Increased Pulsatility of the Intracranial Blood Flow Spectral Waveform on Transcranial Doppler Does Not Point to Peripheral Arterial Disease in Stroke Patients

Kristian Barlinn, MD,*† Stanislava Kolieskova, MD,*‡§
Reza Bavarsad Shahripour, MD,* Jessica Kepplinger, MD,†
Amelia K. Boehme, MPH,|| Timo Siepmann, MD,† Volker Puetz, MD,†
Ulf Bodechtel, MD,† William D. Jordan, MD,¶ and Andrei V. Alexandrov, MD*#

Background: Peripheral arterial disease (PAD) is common in patients with acute cerebral ischemia. Indexes of resistance derived from the systolic and diastolic velocities are routinely used in diagnostic transcranial Doppler (TCD) to detect intracranial arterial disease. We sought to explore whether these indexes can predict the presence of PAD in acute cerebral ischemia. *Methods:* We prospectively evaluated consecutive patients with acute cerebral ischemia. On TCD, peak-systolic and end-diastolic velocities in both middle cerebral and basilar arteries were manually measured to calculate pulsatility index (PI) and resistance index (RI). Increased resistance was defined as PI equal to 1.2 or more and RI equal to .75 or more. Ankle–brachial index (ABI) measurements were performed and an ABI equal to .9 or more was considered predictive of definite PAD. *Results:* We included 95 patients (45 male, 50 female) aged 66 ± 9 years with a median National Institutes Health Stroke Scale score of 3 (interquartile range, 8) points. The ABI was abnormal and consistent with definite PAD in 24 of 95 (25.3%; 95% confidence interval [CI], 16.4-34.2) patients. Increased PI did not differ among patients with and without PAD (20.8% vs. 28.2%, $P = .60$). Only 1 patient with PAD had increased RI as opposed to 4 patients without PAD (4.2% vs. 5.6%, $P = 1.0$). Increased PI was not found to be an independent predictor of PAD (odds ratio [OR], .68; 95% CI, .22-2.12; $P = .51$). Increases in both PI and RI independently predicted arterial hypertension (OR, 1.62; 95% CI, 1.19-2.21; $P = .002$ and OR, 3.20; 95% CI, 1.51-6.77; $P = .002$, respectively). *Conclusions:* Our findings indicate that PAD cannot be inferred from intracranial flow parameters predictive of arterial disease and risk factors such as hypertension among patients with acute cerebral ischemia. **Key Words:** Stroke—peripheral arterial disease—intracranial disease—transcranial Doppler.

From the *Department of Neurology, Comprehensive Stroke Center, University of Alabama Hospital, Birmingham, Alabama; †Dresden University Stroke Center, Department of Neurology, University Hospital Carl Gustav Carus Dresden, University of Technology Dresden, Dresden, Germany; ‡International Clinical Research Centre, St. Anne's University Hospital, Brno, Czech Republic; §Neurology Department, Masaryk University, Brno, Czech Republic; ||Department of Epidemiology, School of Public Health, University of Alabama Hospital, Birmingham, Alabama; ¶Department of Vascular Surgery, University of Alabama Hospital, Birmingham, Alabama; and #Department of Neurology, The University of Tennessee Health Science Center, Memphis, Tennessee.

Received June 2, 2014; revision received August 12, 2014; accepted August 16, 2014.

Dr. Alexandrov serves as consultant to Cerevast Therapeutics, Inc. The other authors have no conflicts to report.

Address correspondence to Kristian Barlinn, MD, Department of Neurology, University Hospital Carl Gustav Carus Dresden, University of Technology Dresden, Fetscherstr. 74, 01309 Dresden, Germany. E-mail: kristian.barlinn@uniklinikum-dresden.de.

