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A Clinical Research on Real-Time Monitoring of Cerebral Edema After Basal Ganglia Hemorrhage Based on Near-Field Coupling Phase Shift Technology

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ABSTRACT A novel method was developed based on near-field coupling phase shift (NFCPS) to perform non-contact and bedside monitoring of cerebral edema in the intensive care unit (ICU). A total of 17 subjects were selected to conduct real-time NFCPS monitoring of cerebral edema and divided into surgical group, conservative group and control group. The data were collected at an interval of 12 h, until the patients left the ICU for various reasons, such as being transferred to the general ward or discharged from the hospital. Continuous collection was conducted for 15 min at each time point and then the phase shift was recorded as the NFCPS value. The computed tomography (CT) images of the surgical group and the conservative group were obtained at the same time points. The surgical group had the most drastic changes (-3.42 ± 6.0 degrees, at 12 h; -12.85 ± 10.58 degrees, at 24 h; -5.04 ± 2.65 degrees, at 36 h; 0.05 ± 5.74 degrees, at 48 h). The overall brain conductivity may show a decreasing trend at first and then a rising trend in patients who suffer from a hemorrhagic stroke. The comparative analysis of NFCPS and CT images revealed that NFCPS can also reflect the pathophysiological changes of the brain. This research demonstrates the robust clinical feasibility of NFCPS in the non-invasive real-time monitoring of cerebral edema. In addition, the change characteristics of the overall brain conductivity in hemorrhagic stroke patients provide guidance for subsequent research.

INDEX TERMS Near-field coupling phase shift, brain edema, stroke, computer tomography.

I. INTRODUCTION

Cerebral edema is a secondary brain injury caused by various physical injuries and biochemical changes. Patients with brain edema suffer from increased water content in brain tissue as well as increased brain volume that leads to increased intracranial pressure (ICP), brain line displacement, brain hernia and even death [1]. Monitoring of cerebral edema is crucially important in clinical practice. Existing methods of monitoring common vital signs (heart rate, respiration, blood pressure, etc.) provide physiological data to guide and individualize therapy, but the pathophysiology of acute brain injury is complex and can involve several secondary pathological cascades. Consequently, current methods cannot directly quantify the development of cerebral edema after intracranial surgery [2], [3]. According to the Guidelines for the Early Management of Patients with Acute Ischemic Stroke (the American heart association/American Stroke association, AHA/ASA, 2018), at present, there is no fully reliable method to predict the process of cerebral

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edema [4]. Currently, the detection of cerebral edema after surgery mainly relies on imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI). However, these techniques are not applicable for critically ill patients who cannot be readily moved and can only be evaluated once thus precluding bedside real-time monitoring [5]–[7]. Admittedly, monitoring the severity of cerebral edema in real time helps medical staff to provide timely treatment. In fact, it is not adequate to track the progress of brain edema through procedural CT and MRI examinations or the doctor's experience. Therefore, a bedside real-time method for monitoring cerebral edema is urgently needed in clinical practice.

Increased ICP is one of the most common symptoms after brain edema [8]. However, the invasive ICP method generally requires placing sensors inside the skull, which may cause bleeding and infection. Besides, pressure-based ICP measurement is an indirect way to reflect the change of brain tissue volume. The ICP rises slowly in the early stage of edema due to the brain compensatory mechanism. When the compensatory capacity is exhausted, the ICP will rapidly rise as a result of a small increase in intracranial volume. Thus, ICP has its limitations as an indicator of brain edema change [9]. Moreover, brain tissue expansion will not have an impact on ICP after decompressive craniectomy, and thus will result in an imprecise response to intracranial real-time changes.

