An Index From Transcranial Doppler Signals for Evaluation of Stroke Rehabilitation Using External Counterpulsation

Li Xiong, Danyang Liu, Yawei Wang, Ka Sing Wong, and Yubo Fan

***Abstract*— This study aimed to develop a sensitive index from transcranial Doppler (TCD) signals for quantitatively evaluating the effects of long-term external counterpulsation (ECP) treatment on stroke rehabilitation. We recruited 27 patients with unilateral ischemic stroke and a good acoustic window within 7 days of stroke onset. 15 of them received 35 daily 1-hour ECP treatment (ECP group) and the others underwent conventional therapy without ECP treatment (No-ECP group). We monitored blood flow in middle cerebral arteries on both sides by TCD, and analyzed them via discrete wavelet analysis method. The overall changes of National Institutes of Health Stroke Scale (NIHSS) and Barthel Index were assessed. A 'big-wave' phenomenon was observed in TCD signals of patients in ECP group after 35 days' treatment, with significant fluctuation in frequency interval from 0.010 to 0.034 Hz as main feature. A new index, which was denoted as *I*, was derived from this phenomenon. The *I* was significantly higher for patients in ECP group than that for patients in No-ECP group after 35-days' treatment ($P < 0.01$). And the *I* was positively correlated with NIHSS change in ECP group ($P < 0.05$). The new index could be used as an effective indicator for evaluating enhancement of endothelial metabolism and neurogenic activity after long-term ECP treatment.**

***Index Terms*— Ischemic stroke, transcranial Doppler, external counterpulsation, wavelet analysis, index.**

I. Introduction

EXTERNAL counterpulsation (ECP) is a noninvasive method to improve perfusion of vital organs [1]. It operates by applying electrocardiography-triggered diastolic pressure to the lower extremities through air-filled cuffs. Diastolic augmentation of blood pressure and simultaneous decreasing of systolic afterload increase blood flow of vital organs, such as the heart, brain and kidneys [2]–[5]. Alexandrov *et al.* reported that ECP induces marked changes in cerebral arterial waveforms, and augments peak diastolic and mean flow velocities of middle cerebral arteries (MCA) in a study of 5 healthy subjects by using TCD [6]. Our previous study showed ECP is feasible for ischemic stroke patients by improving clinical neurological deficit via augmentation of blood pressure and cerebral blood flow velocity, and the cerebral augmentation may last at least 3 weeks after treatment [5], [7], [8]. A clinical trial revealed that 1-hour ECP treatment with a pressure up to 300 mmHg would augment MCA mean flow velocity by 15% in patients with acute ischemic stroke, accompanied by contemporaneous improvements in National Institutes of Health Stroke Scale (NIHSS) score regardless of pressure used [10]. However, most of these studies investigated the instantaneous effect of ECP with 1-hour or a few minutes intervention on cerebral flow velocities, there is still a lack of sensitive index for evaluating the efficacy of long-term ECP treatment on ischemic stroke rehabilitation.

Several experimental studies demonstrated that ECP treatment could improve endothelial function through modifying shear stress responsive gene expression in animals and patients with ischemic heart disease [11]–[14]. Animal experiments also indicated that vascular endothelial function recovery promotes pericyte coverage of brain capillaries, and thus improves cerebral blood flow [15]. But, the effects of ECP treatment on cerebral vascular endothelial function of patients with ischemic stroke were rarely reported. Since endothelial metabolism and neurogenic activity can be observed in certain frequency intervals of blood flow signals [16]–[18], and the noninvasive TCD signals were usually used to analyze cardiovascular and brain interactions [5], [18], we wondered whether there is an index that could be derived from TCD signals of patients with ischemic stroke after long-term ECP treatment, for revealing enhancements of endothelial metabolism and neurogenic activity, and evaluating the efficacy of long-term ECP treatment on ischemic stroke rehabilitation.

In this study, we recruited patients with unilateral ischemic stroke and a good acoustic window within 7 days of stroke onset, and divided them into two groups, i.e., an ECP group and a No-ECP group. The patients in ECP group received 35 daily 1-hour ECP treatment, while the patients in No-ECP group underwent conventional therapy. We compared TCD

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This work involved human subjects or animals in its research. Approval of all ethical and experimental procedures and protocols was granted by the Joint CUHK–NTEC Clinical Research Ethics Committee under CREC Ref. No. 2014.247.

