A Dual Parameter Synchronous Monitoring System of Brain Edema Based on the Reflection and Transmission Characteristics of Two-Port Test Network

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ABSTRACT As a common secondary disease, edema after traumatic brain injury (TBI) can increase brain volume, resulting in elevated intracranial pressure (ICP), brain shift, and cerebral hernia, and can eventually lead to death. The real-time continuous monitoring of edema may significantly reduce mortality and disability. In this paper, a dual-parameter synchronous monitoring system of edema based on the reflection and transmission characteristics of the two-port test network was established; 15 rabbits were chosen to perform 24-h reflection phase shift (RPS) and transmission phase shift (TPS) simultaneously monitoring the experiments of brain edema. With the development of brain edema, the variation law of the RPS and TPS was investigated. Combined with the power amplitude spectrum and the principle of the two-port test network, the influence of frequency on the detection sensitivity of RPS and TPS was analyzed in detail, and the optimal detection frequency point was found. After that, the classification of three different degrees of edema is performed by the BP algorithm. In the animal experiment, the RPS showed a continuous increasing trend within time, and it presented the variation of (9.35910° ± 1.65702°), (12.60117° ± 2.30218°), and (16.33423° ± 2.11118°) after 6, 12, and 24 h, respectively. Meanwhile, the TPS showed a continuous downward trend with the variation of (−12.62555° ± 0.99441°), (−19.23976° ± 1.27488°), and (−27.26285° ± 2.62291°) after 6, 12, and 24 h, respectively. The RPS was negatively correlated with the TPS. The RPS and the TPS together as a recognition feature can achieve 100% accurate classification of three different brain edema severities. Based on these results, it can be concluded that the system established in this paper can monitor gradual increases in brain edema severity. Furthermore, neither the RPS nor the TPS can be set as the recognition feature alone to achieve the completely accurate classification, which shows the necessity of presenting two parameters in the monitoring process.

INDEX TERMS Brain edema, two-port test network, synchronous monitoring, classification.

I. INTRODUCTION
Traumatic brain injury (TBI) is one of the leading causes of death and disability worldwide. TBI serious enough can result in hospitalization or death and is projected to affect 10 million people annually, plus an estimated 57 million individuals previously hospitalized with two or more TBIs [1]. Brain edema is a very common secondary disease after TBI. Previous studies demonstrate that the presence of brain edema is a significant independent prognostic factor in TBI [2–4].
This suggests that brain edema may lead to secondary damage, which disposes the patient to a less favorable outcome. The additional brain injury stemming from edema may result from local ischemia due to increased intracranial pressure, decreased microcirculatory flow, or neurovascular inflammation [5]–[7]. In addition, the intracellular swelling that characterizes cytotoxic edema after TBI may increase production of reactive oxygen species, known to play an important role in the pathophysiology of TBI [8], [9]. Therefore, the real-time continuous monitoring of brain edema plays a significant role in disease observation, treatment guidance, surgery timing determination and prognosis evaluation for patients after TBI.

Currently, the detection of brain edema mainly depends on imaging equipment, intracranial pressure monitoring, and subjective judgment of clinicians. ICP that is divided into invasive and non-invasive methods can reflect intracranial edema through indirect measurement. With regard to the invasive method, the detection sensors are required to be placed into the cranium, causing pain to patients and easily leading to infection [10]. The non-invasive monitoring of ICP can avoid the risk of infection and cerebral hemorrhage, but it presents several disadvantages in terms of large individual differences, slight inaccuracy and less applications. Non-invasive monitoring of brain edema relies mainly on CT, MRI, DWT, and PET imaging, as well as other detection methods. It is useful to measure computerized tomography (CT) and magnetic resonance image (MRI) within 6 hours of a traumatic brain injury [11]. Serial CT findings in the first 2 days are useful to identify patients at high risk for developing symptomatic swelling [12]. However, imaging detection equipment is very expensive, bulky and difficult to operate. The imaging equipment cannot achieve real-time continuous bedside monitoring for brain edema. The occurrence of brain edema can also be found by the subjective judgments of clinicians [13], but the pathogenesis of brain edema is slow and generally does not cause obvious clinical signs, which obstructs even experienced clinicians to make timely and accurate judgment. Therefore, clinical practice needs a new method for bedside and real-time monitoring of edema urgently.