Currently, a series of new methods for non-invasive detection of brain edema have also emerged [10], [11]. Transcranial Doppler ultrasonography (TCD) indirectly reflects changes in ICP by measuring changes of cerebral blood flow (CBF). A multicenter prospective pilot study was conducted in patients with acute brain injury requiring invasive ICP (ICPi) monitoring by Rasulo FA in 2017. The study provided preliminary evidence that the ICP estimated with TCD (ICPtcd) may accurately exclude intracranial hypertension in patients with acute brain injury [12]. However, it will show a poor correlation when the ICP reaches a high level and requires professional operational skills [13]. Flash visual evoked potential (FVEP) is not sensitive in the early stage of acute cerebral edema where ICP shows a slight change. Near Infrared Spectroscopy (NIRS) can detect the bleeding according to the higher absorption of hemoglobin than other configuration by near-infrared light [14]. However, this method cannot detect deep brain lesion. Soldatos T found that the optic nerve sheath diameter (ONSD) measurements correlate with non-invasive and invasive measurements of the ICP, as well as with the head CT scan findings in brain-injured adults. Accordingly, optic nerve sonography may serve as an additional diagnostic tool that could alert clinicians to the presence of elevated ICP, whenever invasive ICP evaluation is contraindicated and/or is not available [15]. Electrical impedance tomography (EIT) is a new technology developed in the last decade to detect brain edema, which is based on the electrical impedance characteristics of biological tissue. However, EIT requires direct contact between electrode and skin to inject current. Besides, the contact impedance will affect the measurement accuracy. Moreover, electric current does not pass easily through the skull due to its high resistivity, which seriously affects the imaging quality [16], [17]. There are also additional new technologies, such as waveform analysis to predict cerebral edema, which is based on the kinetic characteristics of CBF changes [18], non-invasive optical CBF imaging [19], [20], intracranial acoustic communication research, etc. However, the aforementioned methods cannot solve the problems associated with real-time and bedside monitoring of cerebral edema.

Near-field coupling phase shift (NFCPS) is a new method to detect electrical characteristics of biological tissue, which is to use the excitation signal of a certain frequency to generate a main electromagnetic field in the biological tissue, which will produce an eddy current in the tissues and form a coupling electromagnetic field [21]. Several reported studies have proved that the phase difference namely NFCPS between the main electromagnetic field and the coupling electromagnetic field is related to the structure and physiological state of biological tissues [22]–[26]. Pathophysiological changes of the brain induced by edema will cause alteration of the brain average conductivity. Therefore, the occurrence and development of cerebral edema theoretically can be detected by measuring the NFCPS changes. With advantages of non-invasiveness, non-contact, strong penetration and small size, NFCPS is expected to become an effective method for continuously bedside monitoring of brain edema. In addition, NFCPS can be an indicator of edema expansion and ICP increase. It may help medical professionals to evaluate the situation, provide timely treatment and reduce the death and mortality rates.

In the last few years, our research group has been conducting edema monitoring studies using the NFCPS method. In 2013, Jin *et al.* designed a contra-lateral hemisphere cancellation sensor which is based on the symmetrical structure of the left and right hemispheres of the brain [27]. In 2015, a broadband phase shift detection system was designed and implemented by Pan *et al.* [28]. Also, in 2016, Sun *et al.* deduced the theoretical relationship between conductivity and volume change based on a brain model and verified the modelling predictions by experimental results [29]. In addition, in 2017, Yan *et al.* analyzed the experimental results of cerebral ischemia and cerebral hemorrhage in rabbits using a square coil sensor and found that the two types of stroke (ischemic and hemorrhagic) may be distinguished by NFCPS method [30]. Additionally, in the same year, Li *et al.* designed and developed a set of NFCPS for a brain edema real-time continuous monitoring system with high sensitivity and good stability. Their 24-hour NFCPS, ICP synchronous monitoring and brain water content (BWC) parallel measurement experiments in rabbits showed that NFCPS technology can effectively monitor brain edema in real-time [31]–[33]. However, there are still some obstacles for NFCPS real-time bedside monitoring of cerebral edema in humans. Firstly, neither sensitivity, stability nor using convenience of the

pre-established NFCPS monitoring system were suitable for real-time bedside monitoring of cerebral edema in neurosurgical ICU. More importantly, NFCPS can effectively monitor the occurrence and development of brain edema in real time, which has been verified only in animal experiments [34]. The pathological process of actual clinical cerebral edema is very complicated, and there is an obvious difference with animal models. Indeed, in the pathological process of cerebral edema, the variation of the overall brain conductivity remains to be investigated.

