Early Assessment of Acute Ischemic Stroke in Rabbits Based on Multi-Parameter Near-Field Coupling Sensing

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Abstract

Background: Maintaining normal supply of cerebral blood flow (CBF) and preventing secondary damage caused by acute ischemic stroke (AIS) are essential to the treatment of cerebrovascular diseases. Nevertheless, there hasn't been fully accepted method targeting continuous assessment of AIS in clinical.

Methods: Near-field coupling (NFC) sensing can obtain the electromagnetic properties related to the volume of intracranial components with advantages of noninvasiveness, strong penetrability and real-time monitoring. In this work, we built a multi-parameter monitoring system that is able to measure the phase and amplitude changes in electromagnetic wave reflection and transmission. For investigating its feasibility in AIS detection, sixteen rabbits were chosen to establish AIS models by bilateral common carotid artery ligation and then were enrolled for monitoring experiments.

Results: During the six hours after AIS, the reflection amplitude (RA) shows a decline trend with a range of 0.69dB and reflection phase (RP) has an increased variation of 6.48° . Meanwhile, transmission amplitude (TA) and transmission phase (TP) decrease 2.14dB and 24.29° respectively. The statistical analysis illustrates that before ligation, three hours after ligation and six hours after ligation can be effectively distinguished by the four parameters individually. When all those parameters are regarded as recognition features in BP network, the classification accuracy of the three different periods reaches almost 100%.

Conclusion: These results prove the feasibility of multi-parameter NFC sensing to assess AIS, which is promised to become an outstanding point-of-care testing method in the future.

Background

Stroke is the leading cause of long-term disability in developed countries and one of the top causes of mortality worldwide. Acute ischemic stroke (AIS) is responsible for almost 90% of all strokes. According to the Guidelines for the Early Management of Patients with Acute Ischemic Stroke (AHA/ASA, 2019), AIS patients meeting the screening criteria benefit from intravenous thrombolysis within 3 hours [1]. A multi-center retrospective study reported that precise characterization of intracranial blood supply status is required to select suitable treatment methods for cerebral arterial recanalization and tissue reperfusion, which predicts good functional outcomes following AIS [2]. Therefore, early diagnosis and continuously monitoring are the key to emergency treatment and intensive care of patients with AIS.

Owing to the advantages of no secondary pain and wide clinical applicability, the non-invasive detection has developed rapidly in the past decade, but there has been no fully dependable method of early diagnosis and continuous monitoring of AIS. The diagnosis of AIS in clinical mainly relies on imaging methods such as CT, MRI, PET, etc. However, this type of equipment is bulky and generally fixed and the low time resolution leaves a risk of delay in treatment. Transcranial Doppler (TCD) often used for intermittent monitoring utilizes cerebral blood flow velocity (CBFV) for dynamically assessment of AIS. Sympathetic nerve stimulation or infusion of vasoactive drugs may cause changes in cerebral artery diameter, making it difficult to measure CBFV accurately [3]. Furthermore, it cannot detect the flow

velocity in intracranial small vessels and capillaries. It is proved that intracranial small vessels and capillaries play a vital role in the cerebral blood flow (CBF) regulation. The laser doppler flowmeter (LDF) can also measure CBFV, but its detection depth is limited and the measurement result is easily interfered by environmental factors [4]. Near infrared Spectroscopy (NIRS) measures change in blood oxygen and deoxyhemoglobin in blood vessels, by which it can realize continuous and non-invasive monitoring of AIS. The prerequisite is that the amount of light scattering remains unchanged and changes in attenuation are only caused by absorption [5]. However, its detection depth is also limited and the composition of the intracranial tissue after AIS will change significantly, resulting in changes in both light absorption and scattering. The bioelectrical impedance (BEI) method uses electrodes to inject current into the cranium and measures the change of boundary potential to detect AIS. However, it is difficult to guarantee a stable electrical contacts between the electrode and scalp in practice, and the attenuation of injection current and poor penetration caused by the high resistivity of the skull affect the accuracy [6].