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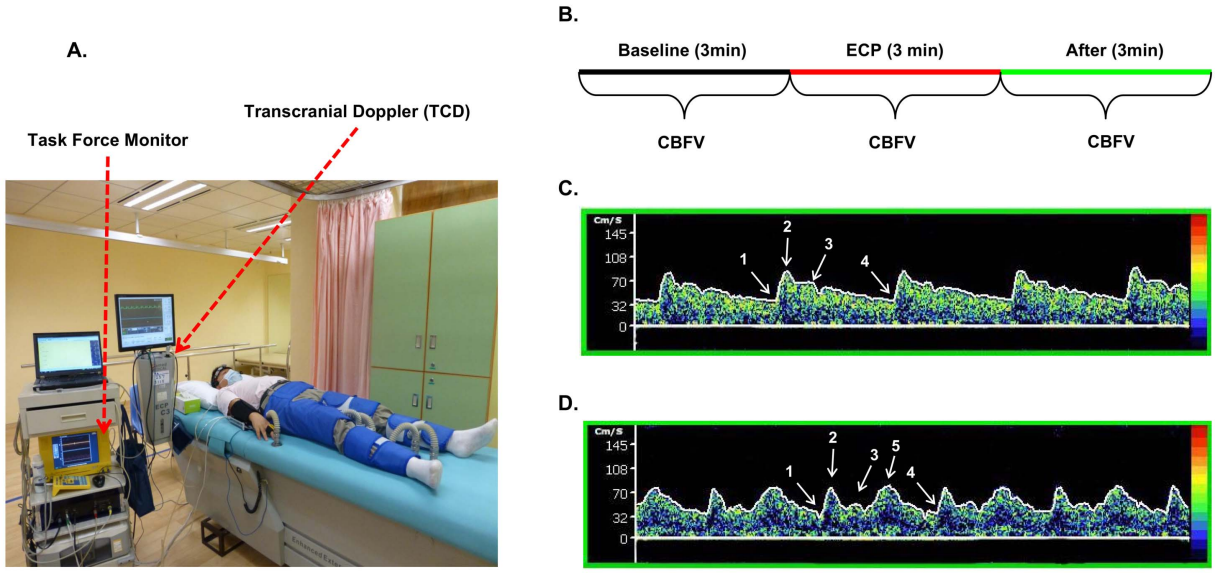

Fig. 1. ECP treatment and TCD monitoring. A: experimental apparatus. B: cerebral blood flow velocity (CBFV) recorded in 3 stages of once treatment, i.e., at baseline, during ECP treatment, and after ECP treatment. C: typical TCD signals of CBFV at the baseline stage. D: typical TCD signals of CBFV during ECP treatment. 1: beginning of systole. 2: peak systole. 3: dicrotic notch. 4: end of diastole. 5: augmented diastole.

signals of patients in these two groups in both time and frequency domain. By analyzing these TCD signals with discrete wavelet analysis method, we proposed a new index, and investigated its correlations with NIHSS and BI index.

II. Methods

A. Participants

We enrolled patients with unilateral ischemic stroke in the anterior circulation territory and a good acoustic window within 7 days of stroke onset. Ischemic stroke was diagnosed according to the definition of World Health Organization. We excluded the patients with evidence of cardioembolic stroke such as atrial fibrillation and rheumatic heart disease, intracranial haemorrhage, arteriovenous malformation, arteriovenous fistula or aneurysm, malignancy, sustained hypertension (systolic $\geq$ 180 mmHg or diastolic $\geq$ 100 mmHg), severe symptomatic peripheral vascular disease, coexisting systemic diseases. All patients were divided into two groups: ECP group received 35 daily 1-hour treatment sessions; No-ECP group underwent conventional therapy without ECP treatment. Written informed consent was obtained from all participants prior to enrollment. This study was approved by the local medical ethics committee (Joint CUHK-NTEC Clinical Research Ethics Committee, CREC Ref. No. 2014.247).

