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Comparison of transcranial doppler ultrasound indices in large and small vessel disease cerebral infarction

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Abstract

Background: Atherosclerotic involvement of large and small cerebral arteries leading to infarction is among the most prevalent subtypes of stroke worldwide. The hemodynamic changes due to these arterial pathologies can be studied non-invasively and in real-time by using transcranial Doppler (TCD) techniques. TCD indices of the studied arteries may guide the clinician in differentiating these two underlying arterial pathologies.

Methods: A cross-sectional study of patients with small and large vessel types of cerebral infraction based on the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) stroke classification was undertaken in the inpatient population of neurology service of Razi Hospital, Tabriz, Iran, from October 2018 to October 2019. After clinical diagnosis, all cases underwent TCD studies, brain magnetic resonance imaging (MRI), and brain and cervical four-vessel magnetic resonance angiography (MRA). The results of TCD indices related to major arteries of the circle of Willis were tabulated and compared between large and small vessel subtypes of cerebral infarction.

Results: A statistically significant difference between right middle cerebral artery (MCA) pulsatility index (PI), left MCA PI, right internal carotid artery (ICA) PI, end-diastolic velocity (EDV), left ICA PI, left ICA EDV, left anterior cerebral artery (ACA) PI, and right vertebral artery (VA) PI measures of the two groups was seen ($P < 0.05$). In comparison to the large vessel group, left ACA, right VA, and bilateral MCAs and ICAs in the small-vessel stroke group demonstrated an elevated PI.

Conclusion: A significant increase of PI occurs in the majority of intracranial arteries of patients with small vessel stroke. This makes PI a valuable marker for differentiating strokes with different underlying pathophysiologies.

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Introduction

Stroke has been known as one of the leading causes of mortality and morbidity worldwide.[1] While one

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patient falls victim to stroke every six seconds, this number is estimated to almost double by 2030.[1] Despite enormous pharmaceutical advances in current treatment strategies, ischemic stroke remains a diagnostic and therapeutic challenge as it encompasses a wide range of clinical presentations, degrees of impairment, and various etiologies. Over the past two decades, transcranial Doppler (TCD) ultrasound has been routinely recommended by the American Academy of Neurology to diagnose cerebrovascular diseases and intracranial vascular interventions.[2] Non-invasive, portable, and inexpensive evaluation of intracranial blood flow has been made possible through the use of a pulsed Doppler system, establishing the role of TCD in the real-time monitoring of cerebrovascular ischemia.[3,4] Despite its inherent disadvantage of high operator dependency, TCD has an established value in delineating some mechanisms of thromboembolic strokes with acceptable reproducibility.[5,6] TCD systolic and diastolic velocity measures serve as resistance indices and have found a broad spectrum of applications for studying steno-occlusive diseases of large and small cerebral vessels.[7] Likewise, the pulsatility index (PI) of TCD has traditionally been recognized as an indicator of downstream resistance of cerebral vasculature.[8] Previous studies have revealed a strong association between increased PI and magnetic resonance imaging (MRI) findings of small-vessel ischemia, leading to the introduction of PI as a promising descriptor of the severity of diffuse small vessel diseases (SVDs).[9] The middle cerebral artery (MCA) PI has been associated with the severity of white matter lesions (WML) with a high negative predictive value (NPV) of 85.6%, leaving little chance of the presence of severe WML in subjects with normal PI measures.[10] However, the PI of the MCA has yet failed to serve as the single screening tool for detecting WML among high-risk individuals.[11] The concept of fundamental heterogeneity in the etiopathogenesis and treatment of large and small vessel strokes warrants investigations to find radio-diagnostic markers capable of differentiating the two pathophysiologically distinct conditions.[12,13] Therefore, the current study compared the TCD-derived blood flow velocity and indices between two groups of patients with large and small vessel infarcts.