In this work, combined with a new sensor that meets the ergonomic needs of patients, a bedside NFCPS monitoring system of cerebral edema using in ICU was constructed. Twenty-three subjects including eighteen stroke patients and five healthy volunteers were collected NFCPS data by this system. All patients admitted to the Southwest Hospital due to a stroke routinely undergo surgical intervention or conservative treatment according to the severity of the stroke. After receiving either of these two different treatments, the patients will show different pathophysiological reactions in the brain, which will result in various changes of the overall brain conductivity. The NFCPS is related to the overall conductivity of the brain. In combination with the CT imaging data, the changing characteristics of the average brain conductivity during two different pathological processes of cerebral edema were investigated. Unlike reported studies, this work is aimed at the transition from animal experiments to clinical research, which will provide a convincing clinical evidence that the NFCPS can effectively monitor cerebral edema after hemorrhagic stroke in real time. Furthermore, it can serve as a significant reference for the changing law of overall brain conductivity in the pathophysiological process of actual cerebral edema.

II. MATERIALS AND METHODS

A. ELECTROPHYSIOLOGICAL BASIS OF THE NFCPS IN DETECTING BRAIN EDEMA

The electrophysiological basis of detecting cerebral edema by NFCPS is that the effect of intracranial diseases can lead to the changes of the brain overall conductivity. Under normal conditions, the brain parenchyma, cerebrospinal fluid and cerebral blood form a dynamic balance in the closed skull. This balance is broken when there is a cerebral hemorrhage or brain edema. As the cranial contents increase, the cerebrospinal fluid (CSF) first compensates to maintain this balance. When cranial contents are further increased, the compensatory capacity of the CSF reaches its limit, and the nervous system maintains balance by regulating the cerebral blood volume. When the cranial contents continue to increase, and various physiological self-regulatory abilities reach saturation, the ICP will rapidly increase, which may lead to hernia and even death in severe cases. Since the volume, distribution and conductivity of the CSF, cerebral blood flow (CBF) and brain parenchyma are different, the changes of components or volume of cranial contents in the above process will lead to changes in the overall brain conductivity. Therefore, NFCPS, which reflects the changes of overall brain conductivity, can monitor the development of cerebral edema in real-time.

B. THE PATHOPHYSIOLOGICAL PROCESS OF CEREBRAL EDEMA UNDER TWO DIFFERENT THERAPIES

The pathological process of clinical patients with cerebral hemorrhage is usually divided into the early hyperacute stage (less than 6 h after cerebral hemorrhage), the acute stage (6 to 72 h), the subacute stage (3 days to 2 weeks) and the chronic stage (after 2 weeks).

Patients who need surgery often have a large amount of bleeding in the early hyperacute stage [35]. With the expansion of the hematoma, the CSF is gradually discharged into the cranial cavity, and the overall brain conductivity generally decreases. Surgical treatment is mostly performed in the acute stage to confine the expansion of the hematoma volume. The edema around the lesion may cause an increase in the overall brain conductivity. After surgery, physiological saline is used to wash and fill the cavity formed after evacuation of the hematoma. Meanwhile, the decompressive craniectomy leaves the skull with a bone window and the inconsistent pressure inside and outside the cavity causes the brain tissue to expand outward. The overall brain conductivity decreases with the increase of the cavity volume. Subsequently, cranial contents, such as brain tissue and CSF, will gradually fill the cavity, and the brain tissue will further expand due to the unsealed skull, resulting in an increase in the overall brain conductivity.

Patients who have less bleeding in the early hyperacute stage receive the conservative treatment. Most hematomas in the acute stage slow down the expansion and begin to coagulate, leading to a decrease in the overall brain conductivity. After that stage, the blood clot is gradually absorbed accompanied by cerebral edema, resulting in an increase in electrical conductivity.

C. NFCPS MEASUREMENT SYSTEM OF CEREBRAL EDEMA IN CLINICAL

As shown in Figure 1, the monitoring system is comprised of four parts: a detection sensor, which includes a detection coil and an excitation coil; a NI PXI system with a signal generator card and an acquisition card; a power amplifier; a phase detector and display platform based on LabView.