B. ECP Treatment and TCD Monitoring

ECP treatment was performed using a device named MC2 of Vamed Medical Instrument Company (Guangdong, China), with a cuff inflation pressure of 150 mmHg used. TCD monitoring was performed at the 1st and the 35th session (once a day for 5 working days per week) in ECP group and on day 1 and day 35 in No-ECP group using ST3 TCD system (Spencer Technologies, Seattle, WA, USA). The subjects lay on the ECP treatment bed and their legs were wrapped with 3 pairs of air cuffs, as shown in Fig.1A. Two 2-MHz probes were mounted on a head frame, which was fitted individually and worn on the head of subjects, to insonate the M1 segments of bilateral MCA with sampling frequency of 1000 Hz. We recorded blood flow velocity of MCA at baseline and during ECP for 3 minutes respectively, as defined in Fig.1B. A 3 min stage after ECP was also recorded, but not analyzed in this study. Typical TCD signals in different stages were depicted in Fig.1C.

C. Wavelet Analysis and Frequency Resolution

As a multi-scale method for analyzing signals both in time and frequency domain, the discrete wavelet analysis method has the best low frequency resolution through decomposing the signal from high frequency to low frequency step by step, which can help identifying the low frequency component more accurately than the Fourier and other signal analysis methods [19]–[24]. As the frequency interval of blood flow oscillation originated from endothelial metabolic and neurogenic activity locate in low frequency domain [18], [25], [26], the wavelet analysis is more suitable for analyzing TCD signals in this study, which had been widely used in the field of biomedical engineering [20], [21], [27]–[29]. The MCA blood flow signals were sampled at a frequency of 1000 Hz, all of which were firstly imported into a moving-average filter. Through averaging 10 adjacent sampling points and replacing them with one, we resampled the signals to 100 Hz before further processing,

$$\overline{x}_j = \sum_{i=10j+1}^{10j+10} x_i \tag{1}$$

where x was the discrete value of the signal, i and j were integer count numbers.

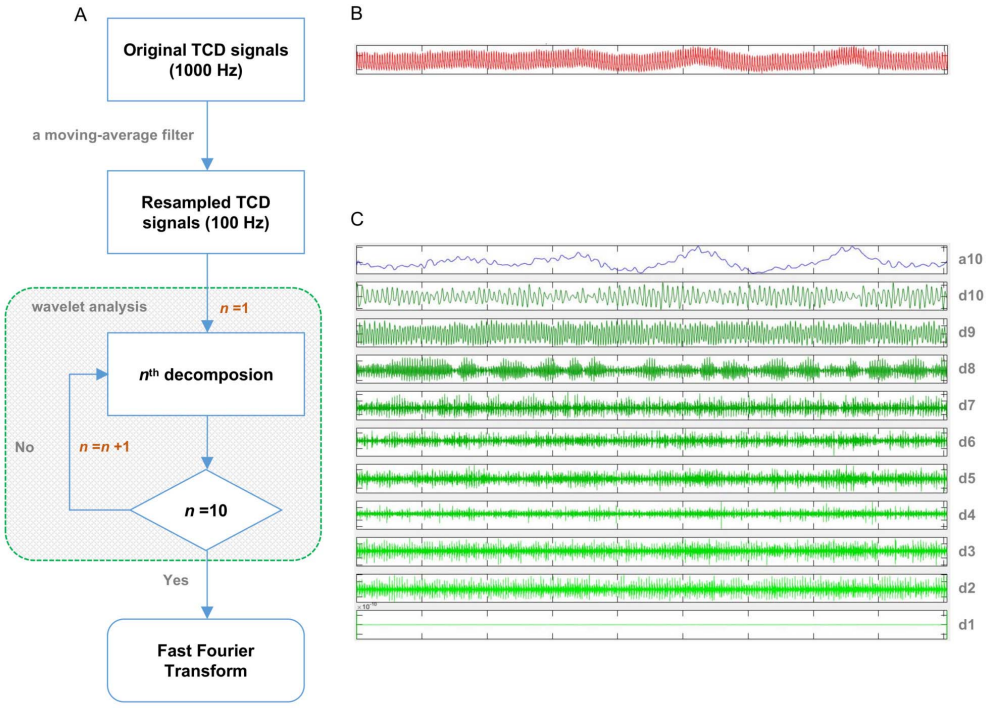

Fig. 2. Procedure of TCD signals analysis. A: flowchart of the analysis procedure. B: Original TCD signals. C: Step by step decomposed TCD signals using wavelet analysis.