Materials and Methods

We studied consecutive patients, over two years from October 2018 to October 2019, with ischemic stroke admitted to the neurology service of Razi Hospital affiliated with Tabriz University of Medical Sciences, Tabriz, Iran. Ischemic stroke was defined as a sudden-onset focal neurological deficit lasting > 24 hours, which could be explained by no alternate etiology and initial brain computed tomography (CT) showing no evidence of intracranial hemorrhage.[1]

The inclusion criteria were confirmation of cerebral infarction by brain MRI supported by diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) sequences, evaluation by TCD within 24-48 hours after admission, vascular imaging performed using contrast-enhanced brain and cervical four-vessel magnetic resonance angiography (MRA), and ruling out cardioembolic etiology and tandem intracranial stenosis.

Patients were excluded if any of the following was present: age < 45 years, bilaterally absent transtemporal windows, critically ill or poorly cooperative patients, patients with combined small and large vessel atherosclerosis, and patients with unknown etiology of their stroke.

MRI and MRA criteria for cerebral large vessel disease (LVD) and SVD were adapted according to the previously established studies.[13-16]

The authors (MH and AP) performed TCD for all the cases using the LOOKI (Atys Medical, France) digital TCD apparatus. A microprocessor-controlled, pulse-wave probe obtained the signals along the intracranial arteries, including internal carotid artery (ICA), posterior cerebral artery (PCA), anterior cerebral artery (ACA), MCA, ophthalmic artery (OA), carotid siphon (CS), vertebral artery (VA), and basilar artery (BA). For all the mentioned arteries, blood flow velocities, including peak systolic velocity (PSV), mean flow velocity (MFV), end-diastolic velocity (EDV), and PI were recorded.

The definitions for different vessels based on TCD criteria, PI, and MFV were adapted from the report of the TCD Subcommittee of the American Academy of Neurology.[2] The Gosling PI was defined as a measure of high flow resistance when it was ≥ 1.2. The OA, which has high resistance flow at baseline, was excluded from the study to carry out a better and uniform comparison between the two groups.

We used the "Trial of ORG 10172 in Acute Stroke Treatment (TOAST)" classification system to define the stroke subtypes in our patients. Then

TOAST classification was compared to the vascular territories of the acute ischemic lesions detected by DWI MRI.[17,18] Patients meeting the TOAST inclusion criteria were assigned to two groups based on predetermined definitions of large and small vessel categories according to the data obtained from imaging patterns in brain MRI and cervical and brain MRA. Tandem intracranial stenosis was ruled out by a normal brain MRA. It is noteworthy that cases with watershed and definite cardioembolic infarction were excluded from the study. To rule out the cardioembolic etiology of stroke, we screened the patients for cardiac sources of emboli due to cardiac arrhythmias [with emphasis on atrial fibrillation (AF)] or structural abnormalities using electrocardiographic (ECG) monitoring and transthoracic echocardiography (TTE), respectively.

Participation in the study entailed no possible risk for the patients. Written informed consent was obtained from all the participants, and the patients were free to leave the study at any point. This study was approved by the Research Ethics Committee of Tabriz University of Medical Sciences (1396.1.51).

The data were analyzed using SPSS software (version 22.0, IBM Corporation, Armonk, NY, USA). Quantitative variables were reported as mean ± standard deviation (SD). The variables were tested for normality using the Kolmogorov-Smirnov test. Independent samples t-test and Fisher's exact test were performed to compare the normal distribution of TCD measures. Qualitative inputs of the two groups were contrasted via a chi-square test. Statistical significance was defined at $P < 0.05$.

Results

None of the 100 patients who had primarily been enrolled left the study. The demographics of the participants are summarized in table 1. The mean age of the participants, irrespective of the type of stroke, was 62.40 years (SD = 12.82). The participants of large and small vessel groups had a mean age of 64.10 (SD = 14.14) and 60.70 years (SD = 11.23), respectively. Slightly over half of the patients were men (55%).

