IEEE Access
Multidisciplinary | Rapid Review | Open Access Journal

Received December 8, 2019, accepted January 18, 2020, date of publication February 11, 2020, date of current version February 24, 2020.

Digital Object Identifier 10.1109/ACCESS.2020.2973250

A Preliminary Study on the Feasibility of Detecting Global Acute Cerebral Ischemia by the MIPS Method

WEI ZHUANG[1], WENCAI PAN[2], LIN XU[1], JINGBO CHEN[1], JIA XU[1], ZELIN BAI[1], GEN LI[1,3], (Member, IEEE), MINGSHENG CHEN[1], (Member, IEEE), JIAN SUN[4], (Member, IEEE), AND MINGXIN QIN[1]

[1]College of Biomedical Engineering, Army Medical University, Chongqing 400030, China
[2]Department of Equipment Division, Xinqiao Hospital, Chongqing 400035, China
[3]School of Pharmacy and Bioengineering, Chongqing University of Technology, Chongqing 400020, China
[4]Department of Neurosurgery, Southwest Hospital, Chongqing 400028, China

Corresponding authors: Mingsheng Chen (chenms83@tmmu.edu.cn), Jian Sun (30067982@qq.com), and Mingxin Qin (173117502@qq.com)

This work was supported in part by the Equipment Project under Grant LJ20182B020149 and Grant LJ2018B020152, and in part by the Chongqing Technology Innovation and Application Demonstration Project under Grant cstc2018jscx-msyb0577.

ABSTRACT Acute cerebral ischemia is an important clinical disease that is usually detected by magnetic resonance imaging or computed tomography. The magnetic inductive phase shift (MIPS) is a new method for detecting cerebral diseases, which is non-invasive, miniaturized, and low-cost. A total of 25 rabbits were studied using a two-coil sensor with a 0.3–200 MHz frequency range, and all the subjects were measured for 1 hour. Based on the rabbit acute cerebral ischemia model, the rabbits were divided into unilateral ligation, bilateral ligation, and non-ligation groups. The results showed that the average MIPS values of the non-ligation, unilateral ligation, and bilateral ligation group were $-0.195 \pm 0.079°$, $-4.873 \pm 1.042°$, and $-9.165 \pm 2.862°$ respectively. MIPS distinguished different severities of cerebral ischemia in rabbits with statistical significance ($p < 0.05$). Laser Doppler flowmetry (LDF) was used as the gold standard for collecting cerebral blood flow data. The strong correlation between the LDF measurements and the phase shift suggested that the phase shift reflects blood flow changes in the brain. Overall, these results suggest that the MIPS detection method has the potential to provide early detection of global cerebral ischemia. Furthermore, this method effectively distinguished different severities of cerebral ischemia.

INDEX TERMS Acute cerebral ischemia, magnetic induction phase shift, laser Doppler flowmetry.

I. INTRODUCTION

Cerebral ischemia is a medical condition in which a certain region of the brain is deprived of oxygen and nutrient-rich blood [1]. Ischemic stroke accounts for about 90% of all strokes and can occur in people of all ages, although risk increases with age [2]. Cerebral ischemia can lead to severe damage to the central nervous system and eventually causes paralysis. The Guidelines for the Early Management of Patients with Acute Ischemic Stroke (AHA/ASA, 2018) have stated a clear benefit of intravenous thrombolysis within 3 h for disabled adult stroke patients meeting the screening criteria, regardless of age and stroke severity [3]. Thus, early detection and diagnosis are the keys to emergency treatment and intensive care of patients with cerebral ischemic stroke.

Many noninvasive detection methods are being used to measure cerebral ischemia, including magnetic resonance imaging (MRI) [4] and computed tomography (CT) [5]. However, such methods present many limitations. On the one hand, these methods are disadvantageous because of their large size, high expense, and high inspection costs, but CT and MRI cannot easily detect early acute cerebral ischemia [4,6]. Moreover, these methods do not help with emergency on-site and pre-hospital diagnoses.

Magnetic induction phase shift (MIPS), which provides the advantages of non-contact, noninvasive, inexpensive, small, and continuous bedside monitoring, is a potential method to detect cerebrovascular disease. MIPS is based on electromagnetic induction and reflects the change of

The associate editor coordinating the review of this manuscript and approving it for publication was Qiquan Qiao.

