Published in final edited form as:

J Stroke Cerebrovasc Dis. 2015 January ; 24(1): 189–195. doi:10.1016/j.jstrokecerebrovasdis.2014.08.014.

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

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Abstract

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],

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The other authors have no conflicts to report.

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.

Keywords

Stroke; peripheral arterial disease; intracranial disease; transcranial Doppler

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 an 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 classification¹⁸ 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 (2MHz) 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 (Fig 1), and MFV was calculated as $EDV + (PSV - EDV)/3$. All measurements were obtained from

stored TCD spectra of the middle cerebral arteries (MCAs) at 50–65 mm and basilar artery (BA) at 85–95 mm insonation depths. We used a sample volume of 12 mm or less.

The PI was manually calculated for each artery by using the Gosling and King formula:¹³ $PI = (PSV - EDV) / MFV$. PI values of 1.2 or more were considered to indicate increased distal resistance to blood flow (normal range, .6–1.1).²⁰ We defined increased PI as 1.2 or more and overall PI as the highest PI of each patient's vessels. Based on our previous findings and the fact that increased resistance results in a drop of flow volume and therewith flow velocity, we considered the combination of PI equal to 1.2 or more and low MFV (<30 cm/second) for the MCA and low MFV (<20 cm/second) for the BA predictive of intracranial arterial disease.¹⁵ We also included a ratio of PI and MFV (calculated as $100 \times PI / MFV$) as this likely reflects intracranial arterial disease and was found to be related to recurrent vascular events in patients with acute ischemic stroke.¹⁶ The highest PI/MFV of each patients' vessels was taken for analysis. As there is controversy as to which index better describes intracranial resistance to flow, we also calculated the Pourcelot RI using the formula²²: $RI = (PSV - EDV) / PSV$, with values equal to .75 or more considered increased. Overall RI was defined as the highest RI of each patient's vessels.

In patients with atrial fibrillation, TCD sweeps were only used for assessment of PI and RI when no arrhythmias were evident. For the present analysis, we only used TCD measurements from the asymptomatic (ie, non-ischemic) site of the brain to avoid confounding effects on TCD RIs because of ischemia-induced changes in cerebral hemodynamics. Extracranial arteries were evaluated by duplex ultrasound, computed tomography, or magnetic resonance angiography as part of routine stroke workup.

ABI Measurement

The ABI measurements were performed according to current American Heart Association guidelines.²³ Bilateral brachial and ankle blood pressure measurements were taken using a standard of care blood pressure cuff adjusted to the patients' arm and leg size and a handheld continuous-wave high-frequency (4- to 8-MHz) Doppler ultrasound device (EZ-Dop or Multi-Dop; DWL). The ankle SBP measurements were taken in both the posterior tibial and the dorsal pedis arteries on each leg. For each side, the average from 2 brachial and ankle SBP measurements was recorded. The ABI was calculated by dividing the highest ankle SBP (posterior tibial or dorsal pedis) of each leg by the higher of the 2 brachial SBP. According to current recommendations for diagnosis of PAD, an ABI of .91–.99 in either leg was considered as borderline and an ABI of .9 or less as abnormal and predictive of PAD.²³ Poorly compressible or noncompressible leg arteries defined as ABI more than 1.4 were excluded from the present analysis. The lowest ABI was considered as each patient's overall ABI.

All patients had to rest in supine position for at least 5 minutes before TCD and ABI examinations. Both examinations were performed within 1 setting without any time delay by the same experienced sonographer.

Statistical Analysis

Continuous and noncontinuous variables are presented as mean $\pm$ standard deviation, median (interquartile range, IQR), and percentages (with corresponding 95% confidence interval, CI). Statistical comparisons between patients with and without PAD were performed using the chi-square test, Fisher exact test, Student *t* test, and Wilcoxon rank sum, where appropriate. Logistic and linear regression models were built to assess if TCD resistance indices were associated with dependent variables of interest. Baseline variables that were significantly different between patients with and without PAD were built into the adjusted models. We also evaluated TCD predictor variables of arterial hypertension with adjustments made for known confounding factors. Significance level was set at .05. Associations are presented as odds ratio (OR) with corresponding 95% CI. Pearson correlation coefficient (for normally distributed data) was used to examine whether there is a relation between PI/RI and ABI/SBP. Statistical analyses were conducted with STATA software (Version 12.1; StataCorp, College Station, TX).