Then the discrete wavelet analysis method was adopted to decompose the signals step by step. Since each step contained a half reduction of frequency, the frequency below 0.1 Hz could be obtained after 10-step wavelet decomposition. Finally, we used the fast Fourier transform to analyze the spectrum of all wavelet components for obtaining the relationship between oscillate amplitude and frequency. The workflow of wavelet analysis was depicted in Fig.2, which was performed with MATLAB 2015a (The MathWorks inc., Natick, MA, USA), with the fourth-order Daubechies (db4) wavelet used to decompose the TCD signals.

D. Clinical Outcome

NIHSS and Barthel Index (BI) were assessed on day 1 and day 35 after enrollment. NIHSS is a systematic assessment tool that provides a quantitative measure of stroke-related neurologic deficit, which can be used as a clinical stroke assessment tool to evaluate and document neurological status in acute stroke patients. The NIHSS has been shown to be a predictor of both short and long term outcome of stroke patients, which is designed to be a simple, valid, and reliable tool that can be administered at the bedside consistently by physicians, nurses or therapists [30], [31]. The Barthel Scale/Index (BI) is an ordinal scale used to measure performance in activities of daily living (ADL), with ten variables describing ADL and mobility scored [32]. We sought help from professional institute for NIHSS and BI assessment, as listed in the acknowledgment.

E. Statistical Analysis

TCD signals of stroke patients were divided into two categories according to its monitoring position, i.e., ipsilateral or contralateral to the infarct. Continuous data were analyzed and presented as mean and standard deviation if normally distributed. Category data were analyzed and presented as number and percentage. Distributions of continuous variables were determined by the Kolmogorov-Smirnov test. Continuous data were analyzed by independent-sample Student t-test when there was a normal distribution and by the Mann-Whitney test if there was a skewed distribution. Category data were analyzed by the Pearson χ^2-test or Fisher's exact test. Paired t-test was used to compare the difference between the ipsilateral side and the contralateral side of two groups. Spearman correlation analysis was performed between a new index described in the results and changes of clinical neurological assessments. All statistical analyses were performed with SPSS (version 19.0, SPSS Inc., Chicago, Illinois, USA). Differences with $P < 0.05$ were considered significant.

III. Results

A total of twenty-seven patients (age 63.7±10.5 years; 24 male) with unilateral ischemic stroke in the anterior circulation territory were enrolled (15 with ECP treatment, 12 without ECP treatment). The mean interval of stroke onset to enrollment was 3.9 days. Stroke patients had moderate neurological deficits with mean admission NIHSS of 7.1 and mean BI score of 60.8. There was a significant difference in stroke subtype between the two groups ($P = 0.001$). All had large artery disease in ECP group. However, 41.7% patients had large artery disease and the left had small vessel disease in No-ECP group. The age, gender, and comorbidity were comparable between the two groups (Tab. I). Current drug use was shown in Tab.I. Calcium-channel blocker was more frequent in No-ECP group than in ECP group ($P = 0.008$).

TABLE I
GENERAL CHARACTERISTICS OF THE PARTICIPANTS

Parameters	ECP group (n=15)	No-ECP group (n=12)	P value
Gender (male/female)	12/3	12/0	0.231
Age (mean±SD), years	65.4±11.7	61.6±8.8	0.358
Days from symptom onset to recruitment (mean±SD)	4.1±1.7	3.6±1.4	0.378
Admission NIHSS (mean±SD)	6.7±2.8	7.6±6.5	0.680
Hypertension (%)	14 (93.3)	7 (58.3)	0.060
Diabetes (%)	7 (46.7)	2 (16.7)	0.217
Ischemic heart disease (%)	2 (13.3)	1 (8.3)	1.000
Hyperlipidemia (%)	6 (40.0)	1 (8.3)	0.091
Previous stroke (%)	5 (33.3)	1 (8.3)	0.182
Smoker (%)	3 (20.0)	5 (41.7)	0.398
Drinker (%)	1 (6.7)	3 (25.0)	0.294
Stroke subtypes	5(33.3)	1(3.3)	0.001
LAD	15 (100.0)	5 (41.7)	
SVD	0 (0.0)	7 (58.3)	
β-Blocker (%)	2 (13.3)	2 (16.7)	1.000
ACE inhibitors (%)	8 (53.3)	4 (33.3)	0.299
CCB (%)	1 (6.7)	7 (58.3)	0.008
HMG-CoA reductase inhibitor (%)	13 (86.6)	12 (100.0)	0.487
Antiplatelet (%)	15 (100.0)	12 (100.0)	1.000

Smoker and drinker include ex- and current smokers and drinkers.
LAD, large artery disease; SVD, small vessel disease; CCB, calcium-channel blocker.