conductivity in biological tissues. The first measurement method based on magnetic induction was proposed in 1968 by Tarjanet et al. [7] and has been applied to study human tumors and brain impedance. In 1999, Griffiths et al. measured saline solutions with conductivities ranging from 0.001 to 6 $S \cdot m^{-1}$ using a single-channel magnetic induction system. They established a simple and intuitive mathematical model for magnetic analysis [8]. In 2007, Gonzalez et al. detected intraperitoneal fluid *in vivo* by inductive phase shift measurements, showing that the bulk phase shift increases as a function of frequency and fluid volume, and the induction phase shift of 7.5%, a 26.5 cc saline injection, was 1.6° [9]. In 2009, they monitored brain ischemia in rats by inductive phase shift spectroscopy, and the phase shift of the ischemic group was close to 20° 24-hour post-surgery at 50 MHz. That experiment suggested that inductive phase shift spectroscopy has the potential to detect the process and level of ischemia in the brain [10]. In addition, in 2013, they distinguished edema patients from hematoma patients and healthy volunteers by establishing a VEPS multi-frequency measurements system and classifier [11]. In 2014, Jin *et al.* [12] detected acute cerebral hemorrhage in rabbits using MIPS, which detected small changes in blood volume and reflected the severity of cerebral hemorrhage. The average change in the MIPS was 0.502 ± 0.119° with a 3 ml injection. In the same year, they designed a symmetric cancellation-type sensor based on the symmetric structure of the brain hemisphere. The average phase shift difference of a 3 ml injection of blood was 1.885 ± 0.242°. Injection speed was 0.33 ml/min, and the entire amount of time for this experiment was 9 min [13]. In 2015, Pan *et al.* [14] established a broadband phase shift detection system to detect cerebral hemorrhage. The average phase shift change induced by a 3 ml injection of autologous blood under FB was −7.75 ± 1.42°, indicating greatly improved detection sensitivity. The injection speed was 0.33 ml/min, and the duration for this experiment was 9 min. Li *et al.* [15] and Zhao *et al.* [16] also studied brain edema in rabbits for 24 hours using a real-time continuous monitoring system. The average phase shift of 24 hour edema detection was −13.112 ± 2.395°, and the system effectively monitored brain edema and classified the severity of the brain edema.

In this study, based on preliminary work by our research group, we established a MIPS detection system to observe the trend of MIPS in terms of ischemia severity and to explore the possibility of early detection of acute cerebral ischemia. A total of 25 rabbits was studied using a two-coil sensor with a 0.3–200 MHz frequency range. Furthermore, the MIPS variation trend at the optimal sensitive frequency (CF) was collected and calculated. Laser Doppler flowmetry (LDF) was used to obtain blood flow changes as the gold standard and reference. To demonstrate that the MIPS method can detect early and acute cerebral ischemia, we designed a MIPS and LDF synchronous measurement system in brain ischemic rabbits and analyzed the correlations between the MIPS and LDF measurements.

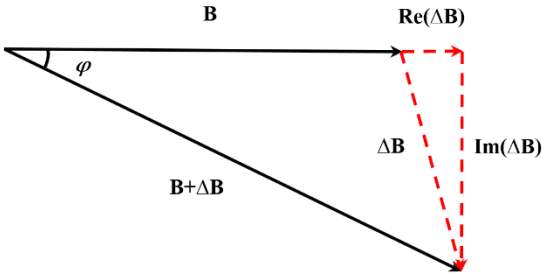

FIGURE 1. Phasor diagram representing primary magnetic field B and secondary magnetic field ΔB. The total magnetic field (B+ΔB) lags the primary magnetic field by an angle φ.

II. MATERIALS AND METHODS

A. MIPS DETECTION PRINCIPLE

In MIPS theory [8], the measured sample is always placed between the excitation coil and the receiving coil, and a primary magnetic field (B) is generated by the sinusoidal excitation current ($Ie^{j\omega t}$) flowing into the excitation coil. This primary magnetic field causes induction currents in the sample, which consequently produce a second magnetic field (ΔB). The receiving coil receives the total magnetic field (B+ΔB). The primary and secondary fields (B and ΔB) are represented by the phasor diagram (Figure 1). The intensity of the induced magnetic field is related to the electrical conductivity of the measured sample, and the changes in electrical conductivity of the measured sample can be determined by detecting the induced magnetic field intensity (ΔB) [17]. The induced current in the receiving coil can be expressed in a complex form as: [18]

$$I(t) = I(\cos(\omega t + \varphi) + j\sin(\omega t + \varphi)) \tag{1}$$

which can be obtained by the following formula:

$$\omega t + \varphi = \tan^{-1}\frac{\mathrm{Im}I(t)}{\mathrm{Re}I(t)} = \tan^{-1}\frac{\sin(\omega t + \varphi)}{\cos(\omega t + \varphi)} \tag{2}$$

We define a basal-induced current phase in the receiving coil as ($\omega t+\varphi$), and the phase influenced by the presence of ischemia as ($\omega t+\varphi'$). The magnetic induction phase shift ($\Delta\varphi$) at a specific frequency and time is given by

$$MIPS = \Delta\varphi = (\omega t + \varphi') - (\omega t + \varphi) = \varphi' - \varphi \tag{3}$$

We used the time-difference method to calculate the phase shift and obtain MIPS. The phase shift was represented as a relative phase shift by subtracting the phase under ischemic conditions from the baseline phase.

