Transcranial Doppler Ultrasound for Screening Cerebral Small Vessel Disease
A Community Study

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Background and Purpose—We explored the association between pulsatility index (PI) as derived from transcranial Doppler ultrasound with various measures of small vessel disease in the community.

Methods—We performed transcranial Doppler and magnetic resonance imaging in 205 consecutive community-dwelling elderly subjects who were participants of the Shanghai Aging Study. We investigated the association between middle cerebral artery (MCA) PI with measures of white matter lesions (WML), lacunes, and microbleeds.

Results—Multiple logistic regression found that MCA PI was associated with severe WML (odds ratio, 1.33 per 0.1 increase in PI; 95% confidence interval, 1.04–1.70; P=0.02). At optimal MCA PI cut-off, the area under curve, positive predictive value, and negative predictive value were 0.70 (95% confidence interval, 0.60–0.80), 34.9%, and 85.6%, respectively, for detection of severe WML. No association was found between MCA PI and measures of lacunes or microbleeds.

Conclusions—PI correlates with WML severity. With a high negative predictive value, the chance of having severe WML with a normal PI is low. Transcranial Doppler may guide selective magnetic resonance imaging scanning for the detection of WML in the community. (Stroke. 2012;43:00-00.)

Key Words: small vessel disease n transcranial Doppler ultrasound

W hite matter lesions (WML), lacunes, and microbleeds observed in magnetic resonance imaging (MRI) are assumed to be manifestations of cerebral small vessel disease (SVD).1 Although these lesions were initially considered as “silent,” recent longitudinal studies show that presence of these lesions greatly increases future risks of dementia, stroke, and mortality.1 Authorities have thus recommended that preventive trials should target SVD, preferably at its “subclinical” stage.1,2 However, using MRI to screen for “subclinical” lesions for recruiting subjects into trials is not cost-effective. To date, simple screening methods for SVD are lacking. The pulsatility index (PI), as derived from transcranial Doppler ultrasound (TCD), has long been proposed to reflect vascular resistance of small vessel.3 We explored the association between PI and measures of SVD and utility of TCD as a screening tool for SVD in the community.

Subjects and Methods

Subjects
Subjects were participants of the Shanghai Aging Study (SAS), which investigated the prevalence of mild cognitive impairment/dementia in Jing’an Temple Community. Inclusion criteria were age 60 years or older, no atrial fibrillation, no contraindication for MRI, no intracranial middle cerebral artery (MCA) stenosis as defined by MCA peak systolic velocity of ≥140 cm/s on TCD, and provision of informed consent. Ethics approval was obtained from Huashan Hospital. This study recruited consecutive subjects of SAS between November 2009 and May 2010. We obtained basic demographic, clinical, and cognitive information for our subjects. We diagnosed dementia using Diagnostic and Statistical Manual, 4th edition.

TCD and MRI Examination
A 2-MHz pulsed Doppler hand-held probe insonated the MCA through temporal window above the zygomatic arch at a depth of 64 mm. The PI was automatically generated according to the formula: PI=(peak systolic velocity−end diastolic flow velocity)/
mean flow velocity. We calculated mean MCA PI by averaging bilateral MCA PI.

MRI examinations were performed on a 1.5-T Scanner (GE) with 3-dimensional T1-weighted, T2-weighted, axial fluid-attenuated inversion recovery, and gradient echo T2-weighted MRI. A single trained neurologist (Y.X.) blinded to TCD results graded these measures. Intraclass correlation based on rerating 20 randomly selected MRI was excellent: age-related white matter changes score was 0.92 (95% confidence interval [CI], 0.82–0.97), number of lacunes was 0.87 (95% CI, 0.72–0.95), and microbleed was 0.94 (95% CI, 0.85–0.98).

**Statistics**

Total WML volume was categorized into quartiles. Number of lacunes and microbleeds were categorized into 0, 1, and ≥2. We performed univariate and multivariate models to test the association between mean MCA PI, clinical variables, and the 3 SVD measures. Because we found that WML quartiles were associated with MCA PI, we made univariate comparison between those with and without severe WML (ie, 4th quartile), followed by multiple logistic regression models to identify independent risk factors for severe WML. Using receiver-operator characteristics analysis, we explored the optimal PI cut-off for detecting severe WML. Because we found that WML quartiles were associated with MCA PI, we used univariate and multivariate models to test the association between MCA PI and SVD measures. Because temporal window was absent in 46 subjects, analysis of the association between MCA PI and SVD measures was eventually performed among 159 subjects.

**Results**

Table 1 shows characteristics of the subjects. Univariate analysis showed that only age, gender, and WML quartiles...
were associated with mean MCA PI. Multivariate linear regression models revealed that only WML quartiles independently associated with mean MCA PI (β=0.25; P<0.01). There was no association between PI with measures of lacunes or microbleeds.

Table 2 shows comparison between those with and without severe WML. Multiple logistic regression found that only age (odds ratio, 1.23; 95% CI, 1.11–1.36; P<0.01) and mean MCA PI (odds ratio, 1.33 per 0.1 increase in PI; 95% CI, 1.04–1.70; P=0.02) were associated with severe WML. In the receiver-operator characteristics, MCA PI differentiated those with and without severe WML at an optimal cut-off of 1.04, with area under curve of 0.70 (95% CI, 0.60–0.80), sensitivity of 63.0%, specificity of 72.0%, positive predictive value of 34.9%, and negative predictive value of 85.6%.

Discussion
In this community study, we found that MCA PI was associated with WML severity (Figure). At optimal PI cut-off, although positive predictive value was low, the negative predictive value was high. Hence, for those with normal PI, the chance of having severe WML is low. For purpose of recruiting subjects with subclinical SVD into clinical studies, TCD may guide selective scanning by arranging MRI only for those with high PI. Note that we failed to find association between other TCD parameters (eg, peak systolic velocity) and WML severity. This emphasizes the unique relationship between PI and WML.

The strengths of this study are the community sample, quantitative measurement for WML severity, and the collection of many clinical data. However, a limitation is the small number of subjects having multiple lacunes (n=20) and microbleeds (n=7). Hence, the association between PI and these lesions requires clarification from a larger study.

In conclusion, PI is associated with WML severity. Further studies are needed to validate TCD as a screening tool for SVD. However, until effective treatments become available, screening “subclinical” SVD using TCD remains a research endeavor.

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Disclosures
None.

References
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