A. Direct-Viewing Difference of TCD Signals Among Patients

A 'big-wave' phenomenon was observed in TCD signals of some patients after completion of 35 treatment sessions, as shown in Fig.3D, which indicated that the MCA blood flow velocity fluctuated in a relatively low frequency (about 0.02 Hz). There were no obvious 'big-wave' phenomenon observed in TCD signals of these patients before treatment, i.e., on day 1 (Fig.3C). The patients who had obvious 'big-wave' phenomenon in TCD signals on day 35 were classified as patients of type 2, compared with type 1 that had no obvious 'big-wave' phenomenon on both day 1 (Fig.3A) and day 35 (Fig.3B). Interestingly, all patients of type 2 (the total number was 11) appeared in the ECP group, which indicated that long-term ECP treatment caused the 'big-wave' phenomenon. Meanwhile, not all of the patients in ECP group were of type 2, which indicated that long-term ECP was not effective to cause the 'big-wave' phenomenon for all patients. For understanding physiological meanings of the 'big-wave' phenomenon, TCD signals with and without 'big-wave' phenomenon were compared in frequency domain and the results were described as following.

B. Frequency Characteristic of the 'Big-Wave' Phenomenon

We calculated frequency characteristics of TCD signals of these two types through using the discrete wavelet analysis and fast Fourier transform, and typical results were depicted in Fig.4. Fig.4A showed that there was no significant difference in the amplitudes of TCD signals of type 1 patients after 35 days treatments in comparison with those on day 1 in all frequency domain. It should be mentioned again that patients of type 1 appeared in both the ECP group and the No-ECP group, who received different treatments (with or without ECP) in different groups. Fig.4B showed that the oscillation amplitude (OA) of TCD signals of type 2 patients on day 35 was obviously higher than those on day 1 in the frequency interval from 0.010 Hz (±0.002 Hz for 11 type 2 patients) to 0.034 Hz (±0.004 Hz for 11 type 2 patients), this frequency interval was reported to be related with endothelial metabolic activity and neurogenic activity [15], [25].

C. Quantitative Differences Caused by the 'Big-Wave' Phenomenon

For quantitatively evaluating the differences caused by the 'big-wave', a dimensionless index I was defined as,

$$I_{\text{stage2 vs stage1}} = \frac{\int_{f_1}^{f_2} A_{\text{stage2}} df}{\int_{f_1}^{f_2} A_{\text{stage1}} df} \tag{2}$$

where A_{stage1} and A_{stage2} represented OA of TCD signals of different stages (as depicted in Fig. 1B) in frequency domain, f_1 and f_2 were the boundaries of the frequency interval as depicted in Fig.4B, whose values were set to be 0.010 and 0.034 Hz respectively. We evaluated 4 kinds of 'stage2 vs stage1' for I, including Baseline_d35 vs Baseline_d1, ECP_d1 vs Baseline_d1, ECP_d35 vs Baseline_d35 and ECP_d35 vs ECP_d1, for quantitatively evaluating effects of long-term ECP treatment. It should be mentioned that, for patients in No-ECP group, the ECP stage was defined as a 3 min stage immediately after the baseline stage.