As an emerging biomedical electromagnetic detection method in recent years, near-field coupling (NFC) sensing focuses on the coupling effect of electromagnetic (EM) wave with the surface and internal tissues of living organisms, which has the advantages of non-invasive, strong penetrating and real-time continuous monitoring. Tissue's physiological and pathological information modifies the amplitude/phase of EM waves. When the NFC sensor emits the EM wave signal to the head, a portion of EM wave is directly reflected, and the rest is transmitted to deep area of brain through skull, forming two signals with different paths. They are defined as reflection signal and transmission signal. Previous researches show that the amplitude and phase shift relative to the emission signal are related to the electromagnetic properties of the whole brain [7,8]. Oziel et al. utilized the Z-parameter to monitor blood accumulation in the head [9]. Their latest research further shows that the change of amplitude/phase increases or decreases or even appears a non-linear trend with the injected blood volume at different measurement frequencies [10-12]. Griffith et al. developed a passive skin patch sensor for the non-invasive detection of brain volume. The physical simulation experiments and human trials results show that this sensor can monitor brain volume changes, significant for auxiliary diagnosis of stroke, cerebral concussion and intracranial pressure (ICP) monitoring [13]. Saied et al. proposed a wearable detection system based on flexible fabric materials for neurodegenerative diseases. The sensor consists of six monopole planar antennas with two independent resonance frequencies (800 MHz and 2.1 GHz). In the brain atrophy and unilateral ventricle expansion simulation experiments, the amplitude-frequency characteristics of the reflection and transmission parameters show different trends, indicating that the system has the potential to distinguish different neurodegenerative diseases [14]. McDermott et al. proposed a dual-frequency symmetrical difference method for stroke diagnosis and verified its feasibility by simulating normal and hemorrhage and blood clot lesions on a 4-layer FEM head model [15]. Jiang et al. used a cylindrical waveguide as a self-resonant cavity sensor to build a detection system with a working frequency band of 100MHz-400MHz and detected the rate and volume of hematoma enlargement on a 3D head model made by a stereolithography machine [16]. The results show that 1 cm³ bleeding can be detected in TE₁₁₁ mode.

Our research team has long been committed to the detection of cerebrovascular diseases based on NFC sensing. We built a real-time continuous brain edema monitoring system based on the frequency-dependent electromagnetic properties of biological tissues and the NFC theory and performed 24-hour monitoring experiments in rabbits, which proved its feasibility in brain edema monitoring [17,18]. Furthermore, we demonstrated the relationship between NFC signal and the two common parameters of neurosurgery intensive care and established NFC monitoring models of the main pathophysiological response after brain injury, combined with machine learning methods [19,20]. Further, a clinical trial was performed in the Department of Neurosurgery, Southwest Hospital, Chongqing, China. The result indicates that the NFC sensing is able to monitor the intracranial pathophysiological change after basal ganglia hemorrhage in real-time [21]. In 2020, we carried out an experimental study on NFC detection of AIS established by the carotid artery ligation in rabbits. The results show that the NFC signal has obvious changes after AIS and the signal shows significant difference between two degrees of carotid artery ligation models, preliminarily proving the feasibility of NFC method of detecting AIS [22]. Previous research only selected the phase of the transmission signal as the detection parameter, thus resulting in the poor consistency of the measurement. More importantly, it is difficult to monitor the dynamic change of the intracranial pathophysiological state after AIS accurately. In addition, our previous studies show that using the features from both the reflection and the transmission signals can classify the three different states after traumatic brain injury with 100% accuracy, which seems to play an important role in improving the reliability of monitoring AIS by NFC sensing [23].

In this study, we established a multiple-parameter NFC monitoring system for AIS by making use of the reflection and transmission characteristics of the two-port test network. In the 6-hour AIS monitoring experiment of 16 rabbits, the amplitude and phase spectrums of reflection and transmission signals within the frequency band (300kHz-200MHz) were obtained at a rate of 1 hour. After analyzing the phase and amplitude information of reflected and transmitted signals jointly, the optimal frequency for AIS detection was found. Based on the changes in reflection amplitude (RA), reflection phase (RP), transmission amplitude (TA) and transmission phase (TP) at the optimal frequency, we investigated the effectiveness of monitoring intracranial states dynamically with the development of AIS. Finally, via BP neural network, the classification of different intracranial states before and after AIS was performed based on the monitoring data of the four parameters. By using the four parameters respectively vs altogether as identification features, the accuracy of the classification was compared.

Methods And Materials

Principle of near-field coupling detection

Figure 7 depicts a two-port test system containing a signal source and a target under test (TUT). The relationship between input and output signals are defined by using incident signals, reflected signals and transmitted signals. When Port 1 is added with an incident signal and Port 2 has no input, some of the incident signal is reflected due to the mismatch of two-port network, that is, the reflected signal, and the rests are transmitted to Port 2 through the TUT, the transmitted signal.