B. MIPS EXPERIMENTAL SYSTEM

The magnetic induction system to detect acute cerebral ischemia is shown in Figure 2. The system includes the following: an RF vector network analyzer (Agilent E5061B; Agilent Technologies, Inc., Palo Alto, CA, USA), a coaxially paralleled dual-coil sensor, an intracranial pressure monitor (Camino MPM-1), laser Doppler flowmetry (LDF, PeriFlux

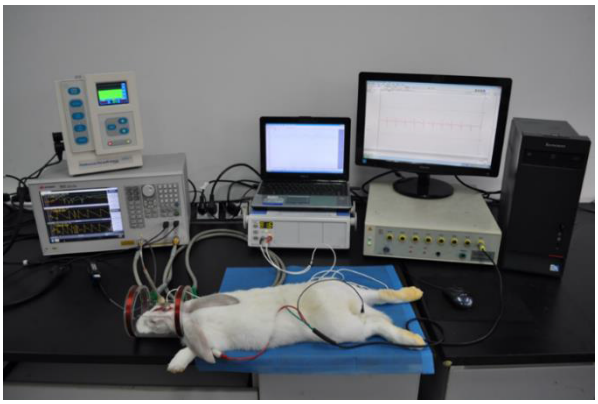

FIGURE 2. Schematic diagram of the monitoring system.

5000), a multichannel physiological signal acquisition instrument (Chengdu Instrument Factory, RM6280C) and a personal computer.

In this study, we used a two-port RF vector network analyzer. The vector network analyzer was set to simultaneously measure the amplitude and phase information of the transmission parameter S_{21}. The output power of the signal source was 10 dBm, and the frequency range of the input signal was 0.3–200 MHz in linear scanning mode.

The two-coil sensor included one excitation coil and one receiving coil, as shown in Figure 3a. Both coils were wound with 1 mm diameter copper wire in a Plexiglas mold with ten turns. Both coils had the same radius of 5.2 cm and were placed symmetrically and in parallel within a 10.5 cm distance. The two-coil sensor was connected to a vector network analyzer through a high frequency coaxial line. We drew the magnitude-frequency characteristic of the transmission parameter S_{21} from 0.3 to 200 MHz in Figure 3b. A frequency point with the maximum amplitude had the highest sensitivity for detecting MIPS; hence, we defined the optimal frequency point as the characteristic frequency (CF). The results showed that the CF of this sensor was 72.32 $\pm$ 0.50 MHz. The amplitude of the primary coil current was 1.2 mA, and maximum magnetic intensity was 0.014 A/m under a frequency of 72.32 MHz and power of 10 dBm, which fully met the requirements of occupational exposure standards by IEEE C95.1.

An intracranial pressure (ICP) monitor was used to measure ICP and reflect changes in rabbit brain edema. To reflect the change of blood flow in a brain region, we used LDF to observe local cerebral blood flow (CBF) perfusion of the rabbits in this study. A multichannel physiological signal acquisition instrument was used to continuously monitor ECG and heart rate.

C. EXPERIMENTAL DESIGN

Twenty-five rabbits (2.2 $\pm$ 0.2 kg, obtained from Daping Hospital, Chong Qing, China) were randomly divided into the experimental groups (unilateral ligation group, n = 10, and the bilateral ligation group n = 10) and the control group

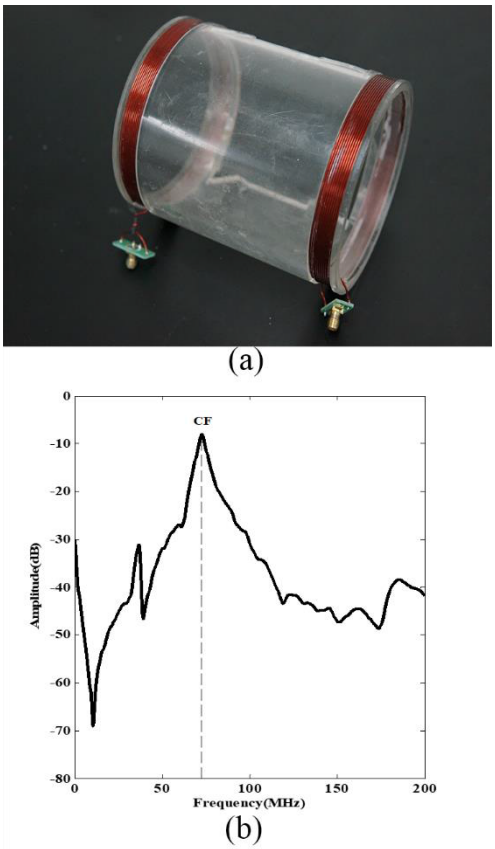

FIGURE 3. The two-coil sensor(a) and magnitude-frequency characteristic from 0.3 MHz TO 200 MHz(b).

(non-ligation group, n = 5). All rabbits received humane care from properly trained hospital professionals. The Animal Experiments and Ethics Committee of the Army Medical University approved all of the experimental protocols, and care of the animals was conducted in accordance with the Declaration of Helsinki and IASP guidelines.