The results of I with different kinds of 'stage2 vs stage1' ipsilateral and contralateral to the infarct side were listed in

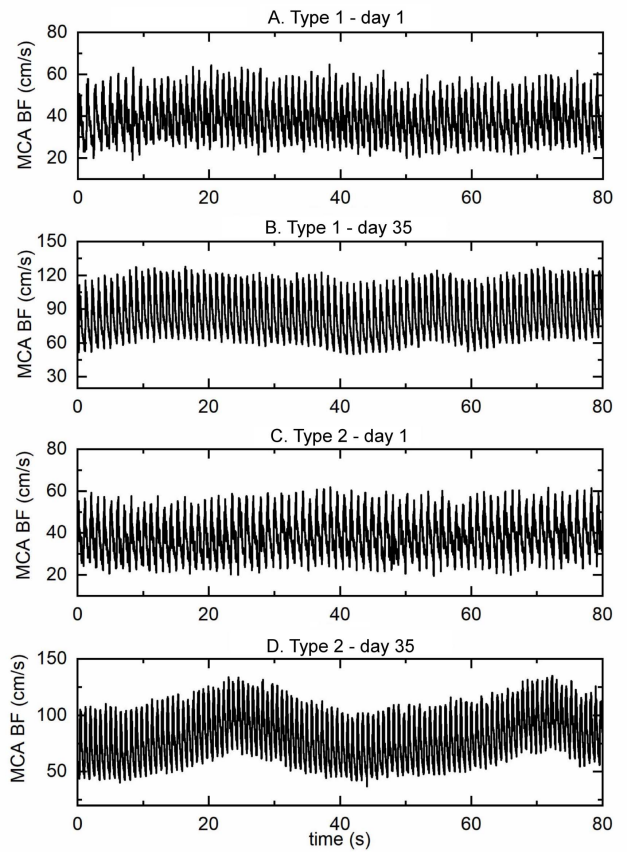

Fig. 3. Typical TCD signals. A: MCA blood flow (BF) signals of type 1 patients on day 1. B: MCA BF signals of type 1 patients on day 35. C: MCA BF signals of type 1 patients on day 1. D: MCA BF signals of type 1 patients on day 35.

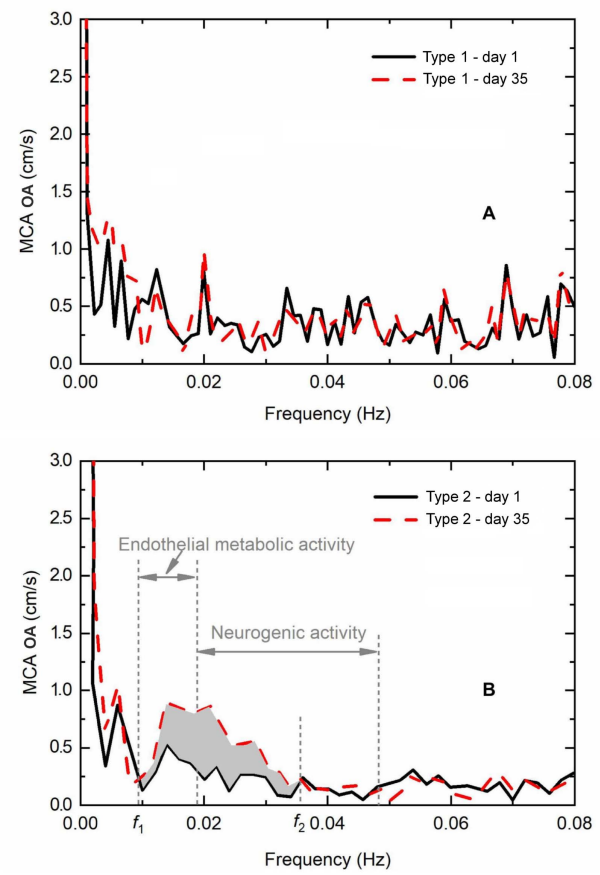

Fig. 4. Frequency characteristics of the 'big-wave' phenomenon. A: characteristics of TCD signals in day 1 and day 35 for patients of type 1. B: characteristics of TCD signals in day 1 and day 35 for patients of type 2.

Tab.II and shown in Fig.5. It could be seen from Tab.II and Fig.5 that, $I_{\text{Baseline\_d35 vs Baseline\_d1}}$ and $I_{\text{ECP\_d35 vs ECP\_d1}}$ in ECP group were significantly higher than those on both sides in No-ECP group (all $P < 0.01$). There were no significant differences of $I_{\text{ECP\_d1 vs Baseline\_d1}}$ and $I_{\text{ECP\_d1 vs Baseline\_d1}}$ on both sides between two groups (all $P > 0.05$).