1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2014.08.014

Peripheral arterial disease (PAD) affects up to 12% of the middle aged and 29% of the elderly adults and is linked to polyvascular disease.[1] Patients with acute ischemic stroke commonly have widespread atheromatous disease with up to 1 in 2 ischemic stroke patients having PAD of any severity.[2-5] Recent studies have shown that ankle–brachial index (ABI) values suggestive of PAD are associated with an increased risk for recurrent stroke and all-cause long-term mortality.[4-6] Although the presence of PAD influences the choice of a specific antiplatelet treatment for secondary prevention of noncardioembolic stroke,[6-8] screening for PAD is not routinely performed during hospital stay and, if any, is commonly restricted to evaluation of patients' self-reported symptoms.[9] However, this approach of subjective measures may not be reliable to detect PAD as only 1 in 3 patients with an abnormal ABI develop clinically apparent symptoms.[10-12] This problem is further confounded by the inability to walk long distances by most patients suffering a disabling stroke. Hence, PAD still remains and underdiagnosed disease in patients with acute ischemic stroke.[2]

Both pulsatility index (PI) and resistance index (RI) are routinely used in diagnostic transcranial Doppler (TCD) studies of stroke patients to assess resistance to intracranial blood flow.[13,14] We recently showed that diffuse intracranial arterial disease is frequent in ischemic stroke patients and can be reliably predicted by abnormal intracranial blood flow parameters on TCD.[15] Specifically, a low mean flow velocity (MFV) in the presence of high PI was shown to be independently associated with diffuse intracranial arterial disease when validated with invasive angiography. Another study found that the degree of diffuse intracranial arterial disease indicated by the values of MFV and PI in this specific TCD pattern is an independent prognostic factor for recurrent vascular events in acute ischemic stroke patients.[16] Similar patterns on TCD were found in subjects suffering from vascular dementia in whom autopsy revealed a correlation between cognitive decline and diffuse atheromatous disease in brain vessels cumulatively adding to 80% or greater reduction of patency of these vessels.[17]

Although both PAD and diffuse intracranial arterial disease share similar risk factors and underlying pathomechanisms, it remains unclear whether there is a predictive relationship between TCD-based measures of diffuse intracranial arterial disease and PAD. To elucidate the association between diffuse intracranial arterial disease and PAD, we sought to explore whether the PI or RI on TCD can predict the presence of PAD in patients with acute cerebral ischemia. Specifically, we hypothesized that an increased resistance to intracranial blood flow is more frequent in patients with acute cerebral ischemia when PAD is also present. If abnormal TCD findings can raise suspicion that stroke patients have coexistent PAD, such information could be used to refer these patients to specific diagnostic evaluation for PAD and consideration for treatment options.

Methods

Study Population

We prospectively evaluated consecutive patients with acute cerebral ischemia (acute ischemic stroke or transient ischemic attack) and 18 years of age or older who were admitted to 2 tertiary stroke centers (University of Alabama at Birmingham Hospital, United States and University Hospital Carl Gustav Carus Dresden, Germany) from June 2011 to March 2014. Demographic characteristics, vascular risk factors, clinical variables, and stroke etiology according to Trial of Org 10172 in Acute Stroke Treatment classification[18] were collected during hospitalization. Patients were found to have arterial hypertension, if they had increased systolic blood pressure (SBP) of 140 mm Hg or more or diastolic blood pressure of 90 mm Hg or more during hospitalization or any antihypertensive medication before. Diabetes mellitus was defined as fasting serum glucose greater than or equal to 7.0 mmol/L or serum glucose greater than or equal to 11.1 mmol/L after an oral glucose tolerance test or prior use of antidiabetic therapy. Dyslipidemia was defined as fasting serum low-density lipoprotein cholesterol greater than or equal to 2.6 mmol/L or total cholesterol greater than or equal to 5.2 mmol/L or prior use of lipid-lowering medication.[19] Smoking status was defined as current use. Atrial fibrillation was diagnosed by electrocardiogram before or during hospitalization. Coronary artery disease was identified through self-reporting and previous medical documentation. Experienced members of the stroke service assessed baseline stroke severity with the National Institutes Health Stroke Scale score. Patients who had neither temporal nor suboccipital acoustic windows on TCD examination were not included. The study was approved by the institutional review boards of both University of Alabama at Birmingham and University Hospital Carl Gustav Carus Dresden. Written informed consent was obtained from each patient before any study-related procedures.

Transcranial Doppler Measurement

TCD (2 MHz) sonography (EZ-Dop or Multi-Dop; DWL, Singen, Germany) was performed at bedside or at the vascular laboratory within 5 days from stroke symptom onset. All TCD studies were performed by stroke neurologists experienced in vascular sonography and certified by the American Society of Neuroimaging or equivalent. We used our standard insonation protocol for a complete TCD examination as previously described.[20,21] Peak-systolic (PSV) and end-diastolic (EDV) velocities were manually measured using an optimized spectral display of a complete 4-cardiac cycle sweep without arrhythmias