Results

We prospectively enrolled a total of 101 patients with acute cerebral ischemia. Five patients with poorly or noncompressible (ABI > 1.4) leg arteries and 1 patient with absent TCD measurements for the asymptomatic site of the brain were excluded from the present analysis. The study population consisted of a total of 95 acute cerebral ischemia patients (45 males and 50 females, mean age was 66.3 ± 9.0 years) with 182 TCD measurements of the nonaffected intracranial arteries available (MCA left, *n* = 55; MCA right, *n* = 47; BA, *n* = 80). Of these patients, 65 (68.4%) had an acute ischemic stroke and 30 (31.6%) had a transient ischemic attack. Median National Institutes Health Stroke Scale score on admission was 3 (IQR, 8) points. Stroke etiology according to the Trial of Org 10172 in Acute Stroke Treatment criteria was classified as large artery atherosclerosis in 58.9%, cardioembolism in 12.6%, small vessel disease in 11.6%, and other or undetermined etiology in 16.9% of patients. Symptomatic intra or extracranial steno-occlusive disease (ie, 70% stenosis or occlusion) was diagnosed in 44 of 95 (46.3%) and asymptomatic extracranial steno-occlusive disease in 4 of 95 (4.2%) patients. Eight of 95 (8.4%) patients had known PAD, and 13 of 95 (13.7%) reported symptoms suggestive of PAD.

Median time elapsed between stroke onset and TCD/ABI examinations were 1.5 days (IQR, 1 day). The mean overall ABI was $.97 \pm .28$. The ABI was borderline or abnormal in 46 of 95 (48.4%) patients including 24 of 95 (25.3%; 95% CI, 16.4–34.2) patients with ABI consistent with PAD ($.9$). PAD was considered severe in 3.2% (ABI $.4$) and mild-to-moderate in 22.1% (ABI, .41–.9). Baseline characteristics were similar in patients with (*n* = 24) and without PAD (*n* = 71), except for dyslipidemia (63% vs. 83%, *P* = .048; Table 1).

On TCD, mean overall PI was $1.06 \pm .23$ with 25 of 95 (26.3%) patients having increased PI (> 1.2) in 1 artery and 19 of 95 (20%) in 2 arteries. An increased PI in combination with low MFV present in 1 artery was found in 6 of 95 (6.3%). No patient had an increased PI and low MFV present in 2 arteries. Mean overall PI/MFV ratio was 3.1 ± 1.5 . The overall PI did not differ among patients with and without PAD ($1.00 \pm .25$ vs. $1.08 \pm .23$, *P* = .14). There were no differences in both increased PI in at least 1 (20.8% vs. 28.2%, *P* = .60) and

increased PI in 2 arteries or (12.5% vs. 11.3%, $P = 1.0$) between patients with and without PAD. We also found no differences regarding combination of increased PI and low MFV in at least 1 artery between patients with and without PAD (4.2% vs. 7.0%, $P = 1.0$). The PI/MFV ratio was not different either (2.58 ± 1.28 vs. 3.24 ± 1.57 , $P = .066$). There was no correlation between overall PI values and the ABI ($r = -.045$, $P = .67$). The overall results did not change after excluding patients who had extracranial steno-occlusive (70% stenosis or occlusion) disease proximal to the insonated site because this may produce downstream flow changes potentially falsifying TCD RIs (eg, increased PI in patients with PAD: 20.8% vs. no PAD: 27.9%, $P = .60$). Likewise, overall results remained the same when we considered only acute ischemic stroke patients with large artery atherosclerosis as the underlying stroke etiology (eg, increased PI in patients with PAD: 25.0% vs. no PAD: 25.0%, $P = 1.0$).

On univariate analysis, increased PI did not emerge as a predictor of PAD (OR, .67; 95% CI, .22–2.04; $P = .48$). After adjusting for dyslipidemia (as this variable was imbalanced between the study groups), the results did not change (OR, .68; 95% CI, .22–2.12; $P = .51$). Similarly, overall PI did not predict ABI ($P = .46$). Interestingly, all patients with increased PI had arterial hypertension compared with those with normal PI (100% vs. 77%, $P = .01$). The overall PI was positively correlated with SBP ($r = .282$, $P = .006$) and strongly predicted arterial hypertension (OR, 1.62; 95% CI, 1.19–2.20; $P = .002$; per .1 unit increase). The latter association did not change after adjustment for known confounders like age and sex (OR, 1.62; 95% CI, 1.19–2.21; $P = .002$).