D. Correlation Between I and Changes of Clinical Outcome

NIHSS and BI scores were successfully assessed in 11 patients in ECP group at baseline stage on day 1 and day 35. Fig.6 showed that $I_{\text{Baseline\_d35 vs Baseline\_d1}}$ on ipsilateral and contralateral sides were positively correlated with the NIHSS change (ipsilateral correlation coefficient = 0.730, $P = 0.011$; contralateral 0.650, $P = 0.030$). There was no significant correlation between the index $I_{\text{Baseline\_d35 vs Baseline\_d1}}$ and BI change on both sides in ECP group (all $P > 0.05$).

IV. Discussion

A new phenomenon, named as 'big-wave', was firstly observed in TCD signals of some ischemic stroke patients who underwent 35 daily 1-hour sessions of ECP treatment in our study. Using the wavelet analysis method, we found that the OA of TCD signals with 'big-wave' phenomenon was obviously enhanced in the frequency interval from 0.010 Hz to 0.034 Hz, which might be caused by endothelial metabolic activity and neurogenic activity.

Frequency intervals of blood flow oscillations had different physiological origins. The intervals of 0.0095-0.021Hz and 0.021-0.052Hz were reported to be originated by endothelial metabolic activity and neurogenic activity, respectively [17], [22]–[25]. For examples, the oscillation of blood flow signals in the frequency interval around 0.03 Hz was found to disappear following local and ganglionic nerve blockade in chronically sympathectomized tissue in human, which suggested that the oscillation in blood flow in this frequency interval is a vascular reaction of the sympathetic nerve activity [19]. The frequency interval around 0.01 Hz represented nitric oxide (NO) related endothelial activity [22], [23]. Therefore, the frequency interval from 0.010 to 0.034 Hz in our study was in consistence with those originated by endothelial metabolic activity and neurogenic activity. This indicated that long-term ECP treatment could enhance endothelial metabolic activity and neurogenic activity in some patients with ischemic stroke.

The novel index I, which can be easily calculated from TCD signals, may be defined as a marker for quantitatively evaluating the enhancement of endothelial metabolism and neurogenic activity. It could also be used as a new predictor of clinical outcome after acute ischemic stroke because of

TABLE II
INDEX *I* OF SUBJECTS ON BOTH SIDES

Index	Stroke Ipsilateral Side		Stroke Contralateral Side	
	ECP group	No-ECP group	ECP group	No-ECP group
$I_{\text{Baseline\_d35 vs Baseline\_d1}}$	1.28±0.30	1.02±0.06	1.28±0.30	1.00±0.06
P Value* (ECP vs No-ECP)	0.005		0.003	
$I_{\text{ECP\_d1 vs Baseline\_d1}}$	1.01±0.05	1.01±0.04	1.01±0.05	1.01±0.05
P Value* (ECP vs No-ECP)	0.970		0.979	
$I_{\text{ECP\_d35 vs Baseline\_d35}}$	1.02±0.04	0.99±0.06	1.01±0.04	0.99±0.04
P Value* (ECP vs No-ECP)	0.166		0.248	
$I_{\text{ECP\_d35 vs ECP\_d1}}$	1.31±0.36	0.99±0.06	1.29±0.34	1.00±0.07
P Value* (ECP vs No-ECP)	0.005		0.005	

*Student's t-test was used to compare difference of index I between ECP and No-ECP group. Paired t-test was used to compare the difference of index I between the ipsilateral side and the contralateral side of ECP and No-ECP group.