The acute cerebral ischemia rabbit model was established using the common carotid artery ligation method [19]. The rabbits were anesthetized through an ear injection of urethane (25%, 5 ml/kg). We removed the hair on the rabbit's neck and head. The center of the neck skin was cut off after disinfection, and the muscles were separated bluntly, thereby exposing and separating the bilateral common carotid arteries. A surgical ligation line was placed under the common carotid arteries. An ICP probe was fixed on the brain ''cross stitch'' 6 mm left of the coronal suture and 1 mm below the sagittal suture. The LDF probe was placed on the brain ''cross stitch'' 6 mm to the right of the coronal suture and 1 mm below the sagittal suture. Then, the electrodes of the physiological signal acquisition instrument were inserted into the thigh subcutaneously to record the ECG. Finally, the surgical ligation line was fastened to block the common carotid arteries unilaterally or bilaterally for the experiment. The same operations were performed on the three groups, and the detection time was 1 hour for all rabbits. The observed

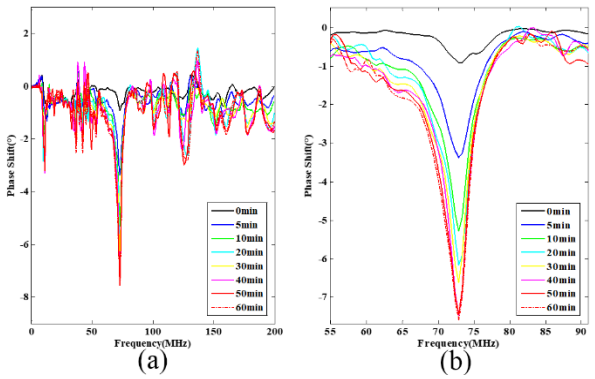

FIGURE 4. (a) Spectra of phase shift as a function of frequency (0.3MHz–200 MHz) for 60min measurement of rabbit No.14. (b) Phase shift around CF, the frequency is on a linear scale.

durations of cerebral ischemia were mainly divided into eight time points to express the results concisely.

In this study, all data are expressed as mean ± standard deviation. We prepared the phase shift spectrum graph of the transmission parameter S_{21} using MATLAB (MathWorks Inc., Natick, MA, USA). Significant differences in the phase shift data were analyzed by the non-parametric Friedman's M-test, and the non-parametric Kruskal–Wallis test We analyzed the relationship between the phase shift and LDF measurements with Pearson's correlation analysis. The statistical analysis was conducted with SPSS12.0 software (SPSS Inc., Chicago, IL, USA), A p-value < 0.05 was considered significant.

III. RESULTS

A. MIPS RESULTS

All rabbits survived the experiment. Notably, the ICP data of the rabbits remained unchanged. In one (no. 14) of the bilaterally ligated rabbits, the ICP remained at 15 ± 2 mmHg, and heart rate decreased from 330 ± 5 to 280 ± 7 after 60 min of ligation time. Figure 4(a) shows the phase shift in the 0.3–200 MHz frequency band during the ligation time. Figure 4(b) illustrates that the phase shift changed with ligation time around the CF. The phase shift increased with the increase of ligation time in a negative way, indicating a strong correlation between the phase shift and ligation time. These results are similar to those reported by Gonzalez *et al.* [10]

The descriptive statistical results of the experimental data at the CF are summarized in Table 1. Five animals were in the non-ligation group, and the unilateral and bilateral groups comprised 10 rabbits. The average phase shift (mean ± SD) in 60 min of the non-ligation group was $-0.195 \pm 0.079°$, the phase shift of the unilateral ligation group was $-4.873 \pm 1.042°$, and the phase shift of the bilateral ligation group was $-9.165 \pm 2.862°$. Friedman's M-test was applied for the phase shift data analysis of the three groups. The p-value of the non-ligated group was 0.363. The p-values of the unilateral and bilateral ligation groups were < 0.05, indicating that the phase shift changed significantly with ligation time. Then,

TABLE 1. Statistical analysis with Friedman's M-test of average phase shift for three groups in which a statistically significant difference of p-value<0.05 was found.

Time(min)	Non-ligation	Unilateral ligation	Bilateral ligation	p-level
0	−0.061±0.046	−0.124±0.209	−0.040±0.437	1.214E-6
5	−0.123±0.055	−1.443±0.522	−2.200±0.567	2.628E-5
10	−0.148±0.039	−2.075±0.689	−3.377±0.913	2.381E-6
20	−0.088±0.023	−3.125±0.590	−6.253±1.573	3.718E-6
30	−0.171±0.113	−3.460±0.545	−7.938±1.754	2.174E-5
40	−0.166±0.022	−4.026±0.825	−8.157±2.179	4.835E-6
50	−0.187±0.029	−4.262±0.985	−8.530±2.269	5.738E-7
60	−0.195±0.079	−4.873±1.042	−9.165±2.862	6.428E-7
p-level	0.363	1.773E-5	1.255E-5	

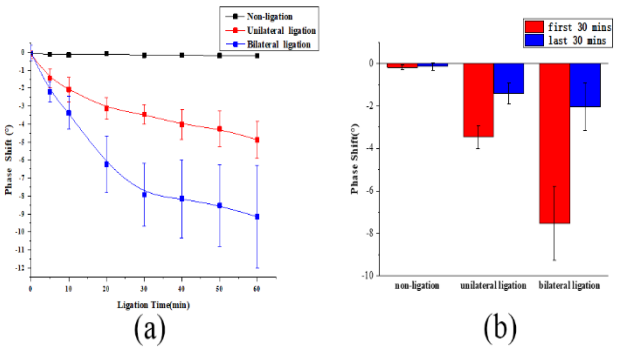

FIGURE 5. (a) Average phase shift of different ligation time for three groups at CF. (b) Phase shift data of first 30 minutes and last 30 minutes.

we used the Kruskal–Wallis test to analyze the differences in the average phase shift among the three groups. The results revealed significant differences among the severe levels of cerebral ischemia ($p < 0.05$), suggesting that we can distinguish different levels of ischemia (non-ligated, unilateral ligation, and bilateral ligation groups) with a phase shift. Above all, the MIPS method provided a new method for detecting early acute cerebral ischemia in rabbits.