Magnetic induction phase shift (MIPS) is a non-contact technology which uses induction to obtain electrical parameters from the sample, eliminating the need for electrodes and their related drawbacks [14]. It is well established that the complex electrical impedance of tissue, when measured over a range of frequencies, can be used for tissue characterization [15]. This suggested to us that our design goals could be accomplished with a device that could measure the complex impedance of tissue thus providing valuable information about tissue structure. The volumetric electromagnetic phase-shift spectroscopy (VEPS) method presented by Gonzalez et al. is self-referencing and can be performed in short time, providing instantaneous information [16]. VEPS can be used for diagnosis to detect brain damage and even distinguish patients with edema from those with hematoma [17]. O’Toole et al. described a multi-frequency magnetic induction spectroscopy (MIS) system suitable for industrial-scale, non-contact, spectroscopic bioimpedance measurement over a bandwidth of 156 kHz–2.5 MHz [18]. However, these measurements were made at a lower frequency range and the limited number of frequencies were restricted to learn detailed information tissue structure. Therefore, in our previous work, a MIPS detection system which can sweep the measured target within the entire frequency range of 300 kHz–200 MHz was constructed [19]. Although this system is basically capable of monitoring gradual increases in the edema solution volume by observing the real-time MIPS change trend, it can’t classify and identify the severity of brain edema. For different individuals, the progression of brain edema after TBI are not the same [20]. Therefore, the classification concerning the severity of brain edema can help clinicians to make accurate judgments more effectively and more directly [21], [22]. In addition, the two-port network test system contains the characteristics of reflection and transmission, as mentioned in the previously reported studies, merely using the reflection phase shift (RPS) or Transmission phase shift (TPS) presents disadvantages in terms of low sensitivity and large individual differences [23]–[25], which has brought difficulties for classifying the severity of brain edema. In addition, how the frequency of excitation signal can impact on test results within a wide frequency band and how the RPS and TPS present their variation law after the pathological changes of brain and the relationship each other are not clearly illustrated. These are of great significance for using the magnetic induction method to detect the cerebrovascular diseases such as cerebral hemorrhage, brain edema, and cerebral ischemia and so on [26]–[30].

In this study, a dual parameter synchronous phase shift spectrum monitoring system of brain edema was established by making use of the reflection and transmission characteristics of the two-port test network. In the 24-hour brain edema monitoring experiment of 15 rabbits, the power amplitude spectrums of reflected and transmitted signals within the frequency band of 300kHz–300MHz were obtained. Then, with the development of brain edema, the variation law of both reflection phase shift spectroscopy (RPSS) and transmission phase shift spectroscopy (TPSS) composed of the phase shifts on 1601 frequency points in the scanning range was studied. Combined with the variation of RPSS and TPSS, the power amplitude spectrum and the two-port network test principle, the influence of frequency on the sensitivity was analyzed in detail, and the optimal detection frequency of RPS and TPS was found. Finally, via BP neural network, the classification of three different degrees of brain edema are performed based on 24-hour data of the RPS and TPS at the optimal frequency. By using RPS and TPS respectively as identification features, and both as identification features together, the accuracy of the classification was compared.

II. MATERIALS AND METHODS

A. EXPERIMENTAL SYSTEM

The dual parameter synchronous phase shift spectrum monitoring system of brain edema, as shown in Figure 1, mainly
The transmission coefficient refers to the relationship between the transmission signal and the incident signal:

\[
\text{Transmission Coefficient} = \frac{V_{\text{transmitted}}}{V_{\text{incident}}} = \tau \angle \varphi
\]  

(2)

where \(\rho\) and \(\tau\) are the amplitude of reflection coefficient and transmission coefficient respectively. \(\theta\) and \(\varphi\) are the phase of reflection coefficient and transmission coefficient respectively.