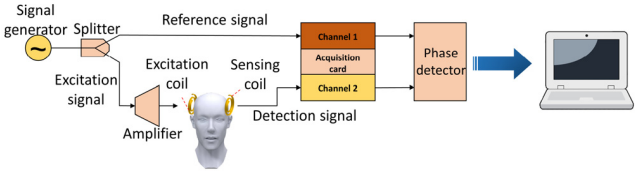

FIGURE 1. Schematic diagram of the NFCPS monitoring system.

The signal generator generates two identical sinusoidal signals, one as excitation signal and the other as

reference signal. The reference signal is directly sent to the phase detection platform via the acquisition card (PXI-5124, NI). The excitation signal is amplified and sent to the excitation coil, generating the main magnetic field. The change of the secondary magnetic field triggered by the measured object in the main magnetic field is determined by the detection coil, followed by the transmission of the detected signal to the acquisition card. The phase detection platform combines the reference signal and the detected signal to obtain the phase shift.

The sampling frequency of the detection system is 200 MHz, and the system gain is 100 times. In the LabVIEW software, the fast Fourier transform phase-detection algorithm is used to calculate the phase shift with 400,000 sampling points and the excitation signal frequency of the system is set to 15.1 MHz, so the system needs 0.02649s to get one NFCPS datum. The sampling rate of the real-time monitoring system is about 37.75Hz. The output signal amplitude of the power amplifier is 5 Vpp, and the power is 80 mW.

Since patients usually stay in bed for recovery after surgery, our research team designed a new type of head-mounted sensor based on Archimedes' coil, which was comfortable and convenient to wear. The sensor was constructed on a printed circuit board and consisted of a coaxial coplanar outer excitation coil and an inner detection coil. The excitation coil had 11 turns, with a wire diameter of 0.5 mm, and a wire spacing of 0.5 mm. The detection coil had 16 turns, with a wire diameter of 0.3 mm, and a wire spacing of 0.3 mm. Considering the physiological structure of the skull, the center of the sensor is placed on the pterion of the skull, which is the thinnest part of the skull.

D. DESIGN OF CLINICAL TRIAL

The pathological process of clinical patients with cerebral hemorrhage is usually divided into four stages. In the early hyperacute stage, the hematoma has intact red blood cells (mainly oxyhemoglobin and secondary perifocal edema). In the acute stage, the blood starts to clot, and brain edema occurs around the lesion. In the subacute stage, inflammation occurs, and red blood cells begin to shrink and dissolve. In the chronic stage, the edema around the hematoma disappears.

A total of 14 patients with basal ganglia hemorrhage (11 patients with left basal ganglia hemorrhage and 3 patients with right basal ganglia hemorrhage) were selected as the surgical observation group. The patients underwent hematoma aspiration and decompressive craniectomy in the early hyperacute period due to the life-threatening conditions. Four patients with basal ganglia hemorrhage (3 patients with left basal ganglia hemorrhage and 1 patient with right basal ganglia hemorrhage) were selected as the conservative treatment group, who were not treated with surgery. Five healthy volunteers were selected as the control group. The NFCPS monitoring of the surgical and conservative treatment groups was started when patients returned to the ICU after surgery or completed the conservative treatment. The data were collected at an interval of 12 h, until the patients left the ICU for various reasons, such as being transferred to the general ward or discharged from the hospital. Continuous data collection was conducted for 15 min at every time point and then the phase shift was recorded as the NFCPS value. The same NFCPS data collection procedure was performed in the control group from the time they were enrolled. All CT examinations were performed at the Radiology Department of the Southwestern Hospital using a SOMATOM Sensation 16 CT system (Siemens Healthcare GmbH, Erlangen, Germany) with a scan time interval of 4,000 ms and a bulb voltage of 120 kV. The thickness of the image layer used in the experiment was 5 mm, and the horizontal planes of the lateral ventricle and the hypothalamus were selected as reference images to ensure that the cerebral edema progression at various time points could be observed on this basis.

When the NFCPS detection was completed, all subjects were analyzed under the requirement of having the NFCPS values at four nodes (12, 24, 36, and 48h) or not. This means that 9 patients in Cerebral Hemorrhage (CH) with operation were eligible. In addition, only 3 patients without surgery met the requirement. Five healthy volunteers were selected as the control group. Accordingly, the final data set was as follows: 9 cases in the surgical group, 3 cases in the conservative group and 5 cases in the control group.