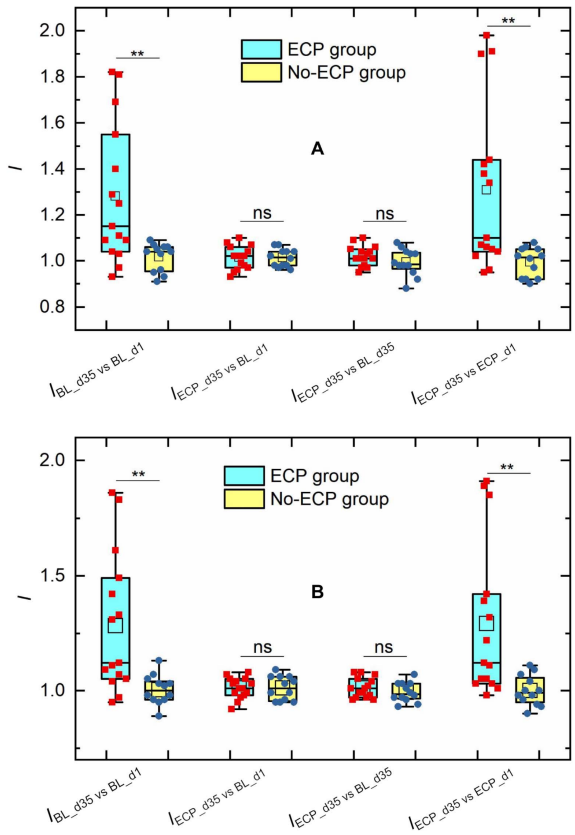

Fig. 5. Comparison of index *I* on both sides in ECP group and No-ECP group. A: on ipsilateral side. B: on contralateral side. Note: the subscript 'BL' in axis labels represented 'Baseline'.

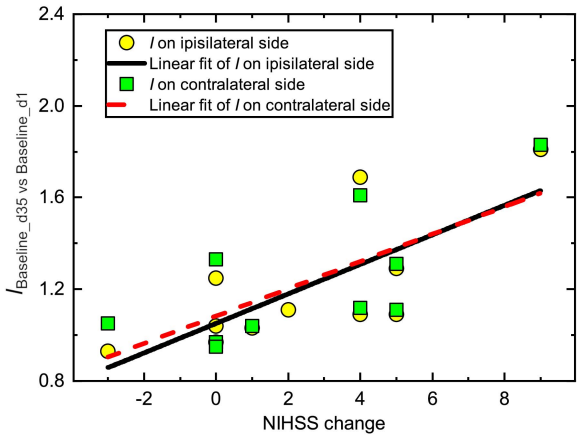

Fig. 6. The correlation between the index $I_{\text{Baseline\_d35 vs Baseline\_d1}}$ and NIHSS change of stroke patients in ECP group.

its positive correlations with a favorable change in NIHSS. However, not all patients who underwent 35 daily 1-hour sessions of ECP treatment showed a significant increase of the index I, which means long-term ECP treatment was not effective for all patients with ischemic stroke. The index I may help us select patients who are more responsive to long-term ECP treatment.

In this study, the mechanism of long-term ECP treatment on enhancing endothelial metabolism and neurogenic activity was not investigated. Shear stress regulates endothelial structure and function by regulating the expression of mechanosensitive genes [5], [9], [11]–[13]. ECP augments blood flow in many ischemic diseases. Therefore, it might improve both structure and function of the vascular endothelium through increasing shear stress in blood vessels [9]. Moreover, an acute increase in shear stress can cause robust NO release, which plays a critical role in vessel relaxation, whereas chronic NO release due to the increased laminal shear stress may be served as an anti-atherogenic and anti-inflammatory molecule [11]. Therefore, we speculated that long-term ECP treatment may promote NO-related endothelial metabolic activity by continuously increasing shear force in blood vessels. This may be beneficial to vascular function and recovery of nerve function.

Limitations of this study included, first, the sample size was relatively small and some follow-up neurological examination was lost. Second, stroke subtype and current medication use such as CCB differences between two groups may partially influence their distinct hemodynamic responses to ECP, although we believed that these differences were not the major reason. Last, factors like concurrent left ventricular dysfunction, hydration status and subject core temperature might influence endothelial metabolism and neurogenic activity.

V. Conclusion

A 'big-wave' phenomenon was observed in TCD signals of some patients after long-term ECP treatment, and the signals' oscillation amplitude in the frequency interval from 0.010 to 0.034 was obviously higher than that of the others, which might be originated from endothelial metabolic and neurogenic activity according to former studies. An index, I, was firstly defined in this study for quantitatively evaluating the 'big-wave' phenomenon. It was found that both I of day 35 vs day 1 of baseline and ECP stages had significant positive correlation with NIHSS change in ECP group. Consequently, it could be speculated that long-term ECP treatment can promote stroke recovery through enhancing endothelial metabolic and neurogenic activity. The new index derived from TCD signals might be built in future medical devices for rapid evaluation of stroke rehabilitation.

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