The size of \(\rho\) and \(\tau\) determines the efficiency of reflection and transmission, affecting the sensitivity and stability of the entire monitoring system. This brings the problem of impedance matching. When the impedance matching is better, the loss of the entire monitoring system is lower, the detection sensitivity is higher, the stability is better and the anti-interference ability is stronger \[32\]. In this study, the power sweep method is adopted to study the impedance matching problem by scanning the amplitude spectrum of the reflection and transmission.

The magnitude of \(\theta\) and \(\varphi\) are related to the dielectric properties of the measured target \[33\]. When its dielectric property is changed, the \(\theta\) and \(\varphi\) will shift, being defined as RPS and TPS respectively. Regardless of the mechanisms of edema, accumulation of fluid and a change in the water composition of the tissue is bound to change the dielectric properties of tissue. Through the RPSS and TPSS variation which contains 1601 RPS and TPS within the frequency range of 300 kHz-300MHz respectively, a dual parameter synchronous dynamic monitoring of brain edema was achieved in this study. Furthermore, the monitoring system is equipped with a software controller to complete the setting of the measurement parameters and realize the real-time continuous data collection of the RPSS and TPSS automatically.

C. ANIMAL EXPERIMENT

All animal experiments were performed in accordance with the guidelines from the Administration of Animal Experiments for Medical Research Purposes issued by the Ministry of Health of China. The protocol used was reviewed and approved by the Animal Experiments and Ethical Committee of Third Military Medical University (TMMU, Chongqing, China). All efforts were made to minimize the suffering of rabbits during experiments. Fifteen rabbits (available from the Laboratory Animal Center of the Third Military Medical University, weighing 2.0-2.6 kg and marked No.1 to No.15) were first injected with urethane (25%, 5 ml) in an ear vein for anesthesia. The hair was removed from the head, and then a hole was drilled beside the “cross stitch” of the brain, forming a 5 mm \(\times\) 5 mm bone window and exposing the dura-mater. Next, a cryopencil was immersed in liquid nitrogen for a sufficient time and was then put into the bone window for freezing. The freezing temperature was \(-196^\circ\text{C}\) and the freezing time was 120 seconds; dental cement was used to seal the bone window.

As shown in Figure 2, the rabbits were placed into the coil sensor after above operation. When the life physical signs of...
the rabbit were stable, a 24- hour continuous collection of the RPSS and TPSS data was conducted with a sampling rate of 2 times / hour.

D. STATISTICAL ANALYSIS
All the data are expressed as the mean±standard deviation from 10 independent experiments at least. In the animal experiment, the RPS after 6, 12 and 24 hours and the TPS after 6, 12 and 24 hours at the optimal detection frequency were analyzed with a paired-samples t-test respectively. The significance level was set at $\alpha = 0.05$. In addition, The Pearson correlation analysis of the 24-hour RPS and the 24-hour TPS was performed at the optimal detection frequency. The significance level was set at $\alpha = 0.05$. Statistical analyses were performed using SPSS software version 19.0 (SPSS Inc., Chicago, USA).