The reflection coefficient refers to the relationship between the reflected signal and the incident signal is defined as:

$$\text{Reflection Coefficient} = \frac{V_{\text{reflection}}}{V_{\text{incident}}} = \rho \angle \theta \quad (1)$$

The transmission coefficient refers to the relationship between the transmission signal and the incident signal is defined as:

$$\text{Transmission Coefficient} = \frac{V_{\text{transmitted}}}{V_{\text{incident}}} = \tau \angle \varphi \quad (2)$$

Where ρ and τ are the amplitude of reflection coefficient and transmission coefficient respectively. θ and φ represent the phase of reflection coefficient and transmission coefficient respectively.

The four parameters are all related to the electromagnetic properties of the TUT. Our previous work has proved that θ and φ are related to the electromagnetic properties of TUT [23]. In this study, θ and φ are defined as RP and TP. Similarly, ρ and τ are defined as RA and TA respectively. In practical circuits, part of the incident signal is transmitted from Port 1 to Port 2 via TUT, some is directly reflected back due to mismatch, and the rest is lost in transit [40]. Therefore, ρ and τ largely depend on the impedance matching degree of the entire network, which is modified by the electromagnetic property of the TUT.

Multi-parameter Near Field Coupling Sensing System

The multi-parameter near field coupling sensing system mainly includes a portable vector network analyzer (Copper Mountain, M5065), a coil sensor suitable for animal experiments, and real-time monitoring software for AIS.

The coil sensor consisted of excitation coil and receiving coil, wounded at both ends of the plexiglass tube by use of 12 turns of AWG32 copper wire. Based on the skull size of the rabbits, the radius of the

coils was customized as $R1 = R2 = 5.4\text{ cm}$, the distance was 12 cm [41].

The vector network analyzer connected to a notebook computer by USB line is the hardware core of the entire system. It connects the coil sensor via coaxial line, which is responsible for providing an excitation source and transmitting a near field to the TUT through the excitation coil and at the same time, the transmission signal from receiving coil is collected, finally, obtaining the NFC measurement result after completing the signal processing and phase calculation.

The real-time monitoring software for AIS, the control and function core of the entire system, is compiled on the host computer and then called by vector network analyzer, which mainly realizes the functions of automatic parameter setting and NFC data collection in real-time. The parameters were listed in Table 1.

Table 1. Measurement parameters of multi-parameter NFC for AIS.

Name of Parameters	Setting
Sweeping band	300kHz to 200MHz
Sweeping points	1601
IFBW	3 kHz
Output power	10 dBm
Trigger source	Internal
Trigger mode	Continuous
Sampling interval	1 hour
Data Format	RA, TA, RP and TP

Experimental Design

For investigating the feasibility of warning and monitoring AIS based on multi-parameter near field coupling, sixteen healthy rabbits (2.0-2.6 kg, available from the Laboratory Animal Center of Army Medical University, marked No.1 to No.16) were enrolled to carry out AIS monitoring experiment. The experiment was carried out in accordance with the Helsinki Declaration and IASP guidelines, respecting animal life, reducing animal stress, pain and injury, and euthanasia was adopted after the experiment.

The common carotid artery ligation method was used to prepare the AIS model [42]. Rabbits were first injected with urethane (25%, 5 ml) via ear vein for anesthesia. Then the hair on their neck and head was removed. The center of the neck skin was cut off after disinfection, and the muscles were separated bluntly, for exposing and separating the bilateral common carotid arteries. Finally, the surgical ligation line was fastened to block the common carotid arteries bilaterally for the experiment.

As shown in Figure 8, after operation the rabbits were monitored for 6 hours by the multi-parameter near field coupling sensing system. They were placed on the plexiglass plate equipped with the coil sensor, where their heads were placed in the sensor's geometric center. The multi-channel physiological signal acquisition and processing system (Chengdu Instrument Factory, RM6240XC) was used to monitor the respiration of the rabbits. When the rabbits breathed normally, we ran the real-time monitoring software for AIS and started to collect RA, TA, RP and TP data synchronously. Meanwhile, the respiratory frequency was observed every one hour to ensure those rabbits in a stable state. For reference, all rabbits were placed in the same marked position before ligation to measure the initial values. After the experiment, the rats were euthanized by air injection method.

