device or other pathophysiological mechanisms. Further studies with a different central blood pressure measuring technique are warranted.

Our present study, along with others,\(^9,21\) illustrates the potential of transcranial Doppler as a noninvasive instrument in clinical research. The technique is widely used in China. In the Rotterdam study, investigators\(^9\) explored the association between transcranial Doppler measurements and the risk of stroke in a general population. Among 2,022 stroke-free participants, followed up for 5.1 years, the incidence of total (n = 122) and ischemic stroke (n = 89) increased with higher MCA flow velocity. The hazard ratios for fatal stroke contrasting top vs. bottom tertiles were 1.74 (95% CI, 1.09–2.77) for mean flow velocity, 1.63 (95% CI, 1.03–2.58) for end-diastolic flow velocity, and 1.33 (95% CI, 0.86–2.08) for peak systolic flow velocity. Moreover, an increased PI at the MCA is often reported in conditions that predispose to cerebrovascular disease, such as diabetes mellitus,\(^22\) hypertension,\(^23\) or advanced age.\(^24\) Kidwell et al.\(^25\) measured the PI at the MCA by transcranial Doppler and performed magnetic resonance imaging in 55 consecutive patients during a 2-year period. The correlations between the PI and brain lesions were 0.52 (P < 0.001) for periventricular hyperintensity, 0.54 (P < 0.001) for deep white matter hyperintensity and 0.31 (P = 0.02) for lacunar disease. After multivariable adjustment, the PI remained an independent predictor of white matter disease.

Our current findings showed a weak but significant association between the PI at MCA and PWV. These observations are in keeping with previous studies,\(^4,26\) showing that the risk of stroke or cerebrovascular events increased with aortic stiffness. Laurent and colleagues\(^4\) enrolled 1,715 hypertensive patients without overt cardiovascular disease in a follow-up study lasting 7.9 years on average. A 1-s.d. elevation (4 m/s) in aortic PWV was associated with a 39% higher risk of fatal stroke. Brandts et al.\(^5\) demonstrated a significant association between the odds ratio of lacunar brain infarcts and PWV in the aortic arch, independent of sex, age, and hypertension duration.

The present study must be interpreted within the context of some potential limitations. First, our study was not prospective and the sample size was relative small. Second, younger or middle-aged patients without high cardiovascular risk made up the majority of our study subjects. They were referred to a hypertension clinic for ambulatory blood pressure monitoring and are not representative of the general population. On the other hand, all participants were off treatment when examined, which enhances the interpretability of our current observations.

Our current findings might have clinical implications. Indeed, the microcirculation in the brain is vulnerable, because the arteries feeding the brain capillaries readily transmit pulsations.\(^27\) In a Japanese study of 56 healthy volunteers, 20–72 years old, the pressure waveform was similar in the proximal aorta and carotid arteries.\(^28\) There was close association (r = 0.913; P < 0.001) between the pressure augmentation index and flow augmentation index. The pressure augmentation index is a measure of wave reflections.\(^29\) The similarities between the carotid flow and pressure augmentation indices indicates that fluctuations in flow are likewise a consequence of wave reflections from peripheral sites. These observations suggest that brain arteries are subjected to high pulsatile circumferential stress and high longitudinal shear stress.

In conclusion, the blood flow in the MCA is closely associated with the pulsatile component of blood pressure in the systemic circulation. Arterial stiffening of the large arteries as measured by PWV is a risk factor for cerebrovascular disease probably because it increases the pulsatile component of blood pressure, which is transmitted to the cerebral capillaries. Further prospective studies of cerebrovascular phenotypes and outcomes with serial measurements of the pulsatile components of blood pressure along with local and segmental arterial stiffness in the large systemic arteries should substantiate our current findings.

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