E. BP NEURAL NETWORK FOR BRAIN EDEMA SEVERITY
Brain edema after TBI is a complex process. Based on the reported work, rabbits developed a severe brain edema 6 hours after freezing outside the dural mater, and the development of edema presented a progressive feature and peaked at the 24th hour [34]. Brain water content obtained by wet-dry weighing method is an accurate quantitative index for evaluating the severity of pathological changes in brain edema. Previous studies have shown that the brain water content of the brain tissue after 6 hours, 12 hours, and 24 hours were (79.875±0.2785)%, (81.016±0.2845)%, (82.126±0.2875)% and there was significant difference [35]. The model of brain edema and the surgical procedure are exactly the same as before. Therefore, 6 hours, 12 hours and 24 hours after freezing were defined as the three degrees of brain edema in this work. By using BP neural network, the classification of the three degrees of brain edema was performed at the optimal detection frequency points. Twelve groups of experimental data (N = 36) were randomly selected as training samples, and three experimental data (N = 9) were used as test samples. In the process of identification, RPS and TPS respectively and both together were used as recognition features, and the test samples were identified for three times. The MATLAB neural network toolbox was used to set up the model, the hidden layer node was set to 6 and the output layer node was set to 1. The hidden layer function was set as hyperbolic tangent sigmoid function and the output layer function was set as linear regression function. The training target was set to 0.00001. What’s more, normalization was performed before the feature entered the neural network training.

III. RESULTS
A. EFFECT OF FREQUENCY ON RPSS AND TPSS DETECTION
The power amplitude spectrums of the reflected and transmitted signals were shown in Figure 3. $f_1$ (64.14859 ± 0.77481MHZ), $f_2$ (136.8913±1.88573MHZ), $f_3$ (202.8847 ± 2.06434) and $f_4$ (285.56394 ± 2.68748) were four frequency points of excitation signal. They presented larger return loss of the reflected signal, and $f_1$ corresponded to $f_6$ (64.14396 ± 0.31592MHZ) which featured in the minimum insertion loss of the transmission signal. This indicated that the return loss of $f_1$ was due to the fact that most of the incident signal was transmitted to port 2 through the brain. Under this condition, the impedance matching was good, the efficiency of the entire monitoring system was higher so that both the RPS and the TPS should present higher sensitivity. In contrast, $f_2$, $f_3$ and $f_4$ corresponded to the three frequency points which feature in larger insertion loss of the transmission signal. It indicated that most of the energy was lost in the signal transmission and reflection process. Then the impedance matching was very poor. The poor impedance matching will lead to the relatively weak energy of the incident signal itself [36]. These combined factors cause the lower sensitivity and stability of the RPS and the TPS.

According to above analysis of power and amplitude spectrum from reflected and transmission signals based on two-port testing principle, it can be inferred that when detecting brain edema on the system established in this work, $f_1$ is the ideal detection frequency point for RPS and $f_6$ is the optimal frequency point for TPS detection. Ideally, the frequency which features in the maximum transmission efficiency should correspond to the frequency of minimum reflection efficiency [37]. In this work, the frequency which features in the maximum amplitude of the transmission signal can be used in both RPS and TPS detection within a certain error range.
FIGURE 4. (a) The 24-hour average RPSS results of the 15 rabbits after freezing. (b) The 24-hour average TPSS results of the 15 rabbits after freezing.

B. RPSS AND TPSS CHANGES IN 24-HOUR

The 24-hour average RPSS results of the 15 rabbits after freezing were shown in Figure 4(a). With the development of brain edema, the RPS of $f_1$, $f_2$, $f_3$ and $f_4$ presented obvious variation where $f_1$ had the largest variation range. And the rest of the frequency points on the band of 300 KHz-300 MHz had no obvious changes. In the 24-hour average TPSS results of the 15 rabbits, as shown in Figure 4(b), the TPS of $f_5$, $f_6$, $f_7$ and $f_8$ showed obvious changes, and the detection sensitivity of $f_6$ was the highest. The remaining frequency points also presented variation but with no obvious variation law, featuring in smaller variation range. These results were consistent with the inference that $f_1$ was the ideal detection frequency point for RPS and $f_6$ was the optimal frequency point for TPS detection.