Selection of Feature Frequency

When rabbits were placed in the specified position of the coil sensor after anesthesia, the initial amplitude spectrums of the entire multi-parameter NFC sensing system in reflection and transmission were shown in Figure 9. In two-port test network, higher return loss represents less incident signal reflected back to Port 1 and lower insertion loss indicates more signals transmitted to Port 2 through the brain. With almost the same level of return loss, lower insertion loss shows higher transmission efficiency [43]. Based on this, three feature frequency points, $f_1(35.622\pm0.219\text{MHz})$, $f_2(59.836\pm0.179\text{MHz})$ and $f_3(189.141\pm0.497\text{MHz})$ were found in sweeping. The f_2 corresponded to the minimum insertion loss of the transmission signal, indicating that the impedance matching was optimal and the efficiency of the entire system was the highest. Under this condition, the four parameters (RA, TA, RP and TP) theoretically demonstrate strong stability and sensitivity. The f_1 and f_3 corresponded to the two frequency points with larger insertion loss of the transmission signal, indicating that most of the energy was lost in the signal transmission and reflection process, thus leading to worse performance in multi-parameter NFC sensing. Therefore, we proposed that the f_2 be the optimal detection frequency of AIS, which would be proved by analyzing the changes of RA, TA, RP and TP in the sweeping and comparing the average variations in the frequency band around the three feature frequency points ($\text{FB}_1=f_1\pm5\text{MHz}$, $\text{FB}_2=f_2\pm5\text{MHz}$, $\text{FB}_3=f_3\pm5\text{MHz}$).

Statistical Analysis

All the data are expressed as mean $\pm$ standard deviation from 16 independent experiments. The four parameters in three periods (before ligation, three hours after ligation and six hours after ligation) were performed intragroup difference statistical analysis by a paired-samples t-test to prove the effectiveness of multi-parameter NFC in distinguishing different pathophysiological states following AIS. The significance level was set at $\alpha=0.05$. Statistical analyses were performed using SPSS software version 22.0 (SPSS Inc., Chicago, USA).

Classification of different ischemic states

Based on the change trend and the statistical results of the four parameters, the classification of three intracranial pathophysiological states was performed by BP neural network. Twelve groups of

experimental data were randomly selected as training samples ($n=36$), and the others were used as test samples ($n=12$). In the process of identification, the four were used respectively or all together 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 3. 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. The output mean P values in three different intracranial pathophysiological states were based on the test samples corresponding to the state before classification ($n=4$). What's more, normalization was performed before the feature entered the neural network training.

Results

Frequency selection for AIS detection

The mean changes ($n=16$) of RA, TA, RP and TP in six hours are shown in Figure 1. With the increase of AIS severity, the four parameters all have large fluctuations at some frequency points in the sweeping band (300kHz-200MHz). However, RA (Figure 1a) and RP (Figure 1b) almost have no large fluctuations over time at those frequency points with poor impedance matching, which shows strong stability compared with TA (Figure 1c) and TP (Figure 1d). Meanwhile, TA and TP hold a larger variation range at the frequency points (f_1 , f_2 and f_3) that have excellent impedance matching than RA and RP, that is, the amplitude and phase of the transmission coefficient is more sensitive than reflection coefficient. This result is consistent with the two-port network test principle and previous researches, proving that the transmission coefficient has more influencing factors than reflection coefficient, and its variation range caused by the change in electromagnetic properties of TUT is greater.

The average variations of the four monitoring parameters within 6 hours in FB_1 , FB_2 and FB_3 are shown in Figure 2. As shown in Figure 2a, the RA in FB_1 and FB_2 generally show a gradual downward trend, while in FB_3 it exhibits a large range of oscillations reflecting poor stability. In Figure 2b, the TA in FB_2 first rises and then gradually decreases. It is more sensitive than that in FB_1 and FB_3 . The RP in FB_2 shows a gradual upward trend in Figure 2c, while it has no obvious changes in FB_1 and fluctuates around the initial value with a large range in FB_3 . Figure 2d depicts that the TP has a gradual downward trend over time in FB_1 and FB_2 but almost remains unchanged in FB_3 . In all, transmission coefficient is more sensitive and less stable than reflection coefficient. However, the change trend of amplitude and phase in FB_3 is just opposite to that mentioned above, showing that these changes in FB_3 come from external interference to a great extent. FB_1 and FB_2 have similar performance, but the sensitivity of FB_1 is lower. Therefore, FB_2 and f_2 are the optimal frequency band and point suitable for AIS detection.