Figure 5(a) shows the average phase shift changes of the different ischemia levels with time at the CF. The phase shift presented an obvious difference among the three groups. The phase shift of the non-ligation group was too small and basically remained unchanged within the 60 min measurement, and the phase shift of the unilateral ligation group was smaller than that of the bilateral ligation group. Notably, the curve slope for the first 30 min was larger than the curve slope for the next 30 min in both the unilateral and bilateral ligation groups. As shown in Figure 5(b), the phase shift of the experimental groups in the first 30 min exhibited much larger changes than that in the last 30 min, particularly in the bilateral ligation group.

B. COMPARING THE PHASE SHIFT WITH THE LDF MEASUREMENTS

Figure 6 shows the relationship between the phase shift and LDF measurements of rabbit no. 14. The trend in the phase shift and LDF measurements was very similar. The phase

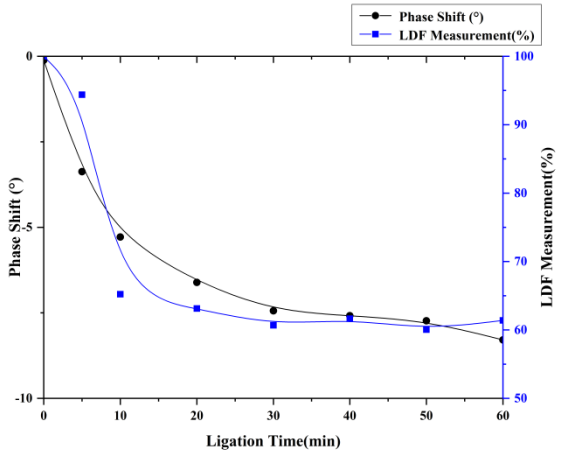

FIGURE 6. The relationship between phase shift and LDF measurement of rabbit No.14.

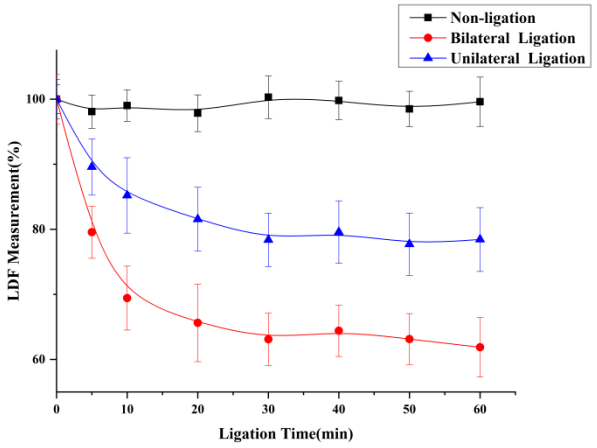

FIGURE 7. The average LDF measurement of three groups.

shift changed gradually with ligation time from −0.12 to −8.29°. The LDF measurement decreased from 100% to 63% in 30 min, and remained dynamically stable for the next 30 min. Then, we drew the average LDF measurements of the three groups in Figure 7. The average LDF measurements of the three groups were very different; the average LDF measurement remained essentially unchanged in the non-ligation group, decreased from 100% to 80% in the unilateral ligation group, and dropped from 100% to 65% in the bilateral ligation group.

CBF is the primary variable in cerebral ischemic rabbits, and a change in CBF can affect whole brain conductivity. This study analyzed the correlation between the phase shift data and LDF measurements using Pearson's correlation coefficient analysis. Table 2 shows the correlations between the phase shift data and the LDF measurements of 20 rabbits. The correlation coefficients of the unilateral ligation group were 0.620–0.783, and the correlation coefficients of the bilateral ligation group were 0.849–0.934. The p-values of the bilateral ligation group were all < 0.05, indicating that the

TABLE 2. Correlation analysis of phase shift and LDF measurement from unilateral ligation and bilateral ligation group.

Group	Sample	Correlation Coefficients	P-value	Group	Sample	Correlation Coefficients	P-value
Unilateral Ligation Group	01	0.767	0.02	Bilateral Ligation Group	11	0.867	0.01
	02	0.732	0.03		12	0.910	0.01
	03	0.721	0.04		13	0.849	0.01
	04	0.620	0.10		14	0.934	0.01
	05	0.709	0.04		15	0.899	0.01
	06	0.679	0.06		16	0.861	0.01
	07	0.705	0.05		17	0.900	0.01
	08	0.698	0.05		18	0.933	0.01
	09	0.783	0.02		19	0.871	0.01
	10	0.723	0.03		20	0.860	0.01

phase shift was strongly positively correlated with the LDF measurement. From Table 2, we can easily determine that the correlations between the phase shift and LDF measurements in the bilateral ligation group were much stronger than those in the unilateral ligation group, demonstrating that the MIPS method is capable of reflecting the changes in CBF caused by intracranial lesions.