Nevertheless, the subjects in the two groups of large and small vessel stroke did not show any statistically significant difference in age and sex distribution. Comparisons of the frequencies of positive family history of ischemic stroke and personal history of hyperlipidemia, migraine, smoking, and alcohol consumption between the two groups did not lead to any statistically significant findings. Meanwhile, the two groups differed regarding the frequencies of diabetes, hypertension (HTN), and ischemic heart diseases (IHDs) ($P < 0.050$). These three conditions were significantly more prevalent in patients with large vessel stroke.

The TCD indices of the arteries mentioned above obtained from patients with large-vessel stroke were juxtaposed with those in the individuals with small-vessel stroke (Table 2). The findings revealed statistically significant differences between right MCA PI (mean ± SD: 0.96 ± 0.25), left MCA PI (mean ± SD: 0.96 ± 0.30), right ICA PI (mean ± SD: 1.58 ± 0.52), EDV (mean ± SD: 15.06 ± 6.26), left ICA PI (mean ± SD: 1.52 ± 0.55), left ICA EDV (mean ± SD: 16.20 ± 2.03), left ACA PI (mean ± SD: 0.98 ± 0.26), and right VA PI (mean ± SD: 0.98 ± 0.35) measures of the two groups ($P < 0.050$). Compared to the large vessel group, left ACA, right VA, and bilateral MCAs and ICAs in the small-vessel stroke group exhibited an elevated PI. Higher EDV values were recorded solely for bilateral ICAs (mean ± SD for the right side: 18.82 ± 8.16, and for the left side: 20.70 ± 3.10) among the subjects with large vessel stroke ($P = 0.008$). A comparison of the TCD indices of other studied arteries showed no statistically significant differences between LVD and SVD groups.

Discussion

The present study yielded 10 statistically significant differences out of 58 comparisons made for TCD indices obtained from two groups of patients, i.e., SVD versus LVD (Table 2). Among these critical findings, 6 (61.8%) were observed in the measurement of PI.

Table 1. The demographic characteristics of the patients and distribution of small vessel disease (SVD) and large vessel disease (LVD)

Variable	Small vessel stroke (n = 50)	Large vessel stroke (n = 50)	Total	P
Age (year) (mean ± SD)	60.70 ± 11.23	64.10 ± 14.14	62.40 ± 12.82	0.186
Men [n (%)]	29 (52)	26 (47)	55 (100)	0.546
Women [n (%)]	21 (46)	24 (54)	45 (100)	0.546

SD: Standard deviation

Table 2. Transcranial Doppler (TCD) indices of the studied arteries of the circle of Willis