Multiple-parameter monitoring outcomes

The change trend of the four monitoring parameters in six hours after bilateral carotid artery ligation at f_2 is shown in Figure 3. The arterial blood supply system of brain tissue is composed of four large arteries, namely the carotid artery and the vertebral-basal artery. Among them, 60% of the blood supply is completed by the carotid artery. When the rabbits suffer from bilateral carotid artery ligation, the blood volume in the skull decreases rapidly, resulting in a drop in the overall electromagnetic properties of the brain. As shown in Figure 3(a)(b)(d), RA, TA and TP show an obvious downward trend in the first three hours, which is consistent with the rapid decrease in the overall electromagnetic properties of the brain caused by early AIS. However, the RP shows an upward trend in the first three hours as shown in Figure 3(c), consistent with previous research [22]. Although the bilateral carotid arteries are ligated, the vertebral-basal artery still supplies blood to the brain tissue, compensating cerebral blood volume through vasodilation and accelerating blood flow velocity several hours after bilateral carotid artery ligation [23]. Compared to the previous period, the rate of AIS slows down. Figure 3 shows that the decline rate of these four monitoring parameters is obviously reduced after 3 hours of bilateral carotid artery ligation. Especially, RA, RP and TP tend to be flat. To summarize, the multi-parameter NFC can reflect the pathophysiological process of AIS.

Figure 4 depicts the paired sample t test ($\alpha = 0.05$) results of the four monitoring parameters among three time points (before bilateral carotid artery ligation, three hours after ligation and six hours after ligation). The four monitoring parameters demonstrate extremely significant differences in these three points before and after ligation, indicating that multi-parameter NFC can effectively distinguish different intracranial pathophysiological states of AIS.

Classification of different intracranial pathophysiological states

The three different intracranial pathophysiological states (1, 2, 3) were classified by the BP network. As shown in Figure 5(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. Figure 5 (b) depicts that the R value is 0.99098 in the given fitting equation, showing that the fitting effect is excellent.

The remaining four groups were set as test samples ($n=12$) and the test results were shown in Figure 6. When the four monitoring parameters are individually used as identification features, the output P value of state 1 ranges from 0.91 to 0.95. However, the output P value of state 2 ranges from 0.62 to 0.75 and those of state 3 ranges from 0.59 to 0.71. It illustrates that the RA, TA, RP or TP can classify normal and AIS states with high accuracy, but the performance for the state differentiation after AIS is poor. When they are all used as identification features, the output P values of the three different states reach 0.99, 0.94 and 0.93. In other words, the four monitoring parameters are all able to reflect the changes at different stages of AIS, but in the state differentiation of AIS, it is better to use all the parameters as the recognition features, which indicates that using the multi-parameter NFC can achieve a more effective classification performance.

Discussion

Although intravenous thrombolysis, mechanical thrombus removal from blood vessels and antiplatelet drugs are effective methods for the treatment of AIS, it is urgent to develop a safe and reliable diagnostic method to achieve individualized and precise management. Completing the diagnosis and thrombolysis at the emergency site will greatly reduce the treatment time window, which is able to improve the prognostic outcome [24]. According to the existing guidelines, real-time monitoring of CBF circulation and timely adoption of appropriate individualized interventions are the key to AIS treatment [1,25]. It will effectively overcome the unsatisfactory treatment effect caused by individual differences such as inducement, age, gender, past medical history (PMH), etc [26]. The current clinical imaging equipment is huge, not suitable for pre-hospital diagnosis and real-time continuous monitoring of patients after admission. Although there is promising prospect for the mobile stroke unit based on CT or MRI, the burden of using the unit is high for most hospitals worldwide, especially in some developing and underdeveloped countries. Some other non-invasive methods, such as TCD, LDF, NIRS and EIT, have inherent defects in detection depth, continuous monitoring or easy operation. NFC sensing has advantages such as non-invasiveness, strong penetrating, and small size. NFC sensing has advantages such as non-invasiveness and strong penetrating. Chen et al. proved the quantitative relationship between the variation range of NFC signal and the volume change of intracranial components combining the MRI images [27]. The volume of CBF will decrease obviously after AIS. In addition, there is evidence that cerebral hemorrhage and AIS have different modes of influence on NFC signals [28]. Therefore, the early AIS detection method based on the development of near-field coupling technology meets the current clinical needs and has the theoretical feasibility. With excellent portability, the multi-parameter NFC system in this work can complete rapid diagnosis at the first site after the onset of AIS. Stroke usually leads to hemorrhage and ischemia, the treatment for them is different, so mishandling brings catastrophic consequences. The multi-parameter NFC sensing obtains more comprehensive information about intracranial pathophysiological states than traditional methods, which recognizes ischemia with high accuracy. Besides, the multi-parameter NFC sensing proposed in this work can continuously evaluate dynamically the perfusion state of cerebral blood flow after the effective intervention of AIS, which helps clinicians to timely discover secondary pathophysiological reactions such as cerebral edema and encephalomalacia.