IV. DISCUSSION

CT and MRI are the most commonly used detection methods in the clinic for diagnosing cerebral ischemia. However, these devices are too bulky and immobile and cannot be used for a pre-hospital diagnosis. Time is the most important indicator when trying to detect and diagnose cerebral ischemia. According to the guidelines [3], the golden time window of intravenous thrombolysis for ischemia stroke is 4.5 hours. However, the detection time resolution of these medical imaging systems is very low because of the long delivery and preparation time. Many groups have reported detection methods for diagnosing brain ischemia, such as near-infrared spectroscopy (NIRS) and electrical impedance tomography (EIT). However, NIRS has some disadvantages in detection depth and invasion. In 2010, Robertson et al. illustrated that NIRS can only detect intracranial hemorrhages > 3.5 ml at a depth of 2.5 cm [20]. In 2018, Neeraja et al. reported that the penetration depth of the sensor is inadequate to compensate for the increased distance between the sensor and brain tissue, thereby resulting in inaccurately high values (>80%) [21]. A shortcoming of EIT is that the highly resistant skull has a natural electrical isolation that limits current penetration and restricts deep imaging of the brain [22]. The main magnetic field created by a detection system can easily penetrate the skull although resistance is very high. According to this basic biophysical principle, we can detect a certain phase difference (MIPS) between the induced magnetic field and the main magnetic field. The change in the phase shift mainly relates to the electromagnetic properties (electrical conductivity) of brain tissues during the MIPS measurement [7]. The coaxial parallel dual-coil structure and the relative position between the rabbit's head and the coil determines that MIPS reflects conductivity changes of the whole rabbit head. A change in conductivity of the whole brain is related to the

physiological change and when ischemia occurred. Ischemia causes changes in the electromagnetic properties of brain tissues [23]. Serguei et al. studied the dielectric properties of swine brain tissues with acute ischemia stroke at 1 GHz using the open-ended coaxial probe measurement technique. They demonstrated that acute ischemic stroke causes immediate changes in the dielectric properties of brain tissue, and the degree of such changes depends on the development of ischemic injury [24].

The cranial cavity can be considered a rigid irregular sphere with an unchanged volume. The irregular sphere is filled with brain tissue, cerebrospinal fluid (CSF), and blood. In this study, we controlled the ligation time to be 1 hour to simulate early rapid cerebral ischemia. Ligation of the common carotid artery significantly reduced the CBF and resulted in a shortage of blood supply. Chen *et al.* [25] demonstrated the quantitative relationship between MIPS and CBF in the rabbit brain hemorrhage model and discussed how CSF affects the electrical properties of brain tissue. In the present study, ICP did not change when brain ischemia occurred, demonstrating that there was no intracranial edema during the early stage. Therefore, we believe that the reduction in CBF was the key factor associated with the conductivity changes. Hence, we used LDF as the gold standard for collecting the CBF data. The complex impedance of biological tissues can be categorized into three dielectric dispersion domains based on the frequency range from KHz to GHz [26]. Three dielectric dispersion domains are marked α, β, and γ, which represent 1 Hz–kHz, 0.1–100 MHz, and 0.1–100 GHz frequency range respectively. The β-domain is mainly caused by a capacitive short circuit of the cell membrane and rotational relaxation of the biopolymer, which reflects the characteristics between the extracellular and intracellular fluid [27]. The measuring characteristic frequency in this study was 72.32 MHz and was located in the β-domain. The CBF of the blood vessels decreased significantly when brain ischemia occurred, which also decreased the exchange of substances between the blood and brain cells; thus, causing a significant change in conductivity. As discussed above, MIPS reflects the change in conductivity of the whole brain.

Gonzalez *et al.* [10] reported focal cerebral ischemia results in rats during 24 hours of long-term monitoring. Unlike them, we detected brain ischemia in rabbits over 1 hour to obtain an early rapid diagnosis and observe global cerebral ischemia, which might be helpful for diagnosing ischemia in elderly patients. As shown in Figure 4, the phase shift at the CF changed significantly, which was similar with the results of Pan *et al.* [14] The power transfer efficiency at CF of the detection system was maximum, and the stronger main magnetic field stimulated the stronger disturbance in the magnetic field of the brain lesions, resulting in a greater measured phase shift. As shown in Figure 5, the phase shift of the non-ligation group remained basically unchanged, whereas the phase shift of the unilateral and bilateral ligation groups changed significantly. The phase shift declined rapidly during the previous period and then decreased much slower during the later period, demonstrating that MIPS has early sensitivity for detecting brain ischemia in rabbits. The strong correlation between the MIPS and LDF measurements illustrates that the MIPS detection method reflects changes in CBF during ischemia (Table 2). The MIPS decreased correspondingly when CBF decreased, and the more the CBF decreased, the more MIPS decreased. We believe that CBF decreased significantly mainly due to ligation of the common carotid artery and the resulting change in conductivity of the whole brain. The changes in brain conductivity were reflected by MIPS. As a consequence, the correlation between the MIPS and LDF measurements demonstrated the feasibility of measuring brain ischemia in rabbits using the MIPS detection method. Taken together, the MIPS method shows the potential for detecting brain ischemia during the early stage and to reflect different levels of ischemia.