Regarding RI, mean overall RI was $.61 \pm .08$ with only 5 of 95 (5.3%) patients having RI of .75 or more. The mean RI did not differ among patients with and without PAD ($.59 \pm .09$ vs. $.62 \pm .08$, $P = .11$). Only 1 patient with PAD had increased RI as opposed to 4 patients without PAD (4.2% vs. 5.6%, $P = 1.0$). After adjustment for age and sex, the overall RI was predictive of arterial hypertension (OR, 3.20; 95% CI, 1.51–6.77; $P = .002$; per .1 unit increase), but not of ABI ($P = .39$). Likewise, there was a mild positive correlation between the overall RI and the SBP ($r = .285$, $P = .005$), but not ABI ($r = -.0414$, $P = .69$).

Discussion

Our study confirmed that conventional indexes of resistance to arterial blood flow in the proximal intracranial arteries are associated with arterial hypertension. However, we did not show that these indexes could predict PAD in patients with acute ischemic stroke. Nevertheless, the high prevalence of mostly asymptomatic PAD in our patients warrants further investigation to identify stroke patients at highest risk of PAD beyond traditional risk factors assessment for polyvascular atherosclerosis.

Although the high comorbidity of ischemic stroke and PAD and its detrimental impact on stroke outcome and recurrence has been firmly established, it still remains largely unknown which stroke patients are at highest risk of PAD and should be evaluated with ABI measurements.¹ Several studies found traditional vascular risk factors such as diabetes mellitus, atrial fibrillation, and increasing age independently associated with PAD in acute stroke patients. However, because pathogenesis seems similar between the 2 diseases, the

phenotypic expression might be entirely different making it difficult, if not impossible, to select stroke patients for ABI screening solely based on vascular comorbidities.^{3,4} Conversely, a one-size-fits-all approach by screening all acute stroke patients is barely feasible in most stroke centers worldwide nor is it supported by current stroke guidelines.²⁴

TCD has been used to assess intracranial resistance to flow and establish surrogate findings from intracranial blood flow measurements for several clinical indications.^{25–27} High resistance to flow in the proximal intracranial vessels has been previously shown to be predictive of diffuse intracranial atherosclerotic disease¹⁵ but, to date, there are no published data on the relation between TCD resistance variables and PAD. To the best of our knowledge, this is the first study that assessed the predictive utility of TCD resistance variables for detection of PAD because multiple vascular territories may be affected by atherosclerosis in stroke patients.¹ However, none of our applied TCD resistance patterns (increased PI alone or in combination with low MFV, PI/MFV ratio, RI alone) was capable of unmasking lower limb location of the disease. One explanation might be that the PI strongly reflects downstream increased resistance to flow particularly present in patients with diffuse atherosclerosis and cerebral small vessel disease secondary to chronic hypertension.²⁸ Thus, our TCD findings might be affected by a different pathophysiologic correlate such as small vessel in addition to large vessel atherosclerotic disease. This might also explain why we found such a strong association between the TCD resistance indexes (PI and RI) and arterial hypertension as the latter contributes decisively to the pathogenesis of cerebral small vessel disease.²⁹ Also, these indexes may not describe the cerebrovascular resistance as precise as previously adopted and several factors (eg, cardiac output, extracranial steno-occlusive disease, blood pressure urges) may confound this complex relationship diminishing its validity in clinical practice.^{30,31}

We have recently shown that the combination of increased PI and low MFV was independently associated with angiographically proven diffuse single and multi-vessel intracranial arterial disease.^{15,32} Others confirmed inference of lower extremity atherosclerosis from the atherosclerotic burden in the precerebral vasculature and vice versa.^{33,34} Moreover, consistent with the established risk factor association between intracranial arterial disease and stroke recurrence, Wijnhoud et al¹⁶ found that the higher the PI/MFV ratio on TCD in patients with recent stroke, the more likely a recurrent ischemic event in any of the cerebral, coronary, or peripheral vascular beds will occur (hazard ratio 1.9 for 1 unit increase in the PI/MFV ratio).³⁵ However, while the overall PI/MFV ratio was higher in our cohort (3.1 vs. 2.0), no association with PAD was evident neither with the PI/MFV ratio nor with the combination of increased PI and low MFV values. These contrary results might be attributable to a smaller sample size (as only 1 patient with PAD had the latter TCD pattern) and increasing susceptibility to a type II error in our series. On the other hand, we may speculate that intracranial arterial disease does not constitute an appropriate surrogate to uncover stroke patients with PAD because the etiology of stroke varies considerably and patients with other stroke subtypes (eg, cardioembolism, undetermined cause, and so forth) and free of intracranial arterial disease are also prone to PAD.^{3,4,36} Concordantly, we could not find profound differences in stroke etiology between patients with and without PAD. Thus, although overall negative, it is not a surprise that our additional analysis focusing on patients with atherothrombotic stroke (ie, due to large artery

atherosclerosis) remained insignificant in terms of association between intracranial TCD resistance parameters and PAD.