The multi-parameter NFC sensing system established in this work has high performance. Cerebral blood flow is a tissue with high electromagnetic properties in the brain. The increase or decrease of its volume will significantly change the overall electromagnetic properties of the brain. Therefore, the NFC signal theoretically has an obvious discrimination between AIS and normal state. However, the limitation of the selection of excitation signal frequency and the inherent weak electromagnetic properties of biological tissues make NFC perform poorly in actual detection. The traditional common methods are to use a single or several limited frequencies, which is difficult to accurately obtain the one with optimal detection performance [29,30]. Meanwhile, some reported studies of the research groups worldwide have made progress in improving the radiation intensity and uniformity of the near field, providing a vital reference in coil sensor design [31-33]. However, these proposed methods are only suitable for pure electromagnetic

simulation calculation and physical experiment to investigate the performance of NFC detection. The characteristics of the TUT itself are ignored and there is a huge gap with the actual situation. Therefore, the sensitivity increase is very limited. Our previous studies show that it is advisable to obtain the phase change on a wide frequency band through sweeping and then to screen the excitation frequency with the optimal detection performance [34]. But this method could not achieve the effect of finding the optimal excitation frequency in advance and only when the monitoring experiment was finished can the frequency or frequency band with obvious changes in NFC signal caused by brain injury be observed. In this work, we explored the impedance matching performance of multi-parameter NFC sensing system with the rabbit AIS model based on the two-port network test principle in a wide band. Then, three feature frequency points were found and one of them was regarded as the optimal excitation frequency by the joint analysis of the initial reflection and transmission amplitude spectrum. The results of frequency selection for AIS detection prove that the optimal excitation frequency has the best detection performance. The frequency selection method proposed in this work can quickly determine the optimal excitation frequency and continuously collect high-performance NFC signals to achieve monitoring AIS in real-time.

Multi-parameter NFC sensing based on RA, TA, RP and TP is able to monitor the changes dynamically in the intracranial pathophysiological state after AIS more accurately. Similar to near-infrared light, electromagnetic waves will be reflected and transmitted when passing through the brain, but the traditional NFC detection focus on the transmission parameters and ignore the reflection ones, the reason of which is that the transmission parameters contain more information on the changes of the internal electromagnetic properties of the TUT than that of the transmission parameters. In addition, sufficient research evidence shows that the phase is more sensitive than the amplitude but the stability is poorer, which is consistent with the broadband spectrum results on the AIS model in this study [35]. So, TP is often used as a single parameter to detect cerebrovascular diseases, and it is difficult to monitor the complicated intracranial pathophysiological development after AIS. After AIS, the cerebral blood flow (CBF) decreases rapidly, and the CBF regulation will gradually intervene with increased time through cerebral arterial vasodilation and intravascular flow velocity rising [36]. According to the electromagnetic properties of biological tissues, the cerebrospinal fluid is the highest among intracranial contents, followed by the CBF, and the brain parenchyma is the lowest [37]. From the occurrence of AIS to the loss of compensation, the NFC signal theoretically first declines or rises and then gradually stabilizes. In previous work, we measured TP only on the AIS model established by unilateral and bilateral common carotid artery ligation. And the laser Doppler cerebral blood flow velocity (CBFV) was regarded as a reference. The monitoring outcomes show that both TP and laser Doppler CBFV have continuous downward trends over time. Statistical analysis illustrates that there is a correlation between them and TP can distinguish different ligation methods. Laser Doppler CBFV is mostly related to the focal blood supply from the major blood vessels and its downward trend proves the occurrence of ischemia to a certain extent. But the TP reflecting changes in the volume of the global CBF does not match the overall intracranial electromagnetic properties at different periods after AIS. Indeed, it is difficult for a single NFC parameter to reflect the complex pathophysiological process of AIS accurately, therefore, we proposed