The detection method used in this study was completely non-invasive. The MIPS data analysis completely demonstrated the feasibility of this method for early detection of acute cerebral ischemia in rabbits. We were able to clearly distinguish differences in healthy rabbits (non-ligation group), generally ischemic rabbits (unilateral ligation group), and severely ischemic rabbits (bilateral ligation group) to achieve rapid detection and diagnosis of acute cerebral ischemia. The changes in CBF and MIPS showed a certain degree of correlation, indicating the validity of our experimental results.

The results of this study show that the MIPS method provides a new way to detect and diagnose the severity of global acute cerebral ischemia. However, some limitations, should be mentioned; we only preliminarily discussed the relationship between the change in MIPS and CBF, without studying changes in other brain tissues. More parameters, such as imaging data, need to be collected for further comprehensive and in-depth analyses.

V. CONCLUSION

We developed the MIPS method to detect acute cerebral ischemia in rabbits. Our experimental results show the possibility of early detection of global acute cerebral ischemia and the potential to distinguish the severity of cerebral ischemia in rabbits. This preliminary study was mainly based on a rabbit model, so further experiments with large animals, such as monkeys, are required as the next stage. Given that current experiments were focused on global acute cerebral ischemia, further research remains necessary to study local cerebral ischemia, which is closer to the actual clinical situation. We also need to analyze the MIPS data and study the imaging algorithm to obtain imaging data for clinical needs. Although clinical cerebral ischemia is a highly complex process, this preliminary study provides the feasibility of detecting global acute cerebral ischemia using the MIPS method.

ACKNOWLEDGMENT

(Wei Zhuang, Wencai Pan, and Lin Xu contributed equally to this work.)