Our study has limitations. First, no formal sample size estimation was performed, and our study is limited by a relatively small number of patients especially of those who suffered from PAD, although the frequency of PAD in acute ischemic stroke patients observed in our study is consistent with that one reported in the literature.² Moreover, the frequency of PAD may have been underestimated in our sample as patients with poorly and noncompressible arteries, indicating vascular stiffness and calcification and possibly PAD equivalents with increased cardiovascular morbidity and mortality, were not considered in the present analysis.^{37,38} Therefore, future studies should consider toe–brachial index measurements in patients with noncompressible leg arteries to explore the clinical implication of these findings in acute ischemic stroke patients. Second, we cannot exclude observation bias because sonographers also helped consent patients, explained symptoms, and relevance of PAD and thus hear about possible patients symptoms during these discussions. Also, the TCD and ABI tests were performed within the first days of acute stroke. Consequently, altered cerebral hemodynamics may have had an impact on obtained TCD flow and RIs. To avoid this bias, we excluded vessels containing acute occlusions and used TCD data exclusively from the asymptomatic (ie, nonischemic) sites of the brain. Also, our additional analysis excluding patients with severe asymptomatic steno-occlusive disease in the precerebral vasculature did not change the overall results. Finally, we did not keep a screening log precluding any comparisons between patients with present and absent acoustic windows, and we cannot comment on the histopathologic correlate of the underlying intracranial blood flow changes because this is beyond the capability of TCD technique.

Conclusions

Our data indicate that PAD cannot be inferred from intracranial flow parameters predictive of arterial disease in patients with acute cerebral ischemia. Consistent with previous research, our data suggest that PI and RI can be used to predict hypertension in acute cerebral ischemia. The high comorbidity of ischemic stroke and polyvascular atherosclerotic disease warrants further studies to enhance early detection of PAD in the routine workup for stroke.

Acknowledgments

Dr. Alexandrov serves as consultant to Cerevast Therapeutics, Inc.

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Figure 1. Spectral Doppler waveform examples showing (A–C) normal pulsatility in a patient with an ankle–brachial index (ABI) of 1.16, and (D–E) increased pulsatility in a patient with an overall ABI of .48 suggestive of peripheral arterial disease. Abbreviations: BA, basilar artery; EDV, end-diastolic velocity; L-MCA, left middle cerebral artery; PI, pulsatility index; PSV, peak-systolic velocity; RI, resistance index; R-MCA, right middle cerebral artery.

Table 1

Baseline characteristics of patients with and without PAD, N = 95

Variable	PAD (n = 24)	No PAD (n = 71)	P value
Sex, male, n (%)	12 (50)	33 (47)	.82
Age, mean $\pm$ SD, y	66.8 $\pm$ 8.3	66.1 $\pm$ 9.3	.73
Race, n (%)			
Caucasian	17 (71)	55 (77)	.58
African-American	7 (29)	16 (23)	
NIHSS, median (IQR)	5 (0–14)	2 (0–17)	.11
Previous stroke/TIA, n (%)	7 (29)	25 (35)	.63
Vascular risk factors, n (%)			
Arterial hypertension	19 (79)	60 (85)	.54
Dyslipidemia	15 (63)	59 (83)	.048
Nicotine	10 (42)	28 (39)	1.0
Diabetes mellitus	10 (42)	17 (24)	.12
Coronary artery disease	7 (29)	21 (30)	1.00
Atrial fibrillation	4 (17)	8 (11)	.49
TOAST stroke subtype, n (%)			
Large artery atherosclerosis	16 (67)	40 (56)	.08
Cardioembolism	6 (25)	6 (8)	
Small vessel disease	1 (4)	10 (14)	
Other cause	0	2 (3)	
Undetermined cause	1 (4)	13 (18)	
Symptomatic arterial obstruction, n (%) [*]	13 (54)	31 (44)	.48
Asymptomatic arterial obstruction, n (%) [†]	1 (4)	3 (4)	1.0

Abbreviations: IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; PAD, peripheral arterial disease; SD, standard deviation; TIA, transient ischemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

^{*} Intra/extracranial stenosis 70% or occlusion.

[†] Extracranial stenosis 70% or occlusion.