Artery	Stroke subtype	PI		PSV (cm/sec)		EDV (cm/sec)		MFV (cm/sec)	
		Mean ± SD	P	Mean ± SD	P	Mean ± SD	P	Mean ± SD	P
Right	LVD	0.83 ± 0.18	0.003	72.44 ± 18.96	0.267	31.72 ± 11.06	0.238	45.56 ± 13.87	0.159
MCA	SVD	0.96 ± 0.25		68.12 ± 19.73		29.00 ± 11.83		41.66 ± 13.58	
Left	LVD	0.82 ± 0.18	0.009	68.06 ± 17.95	0.817	28.82 ± 11.13	0.638	41.34 ± 11.23	0.987
MCA	SVD	0.96 ± 0.30		67.16 ± 20.64		27.86 ± 9.10		41.38 ± 13.54	
Right	LVD	1.33 ± 0.39	0.008	61.02 ± 18.58	0.349	18.82 ± 8.16	0.011	32.88 ± 10.99	0.072
ICA	SVD	1.58 ± 0.52		57.58 ± 17.94		15.06 ± 6.26		29.22 ± 9.06	
Left	LVD	1.30 ± 0.37	0.022	64.10 ± 8.01	0.349	20.70 ± 3.10	0.008	34.80 ± 2.02	0.085
ICA	SVD	1.52 ± 0.55		60.30 ± 6.10		16.20 ± 2.03		30.90 ± 4.11	
Right	LVD	0.91 ± 0.22	0.338	14.10 ± 3.04	0.988	17.20 ± 6.71	0.431	25.80 ± 7.47	0.663
ACA	SVD	0.96 ± 0.26		43.10 ± 12.40		16.30 ± 5.36		25.00 ± 10.90	
Left	LVD	0.85 ± 0.24	0.010	44.52 ± 12.40	0.834	17.80 ± 5.59	0.897	26.60 ± 7.58	0.879
ACA	SVD	0.98 ± 0.26		43.92 ± 15.97		17.64 ± 6.63		26.40 ± 9.34	
Right	LVD	0.83 ± 0.20	0.491	23.10 ± 6.53	0.988	9.86 ± 3.03	0.747	14.58 ± 4.16	0.636
PCA	SVD	0.86 ± 0.22		23.08 ± 6.33		10.04 ± 2.49		15.04 ± 5.45	
Left	LVD	0.87 ± 0.22	0.770	23.92 ± 5.71	0.662	10.40 ± 3.23	0.695	14.90 ± 3.86	0.676
PCA	SVD	0.86 ± 0.27		23.38 ± 6.57		10.16 ± 2.86		14.58 ± 3.77	
Right	LVD	1.00 ± 0.31	0.824	54.18 ± 20.86	0.971	20.72 ± 9.33	0.839	31.90 ± 12.65	0.917
CS	SVD	0.99 ± 0.23		54.32 ± 17.84		21.06 ± 7.19		32.14 ± 10.30	
Left	LVD	1.08 ± 0.26	0.416	55.00 ± 16.43	0.394	20.72 ± 8.17	0.363	32.24 ± 10.62	0.341
CS	SVD	1.03 ± 0.26		52.24 ± 15.77		19.32 ± 7.11		30.32 ± 9.39	
Right	LVD	0.85 ± 0.20	0.024	40.72 ± 13.97	0.877	17.00 ± 6.42	0.962	24.82 ± 8.60	0.894
VA	SVD	0.98 ± 0.35		41.14 ± 13.00		17.06 ± 6.00		25.04 ± 7.84	
Left	LVD	0.90 ± 0.31	0.715	36.32 ± 13.72	0.162	15.00 ± 6.50	0.227	22.14 ± 8.53	0.181
VA	SVD	0.92 ± 0.25		39.84 ± 11.14		16.50 ± 5.80		24.26 ± 7.11	
BA	LVD	0.94 ± 0.25	0.980	47.00 ± 17.53	0.868	18.78 ± 8.18	0.883	28.18 ± 10.80	0.859
	SVD	0.91 ± 0.54		39.84 ± 11.14		19.00 ± 6.68		28.54 ± 9.37	

ACA: Anterior cerebral artery; MCA: Middle cerebral artery; PCA: Posterior cerebral artery; ICA: Internal carotid artery; VA: Vertebral artery; BA: Basilar artery; CS: Carotid siphon; LVD: Large vessel disease; SVD: Small vessel disease; PSV: Peak systolic velocity; EDV: End-diastolic velocity; PI: Pulsatility index; MFV: Mean flow velocity; SD: Standard deviation

PI measures of bilateral MCAs, bilateral ICAs, left ACA, and right VA were significantly higher in patients with SVD than their counterparts from the LVD group. A PI value > 1.2 in the presence of positive end-diastolic flow (EDF) in a single artery is highly suggestive of an intracranial arterial steno-occlusive disease. Hence, an elevated PI value is considered an expected finding in small vessel strokes.[5]