Figure 5 showed the 24 hours variation trend of the RPS at $f_1$ and the TPS at $f_6$. The RPS at $f_1$ showed a continuous increase trend within time, and it presented the variation of $9.35910 \pm 1.65702\degree$, $12.60117\degree \pm 2.30218\degree$ and $16.33423 \pm 2.11118\degree$ after 6, 12 and 24 hours respectively. Meanwhile, the TPS on the frequency of $f_6$ performed a downward trend in 24-hour, which was consistent with our previous work. It showed the variation of $-12.62555 \pm 0.99441\degree$, $-19.23976 \pm 1.27488\degree$ and $-27.26285 \pm 2.62291\degree$ after 6, 12 and 24 hours respectively. Edema can lead to the variation in the total dielectric coefficient of the brain, thus inevitably leading to variation in the reflected signals [16], [17], [19]. Hence the continuous increase trend of the RPS at $f_1$ can also reflect the development of brain edema.

For the RPS after 6, 12 and 24 hours and the TPS after 6, 12 and 24 hours, the paired T-test, featuring in a significant level of 0.05, were conducted. And the results were shown in Table 1. The P values of each group were less than 0.05, indicating that there were significant differences in the RPS and TPS at 6h, 12h and 24h after freezing. Therefore, the RPS and the TPS at the 3 time points (6, 12, 24 hours post freezing) were used for classification of brain edema severity levels in this study.

C. CLASSIFICATION OF BRAIN EDEMA SEVERITY

Three different severity levels (1, 2, 3) of the brain edema corresponding to the RPS and TPS were classified. Twelve group were selected as training samples ($N = 36$). As shown in Figure 6 (a), the number of training sessions reached 1000 times and took 4 seconds under ordinary PC. As the number of training increased, the mean square error gradually decreased, indicating that the training gradually converged. As shown in Figure 6 (b), the R value was 0.97992 in the given fitting equation, indicating that the fitting effect was very good.
The rest three groups (A, B, C) were set as test samples (N = 9), which were numbered in the chronological order as A1, A2 and A3; B1, B2 and B3; C1, C2 and C3 respectively. The test results were shown in Figure 7.

When the RPS was identified as an identification feature, the A1 was mistakenly recognized as 2, the C2 was mistakenly recognized as 1 and the C3 was mistakenly recognized as 2, but the remaining test samples presented correct recognition, so the correct rate of recognition was 66.67%; when the TPS was identified as a recognition feature, the B1 was mistakenly recognized as 2 and the C3 was mistakenly recognized as 2, so the correct rate of recognition was 77.78%. However, when both the RPS and TPS were identified as identification features, all the 9 test samples were identified correctly and the correct rate of recognition was 100%. In the 24-hour rabbit’s brain edema monitoring experiment, both the RPS and TPS can reflect the increases in the brain edema solution, but in the classification of different degrees of severity, it was better to use both the TPS and the RPS as the recognition features, which presented a better outcome than the respective way. This indicates that using the parameters of RPS and TPS can achieve a more effective classification concerned.

IV. DISCUSSION

The establishment of the brain edema monitoring system that is safe for animals or human beings was based on the two-port test network and it shows several advantages, namely, being non-invasive, non-contact, small size and so on. After the edema, the changing of brain volume and the brain water content cause the variation in the total average dielectric coefficient of the brain, so that the RPSS and the TPSS are changed. In the previous work, the target field accounts for a small proportion of the whole disturbing magnetic field. Hence, the signal of interest is extremely weak [23]–[30]. In this work, within the frequency range of 300kHZ-300MHZ, combined with the power amplitude spectrum which reflects the signal reflection and transmission efficiency of the two-port network and the variation of the RPSS and the TPSS which reflected the increase of the brain edema solution volume, the optimal detection frequency featuring in the better impedance matching and the higher sensitivity and stability of the RPS and the TPS were found.