E. STATISTICAL ANALYSIS

All of the data were expressed as the mean $\pm$ standard deviation from six independent experiments at least. The exponential decay function was selected to carry out the non-linear regression analysis in Origin 9.1 (Origin Lab, Massachusetts, MA, USA). The values of all regression coefficients were determined, and the variance significance F test was carried out. The significance level was set at $p < 0.05$. Quadratic function was chosen to perform similar nonlinear regression analysis of three groups with significance level of 0.05.

In SPSS software version 19.0 (SPSS Inc., Chicago, IL, USA), NFCPS of patients and healthy volunteers at four time points was tested by multiple related samples Friedman. The significance level (α) was set at 0.05.

III. RESULTS

A. COMPARATIVE ANALYSIS BETWEEN NFCPS AND CT IMAGES

The CT images of patient E00000002 (female, 51year old) from the time of hospitalization to 72 h after surgery are shown in Figure 2. This patient underwent intracranial hematoma clearance, ICP monitoring probe implantation and bone flap decompression. The intraoperative ICP was lower than 10 mmHg, and the bone window size was 10$*$10 cm.

Based on the CT image of pre-hospital examination, professional analysis and intraoperative observation of the hematoma size was about 60 mL, as diagnosed by a panel of experienced doctors. In the CT image at 12 h after the surgery, the bone window can be seen in the left occipital lobe part of the skull and the black area was the cavity left after

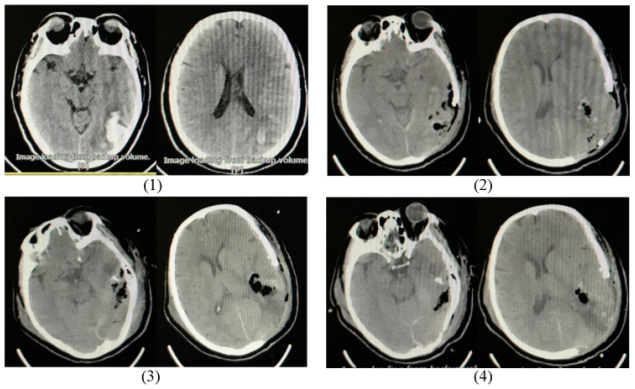

FIGURE 2. CT scan of patient E00000002 in CH with operation group. From (1) to (4), the time points of CT images are pre-operation, 12h after operation, 48h after operation and 60h after operation.

hematoma clearance, which was filled with saline. The brain tissue around the bone window expanded slightly outward, and the volume increased in the cavity that was filled with normal saline and diluted blood through observing the CT image at 48 h after the surgery. After that, the normal saline in the cavity was slowly absorbed and the brain tissue expanded further outwards in the CT image at 60 h after the surgery.

The NFCPS was 1.88, −0.88, and −4.76 degrees at 12, 24 and 36 h after surgery, respectively, revealing a decreasing trend. This reversal occurred as a result of the open wound in the skull, which led to the pressure inside the cavity that caused the expansion of the cavity volume. Therefore, the change of the cavity volume was the main reason of the change in the NFCPS at this stage. From 36 h after surgery onwards, with the absorption and metabolism of normal saline, the brain tissue and CSF constantly filled the cavity. In addition, the brain edema was further aggravated and became a leading factor in this progression. Consequently, the overall brain conductivity increased and the NFCPS changed from −4.76 to 12.24 degrees.

A comparison of the NFCPS results with the CT images, revealed that there is a close relationship between the intracranial pathophysiological state and the NFCPS, which reflects changes in the overall brain conductivity. Before surgery, the NFCPS decreased first and then increased, and similarly after surgery, the NFSPS decreased first and then increased.

B. RELATIONSHIP BETWEEN THE NFCPS AND CRANIAL CONTENT CHANGE

As shown in table1, there were 9 patients with NFCPS monitoring data of the surgical group. The data revealed that all the subjects showed a downward trend first and then a rising trend, which is consistent with the inference made above. The sample data of the 3 cases of CH group without surgery, which also reveal a decreasing trend first and then an increasing trend. The NFCPS data of the 5 healthy patients from the control group (average age: 20.6 years old) showed reveled no clear changing.