multi-parameter NFC sensing in this work. We conduct an experimental study on an animal model established by bilateral carotid artery occlusion causing more rapid injury in order to study the feasibility of multi-parameter NFC Sensing for early assessment of AIS and to facilitate comparison with previous experimental work. The slopes of the four NFC parameters in this study within 6 hours after the occurrence of AIS show different degrees of decrease over time, which is consistent with the physiological process in which the intracranial blood volume decreases rapidly in the early stage of AIS and then stabilizes with VA compensation. Clinical studies show that VA compensation has individual differences and has a reliable correlation with the prognosis of AIS. In addition, timely effective intervention before the loss of VA compensation can effectively reduce the incidence of irreversible neurological damage, so it is potential for multi-parameter NFC sensing to apply to the personalized management and early warning assessment of irreversible neurological damage for AIS patients with different VA compensation levels. With the continuous development of AIS, we infer that the irreversible infarction is gradually informing, the available space for CBF is reduced with the expanding of infarction area, and the absolute values of the change in the four NFC parameters will further increase.

When the proposed four parameters are all used as identification features together, three different intracranial pathophysiological states are accurately identified. It is of great significance for clinicians to take effective treatment of AIS in time and prevent poor prognosis. The four parameters all have obvious upward or downward trends in the 6-hour monitoring of AIS. The statistical analysis of differences was used for feature selection, and the results illustrated that they could effectively differentiate the three different states. Therefore, we regarded them as inputs for model training based on BP neural network. By changing the weight and threshold of the internal connection, the minimum error between the output value and the target value is achieved, thereby achieving the purpose of modeling. In this work, the established training model has fast convergence speed and good fitting performance, which meets the expected requirements. The differences in compensatory ability, depth of anesthesia and physical conditions make the rabbits appear different changes in the same parameter at the optimal frequency [38]. Therefore, when the four parameters are used as identification features alone, the classification performance of three different states is poor. When they are all used as identification features, the accuracy of classification reaches almost 100%, which strengthens the value of multi-parameter NFC sensing.

In practical terms, the intracranial pathophysiological process after AIS is very complex. For comparison, this work only verified the feasibility of multi-parameter NFC sensing to monitor AIS in early stage. We will further explore the relationship between the intracranial pathophysiological response after the formation of irreversible infarcts and the proposed four monitoring parameters, through which we may establish the corresponding multi-parameter NFC model. Also, the traditional single excitation-single receiving coils were still used to show the superiority of multi-parameter near-field coupled sensing more directly. In subsequent researches, a new type of symmetric differential coil sensor will be built based on approximate axisymmetric of brain. The BP network has some shortcomings, the initial weights and thresholds are created artificially for example, which may lead to bias in the model [39]. In addition, the

selection of samples is critical to the quality of the training model. In the next step, we will improve the algorithm based on expanding the sample size and comparison with other algorithms.

Conclusion

This work established a multi-parameter NFC sensing system of AIS based on the reflection and transmission characteristics of the two-port test network, which has advantages of noninvasiveness, noncontact, good portability, and real-time continuous monitoring. Combining the impedance matching, three feature frequency points were found through joint analysis of reflection and transmission amplitude spectrum. By analyzing the changes of RA, TA, RP and TP in the sweeping band and comparing the average variations around the feature frequency, we proved that the optimal detection frequency of AIS is among the three points. During the 6 hours after bilateral carotid artery ligation in rabbits, the RA, TA, RP and TP at the optimal detection frequency first change rapidly and then gradually stabilize, indicating the feasibility of monitoring the intracranial pathophysiological development in early stage of AIS. When the four parameters are all used as identification features, the classification accuracy of the three different intracranial states reaches almost 100%. This study provides a new solution to early detection of AIS, and lays the foundation for the next step to predict large intracranial infarction accurately and to propose a personalized clinical monitoring plan.