Comorbid risk factors, such as diabetes and HTN, play a contributory role in developing small vessel strokes.[12] Risk factors of lacunar infarcts increase the distal vascular resistance via increasing the systolic flow and decreasing the diastolic flow, which results in a higher PI. In another study, increased PI values were associated with larger volumes of infarct in lacunar stroke and hence, might serve as a surrogate marker to estimate the extent of ischemia.[19] Higher values of PI are regarded as poor prognostic factors and are independent determinants of clinical outcomes and long-term mortality.[19] In a study conducted by Kidwell et al., age and HTN were correlated with increasing PIs, and PI was identified as an independent indicator of the severity of SVD.[9] Similar results were obtained in the study of Ghorbani et al. They emphasized the clinical applicability of PI as a reflection of downstream resistance in cerebral circulation and suggested that PI should be used as a promising predictor of the presence and severity of the SVD.[20]

The findings of the current study are consistent with the studies mentioned above, further supporting the speculation on the diagnostic role of PI in detecting SVDs. However, with a modest difference, we addressed the higher PIs obtained from patients with SVD than those measured in patients with LVD. The notably lower PI measures in the LVD group could be explained by the etiopathogenesis of large-vessel strokes, mediated by either a thrombotic or an embolic event. According to Spencer's classification of ultrasound characteristics of steno-occlusive lesions, a decremental pattern for distal resistance is anticipated in a large-vessel lesion.[21] Regardless of the categories, decreasing PI is evident in all the

primary (intra-stenotic), secondary (post-stenotic), and tertiary (collateral territories) changes.[22] On a closer look, it is evident that all the arteries with significantly lower PIs in the LVD group share similar anatomic characteristics in terms of inherent vascular tortuosity (Table 2). PI is independent of the insonation angle,[23] and this minimizes the Doppler shift measurement errors in flow velocities.[24] Likewise, TCD velocity estimates of less tortuous arteries turned out to be closer to real values.[25] Laboratory studies have shown and proved that changes in PI are mostly related to the elasticity and compressibility of the vessel wall. Atherosclerosis changes the vessel diameter and elasticity and therefore, decreases the diastolic value which leads to an increase of PI.[26] MCA is a major intracranial artery among the arteries with a significant PI difference between the two groups in the present study (bilateral MCAs, bilateral ICAs, left ACA, and right VA). MCA was also the most commonly affected vessel in the patients with large-vessel stroke (36 of 50), partly explaining the significant differences noted in PI measures of bilateral MCAs of the two stroke groups.

Decreased ICA PI is justifiable by its relatively straight extracranial anatomical course and by the fact that patients with large-vessel stroke had to meet the inclusion criterion of at least 50% stenosis on cervical carotid Doppler.[27] ACA was the third most common artery segment affected by the stroke following MCA and VA in the present study. In 4 out of 50 cases of large vessel strokes, ACA was the affected vessel; however, unlike the bilateral pattern of MCAs and ICAs, ACA was involved ipsilaterally, including three left ACA stroke cases and one case of right ACA stroke. Owing to the relatively large caliber of the artery, its anatomic trajectory, and frequent involvement with large vessel strokes, left ACA PIs were noticeably lower in the corresponding group.[28] This unilateral statistical significance is partly attributed to the predominance of left-side ACA involvement in our patients.

This study had some limitations. In the present study, TCD indices of each artery in the small-stroke patient group were compared to that of the large-stroke patient group on precisely the same side, regardless of the actual side of the artery potentially affected by the stroke. If only affected arteries were to be included in the study, we could unravel more statistically plausible differences. Patients with large vessel stroke often suffer from metabolic syndrome risk factors, leading to the simultaneous presence of white matter or periventricular hyperintensities on brain MRI, which could be compatible with small-vessel stroke as well. This overlap can influence the results and the overall interpretation derived from them.

Conclusion

PI is an indicator of distal vascular resistance, making it the most credible TCD index in detecting small vessel strokes. PI significantly increases in the majority of intracranial arteries of patients with small vessel stroke. Therefore, it is reasonable to deduce that higher values of PI in the setting of large vessel stroke represent the simultaneous presence of large and small vessel strokes. This makes PI a valuable marker for differentiating strokes with differences in the underlying pathophysiology.

Conflict of Interests

The authors declare no conflict of interest in this study.

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