The mechanism of the frozen traumatic brain injury model was single, simple, and easy for qualitative research [38]. The blood-brain barrier in rabbits after freezing was damaged, and vasogenic brain edema rapidly occurred accompanied by cytotoxic brain edema. And the development of edema was progressive and peaked after 24 hours. The BWC at the 24th hour after freezing was significantly higher than that of the rabbits without freezing [19], [35]. The RPS and the TPS showed a trend of a rapid variation in the early period, but a gradual decline in the late period, which was consistent with the mechanism of this brain edema model induced by freezing. Compared with the RPSS and TPSS results of animal experiments, it is not difficult to find that the RPSS is more consistent, but the TPSS is quite different, which is determined by different properties between the transmitted signals and the reflected signals. When the incident signal is transmitted to the measured target through port 1, a part of the signal penetrates the measured target and reaches port 2, that is, the transmission signal. The other part of the signal does not penetrate the measured target, but directly being reflected back to port 1, that is, the reflected signal. Hence the TPSS contains more information on the changes of the internal dielectric coefficient of the measured target than that of the RPSS [39]. According to the law of energy conservation, the energy sum of the reflected signal and the transmitted signal is equal to the energy of the incident signal, and the change of the transmitted signal strength will inevitably cause the change of the reflected signal [40]. The Pearson correlation analysis of the 24-hour RPS and the 24-hour TPS with a significance level of 0.05 was performed at the optimal detection frequency. The results are shown in Table 2. The correlation coefficient between the 24-hour RPS and the 24-hour TPS of 15 rabbits was between -0.993 and -0.949,
TABLE 2. Correlation analysis of RPS and TPS.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Correlation Coefficient</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.1 rabbit</td>
<td>-0.986</td>
<td>2.068×10^-38</td>
</tr>
<tr>
<td>No.2 rabbit</td>
<td>-0.967</td>
<td>1.876×10^-29</td>
</tr>
<tr>
<td>No.3 rabbit</td>
<td>-0.959</td>
<td>2.236×10^-26</td>
</tr>
<tr>
<td>No.4 rabbit</td>
<td>-0.971</td>
<td>8.338×10^-31</td>
</tr>
<tr>
<td>No.5 rabbit</td>
<td>-0.987</td>
<td>4.060×10^-39</td>
</tr>
<tr>
<td>No.6 rabbit</td>
<td>-0.985</td>
<td>9.528×10^-38</td>
</tr>
<tr>
<td>No.7 rabbit</td>
<td>-0.971</td>
<td>7.858×10^-33</td>
</tr>
<tr>
<td>No.8 rabbit</td>
<td>-0.988</td>
<td>1.442×10^-39</td>
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<tr>
<td>No.9 rabbit</td>
<td>-0.986</td>
<td>6.269×10^-38</td>
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<td>No.10 rabbit</td>
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<tr>
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<td>3.565×10^-29</td>
</tr>
<tr>
<td>No.12 rabbit</td>
<td>-0.989</td>
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</tr>
<tr>
<td>No.13 rabbit</td>
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<td>2.809×10^-25</td>
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<tr>
<td>No.14 rabbit</td>
<td>-0.993</td>
<td>2.300×10^-45</td>
</tr>
<tr>
<td>No.15 rabbit</td>
<td>-0.986</td>
<td>2.068×10^-38</td>
</tr>
</tbody>
</table>

V. CONCLUSION

This study established a dual parameter synchronous phase shift spectrum monitoring system of brain edema based on the reflection and transmission characteristics of the two-port network test system. This method has advantages of noninvasiveness, noncontact, good portability, and real-time continuous bedside monitoring. Combined with the power amplitude spectrum of the reflected and transmitted signals and the two-port network test principle, the optimal detection frequency of RPS and TPS with a better impedance matching is found. Based on the RPS and TPS at the optimal detection frequency, three different degrees of brain edema were classified correctly, and the correct rate of recognition was 100%. But the three different degrees of brain edema were only determined by the BWC which is too simple for clinical application. Therefore, other experimental animal models such as weight-drop-induced TBI will be used to mimic closed-he ad injury in humans [44]. Combined with the neurological function score (NFS) [45], the RPS, the TPS, and the ICP monitoring results and the imaging results, the weighted regression analysis will be performed to complete a more comprehensive classification of brain edema, which contributes to the clinical trials in the future.

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REFERENCES


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