Abbreviations

CBF: cerebral blood flow; AIS: acute ischemic stroke; NFC: near-field coupling; BP: back propagation; CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography; TCD: transcranial doppler; CBFV: cerebral blood flow velocity; LDF: laser doppler flowmeter; NIRS: near infrared spectroscopy; EIT: electrical impedance tomography; BEI: bioelectrical impedance; ICP: intracranial pressure; FEM: Finite Element Method; TUT: target under test; FB: frequency band;

Declarations

Ethics approval and consent to participate

These experiments were conducted under the guidance of the Administration of Animal Experiments for Medical Research Purpose issued by the Ministry of Health of China. The protocol was reviewed and approved by the Animal Experiments and Ethical Committee of Chongqing University of Technology. Animal care was performed in accordance with the Declaration of Helsinki and the guidelines issued by the International Association for the Study of Pain.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

J.S. and Y.C. were responsible for the design and overall investigation; G.L. and J.S. were responsible for measurement system design; W.Z., B.X., S.H. and Z.B. performed the experiments; S.Y., M.J., L.Z. and J.C. analyzed the data; G.L. and Y.C. contributed reagents and materials; G.L. and S.Y. wrote the paper.

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Figures

Figure 1

The 6-hour mean changes ($n=16$) of reflection amplitude (RA), reflection phase (RP), transmission amplitude (TA) and transmission phase (TP) in AIS monitoring experiment. The frequency range is from 300 kHz to 200 MHz. (a) is RA and (b) represents TA. The results of RP and TP are shown in (c) and (d) respectively.

Figure 2

The average variations of the four monitoring parameters within 6 hours in FB1 (35.622 ± 5 MHz), FB2 (59.836 ± 5 MHz) and FB3 (189.141 ± 5 MHz). (a) is RA and (b) represents TA. The results of RP and TP are shown in (c) and (d) respectively. The variation trends of monitoring parameter over time in different frequency bands are drawn by three colors (green, red and blue).

Figure 3

The change trend of reflection amplitude (RA), reflection phase (RP), transmission amplitude (TA) and transmission phase (TP) in six hours after bilateral carotid artery ligation at f_2 (59.836 ± 0.179 MHz). (a) is RA and (b) represents TA. The results of RP and TP are shown in (c) and (d) respectively.

Figure 4

The paired sample t test ($\alpha=0.05$) results of reflection amplitude (RA), reflection phase (RP), transmission amplitude (TA) and transmission phase (TP) among three time points (before bilateral carotid artery ligation, three hours after ligation and six hours after ligation). (a) is RA and (b) represents TA. The results of RP and TP are shown in (c) and (d). The number of symbol (*) reflects the size of P value. Symbol (***) indicates extremely significant ($P \leq 0.001$).

Figure 5

The classification training of three different intracranial pathophysiological states (1, 2, 3) using BP algorithm. The training target was set to 0.00001. (a) represents the change trend of mean squared error (MSE) with increasing number of epochs. (b) depicts regression analysis of the BP algorithm. The R value is 0.99098.

Figure 6

The classification tests of three different severity levels (1, 2, and 3) after training. Four groups were randomly set as test samples ($n=4 \times 3=12$). The four parameters are used individually and all as

recognition features. Then they were input into the training model in turn. The mean P values are calculated by the outputs the training model ($n=4$), which depicts the classification accuracy, ranging from 0 to 1. Larger mean P value corresponds to higher accuracy.

Figure 7

Two-port test principle containing a signal source and a TUT. An incident signal ($V_{incident}$) is added with Port 1. $V_{reflection}$ is the reflected signal and $V_{transmitted}$ is the transmitted signal. The two signals have different paths in the two-port test system and the total size of them is theoretically equal to that of $V_{incident}$.

Figure 8

Experimental platform to monitor AIS in rabbits. It includes the multi-parameter near field coupling sensing system and the multi-channel physiological signal acquisition and processing system (Chengdu

Instrument Factory, RM6240XC). They are responsible for collecting the multiple NFC parameters and the respiratory frequencies.

Figure 9

The initial average amplitude spectrum ($n=16$) of the entire multi-parameter NFC sensing system containing rabbits in reflection and transmission. The frequency range is from 300 kHz to 200 MHz. In two-port test network, lower reflection amplitude (RA) represents less incident signal reflected back to port 1 and higher transmission insertion amplitude (TA) indicates more signals transmitted to port 2 through the brain. $f_1(35.622 \pm 0.219 \text{ MHz})$, $f_2(59.836 \pm 0.179 \text{ MHz})$ and $f_3(189.141 \pm 0.497 \text{ MHz})$ were regarded as three feature frequency points based on this.