REFERENCES

[1] M. E. Raichle, "The pathophysiology of brain ischemia," *Ann Neurol.*, vol. 13, no. 1, pp. 2–10, Jan. 1983.
[2] L. R. Caplan, Ed., *Caplan's Stroke: A Clinical Approach*. Cambridge, U.K.: Cambridge Univ. Press, 2016.
[3] W. J. Powers, A. A. Rabinstein, T. Ackerson, O. M. Adevoe, N. C. Bambakidis, and K. Becker, "2018 guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association," *J. Vascular Surg.*, vol. 67, no. 6, p. 1934, Jun. 2018.
[4] S. K. Kim, W. Yoon, T. S. Kim, H. S. Kim, T. W. Heo, and M. S. Park, "Histologic analysis of retrieved clots in acute ischemic stroke: Correlation with stroke etiology and gradient-echo MRI," *Amer. J. Neuroradiol.*, vol. 36, no. 9, pp. 1756–1762, Sep. 2015.
[5] A. Varga, G. Di Leo, P. V. Banga, C. Csobay-Novák, M. Kolossváry, P. Maurovich-Horvat, and K. Hüttl, "Multidetector CT angiography of the Circle of Willis: Association of its variants with carotid artery disease and brain ischemia," *Eur. Radiol.*, vol. 29, no. 1, pp. 46–56, Jan. 2019.
[6] H. C. Roberts, W. P. Dillon, A. J. Furlan, L. R. Wechsler, H. A. Rowley, N. J. Fischbein, R. T. Higashida, C. Kase, G. A. Schulz, Y. Lu, and C. M. Firszt, "Computed tomographic findings in patients undergoing intra-arterial thrombolysis for acute ischemic stroke due to middle cerebral artery occlusion: Results from the PROACT II trial," *Stroke*, vol. 33, no. 6, pp. 1557–1565, Jun. 2002.
[7] P. Tarjan and M. Richard, "Electrodeless measurements of the effective resistivity of the human torso and head by magnetic induction," *IEEE Trans. Biomed. Eng.*, vol. BME-15, no. 4, pp. 266–278, Oct. 1968.
[8] H. Griffiths, W. R. Stewart, and W. Gough, "Magnetic induction tomography: A measuring system for biological tissues," *Ann. New York Acad. Sci.* vol. 873, no. 1, pp. 335–345, 1999.
[9] C. A. Gonzalez, L. Horowitz, and B. Rubinsky, "*In vivo* inductive phase shift measurements to detect intraperitoneal fluid," *IEEE Trans. Biomed. Eng.*, vol. 54, no. 5, pp. 953–956, May 2007.
[10] C. A. González, C. Villanueva, C. Vera, O. Flores, R. D. Reyes, and B. Rubinsky, "The detection of brain ischaemia in rats by inductive phase shift spectroscopy," *Physiol. Meas.*, vol. 30, no. 8, pp. 809–819, Aug. 2009.
[11] C. A. Gonzalez, J. A. Valencia, A. Mora, F. Gonzalez, B. Velasco, M. A. Porras, J. Salgado, S. M. Polo, N. Hevia-Montiel, S. Cordero, and B. Rubinsky, "Volumetric electromagnetic phase-shift spectroscopy of brain edema and hematoma," *PLoS ONE*, vol. 8, no. 5, May 2013, Art. no. e63223.
[12] G. Jin, J. Sun, M. Qin, C. Wang, W. Guo, Q. Yan, B. Peng, and W. Pan, "A special phase detector for magnetic inductive measurement of cerebral hemorrhage," *PLoS ONE*, vol. 9, no. 5, May 2014, Art. no. e97179.
[13] G. Jin, J. Sun, M. Qin, Q. Tang, L. Xu, X. Ning, J. Xu, X. Pu, and M. Chen, "A new method for detecting cerebral hemorrhage in rabbits by magnetic inductive phase shift," *Biosensors Bioelectron.*, vol. 52, pp. 374–378, Feb. 2014.
[14] W. Pan, Q. Yan, M. Qin, G. Jin, J. Sun, X. Ning, W. Zhuang, B. Peng, and G. Li, "Detection of cerebral hemorrhage in rabbits by time-difference magnetic inductive phase shift spectroscopy," *PLoS ONE*, vol. 10, no. 5, May 2015, Art. no. e0128127.
[15] G. Li, K. Ma, J. Sun, G. Jin, M. Qin, and H. Feng, "Twenty-four-hour real-time continuous monitoring of cerebral edema in rabbits based on a noninvasive and noncontact system of magnetic induction," *Sensors*, vol. 17, no. 3, p. 537, Mar. 2017.
[16] S. Zhao, G. Li, S. Gu, J. Ren, J. Chen, L. Xu, M. Chen, J. Yang, K. W. Leung, and J. Sun, "An experimental study of relationship between magnetic induction phase shift and brain parenchyma volume with brain edema in traumatic brain injury," *IEEE Access*, vol. 7, pp. 20974–20983, 2019.
[17] H. Scharfetter, R. Casanas, and J. Rosell, "Biological tissue characterization by magnetic induction spectroscopy (MIS): Requirements and limitations," *IEEE Trans. Biomed. Eng.*, vol. 50, no. 7, pp. 870–880, Jul. 2003.
[18] A. D. Yaghjian and S. R. Best, "Impedance, bandwidth, and Q of antennas," *IEEE Trans. Antennas Propag.*, vol. 53, no. 4, pp. 1298–1324, Apr. 2005.
[19] M. L. Smith, G. Bendek, N. Dahlgren, I. Rosén, T. Wieloch, and B. K. Siesjö, "Models for studying long-term recovery following forebrain ischemia in the rat. 2. A 2-vessel occlusion model," *Acta Neurol. Scandinavica* vol. 69, no. 6, pp. 385–401, 1984.
[20] C. S. Robertson, E. L. Zager, R. K. Narayan, N. Handly, A. Sharma, D. F. Hanley, H. Garza, E. Maloney-Wilensky, J. M. Plaum, C. H. Koenig, A. Johnson, and T. Morgan, "Clinical evaluation of a portable near-infrared device for detection of traumatic intracranial hematomas," *J. Neurotrauma*, vol. 27, no. 9, pp. 1597–1604, Sep. 2010.
[21] N. Ajayan, K. Thakkar, K. R. Lionel, and A. P. Hrishi, "Limitations of near infrared spectroscopy (NIRS) in neurosurgical setting: Our case experience," *J. Clin. Monit. Comput.*, vol. 33, no. 4, pp. 743–746, Aug. 2019.
[22] J. Song, R. Chen, L. Yang, G. Zhang, W. Li, Z. Zhao, C. Xu, X. Dong, and F. Fu, "Electrical impedance changes at different phases of cerebral edema in rats with ischemic brain injury," *BioMed Res. Int.*, vol. 2018, pp. 1–10, Jun. 2018.
[23] E. Gersing, "Impedance spectroscopy on living tissue for determination of the state of organs," *Bioelectrochem. Bioenergetics*, vol. 45, no. 2, pp. 145–149, May 1998.
[24] S. Semenov, T. Huynh, T. Williams, B. Nicholson, and A. Vasilenko, "Dielectric properties of brain tissue at 1 GHz in acute ischemic stroke: Experimental study on swine," *Bioelectromagnetics*, vol. 38, no. 2, pp. 158–163, Feb. 2017.
[25] M. Chen, Q. Yan, J. Sun, G. Jin, and M. Qin, "Investigating the relationship between cerebrospinal fluid and magnetic induction phase shift in rabbit intracerebral hematoma expansion monitoring by MRI," *Sci. Rep.*, vol. 7, no. 1, 2017, Art. no. 11186.
[26] O. G. Martinsen and S. Grimnes, *Bioimpedance and Bioelectricity Basics*. New York, NY, USA: Academic, 2011.
[27] J. L. Schepps and K. R. Foster, "The UHF and microwave dielectric properties of normal and tumour tissues: Variation in dielectric properties with tissue water content," *Phys. Med. Biol.*, vol. 25, no. 6, pp. 1149–1159, Nov. 1980.