TABLE 1. NFCPS in CH with operation group, CH without operation group and health volunteer group.

Group	Sample	Time			
		12 h	24 h	36 h	48 h
CH with operation	E00000001	-3.06	-30.75	-10.43	-4.81
	E00000002	1.88	-0.88	-4.76	-2.18
	E00000003	0.90	-17.14	-4.76	-3.73
	E00000004	-18.17	-28.02	-2.02	13.99
	E00000005	-0.24	-4.44	-7.84	-3.06
	E00000006	-0.23	-6.77	-4.69	-4.60
	E00000007	-7.75	-9.16	-1.99	1.32
	E00000008	0.74	-0.64	-6.25	-1.47
	E00000009	-4.91	-17.85	-2.61	4.94
CH without operation	C00000001	-9.46	-14.58	-11.13	-3.22
	C00000002	-9.01	-10.5	-9.30	-6.34
	C00000003	-1.37	-6.50	-1.09	-0.24
Health volunteer	H00000001	-0.09	-0.60	-0.24	-0.56
	H00000002	-0.60	-1.20	-0.60	-0.65
	H00000003	-0.60	-0.30	-0.90	-0.82
	H00000004	-0.90	-0.12	-0.90	-0.70
	H00000005	-1.20	-0.90	-0.60	-0.90

TABLE 2. Friedman test results of NFCPS at four TIme points.

Group	N	χ^2	Degree of freedom	P
Patient	12	17.9	3	Less than 0.0001
Health volunteer	5	0.191	3	0.979

As shown in Table 2, the statistic value of χ^2 in patients with cerebral hemorrhage (n = 12) was 17.9, the degree of freedom was 3, and the corresponding P value was less than the significance level ($\alpha = 0.05$), revealing that there were significant differences in the amount of NFCPS change at the four time points. In addition, the χ^2 statistic value of healthy volunteers (n = 5) was 0.191, the degree of freedom was 3, and the corresponding P value was 0.979, which was greater than the significance level of 0.05, indicating that NFCPS signal in health volunteers did not change significantly over time. These statistical results show that healthy volunteers and patients with cerebral hemorrhage can be effectively distinguished by monitoring changes in NFCPS signals.

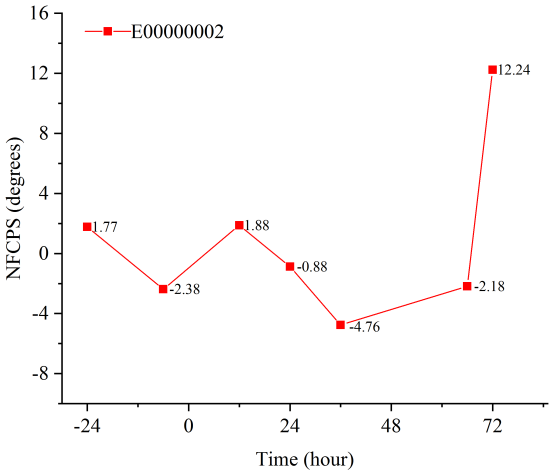

FIGURE 3. NFCPS change of patient (E00000002) in CH with operation group.

Under the condition of the conservative treatment, CH was essentially controlled. Otherwise, patients in the CH group without surgery were usually in the acute stage. In this stage, blood gradually clotted, and brain edema appeared around the lesion, corresponding to a decrease in conductivity and NFCPS. After that, inflammation occurred and red blood cells began to shrink and dissolve, causing an increase of the NFCPS. Based on the above results, it can be concluded that after surgery or conservative treatment the overall brain conductivity decreases first and then increases.

The NFCPS changes in the surgical group, conservative treatment group and control group (mean ± SD) are shown in Figure 4. These results reveal that the control group has the smallest change (-0.68 ± 0.37 degrees, at 12 h; -0.62 ± 0.25 degrees, at 24 h; -0.65 ± 0.25 degrees, at 36 h; 0.73 ± 0.15 degrees, at 48 h). The cranial contents of the control group were basically unchanged. The changes in the NFCPS were the smallest with small standard deviation among different subjects.

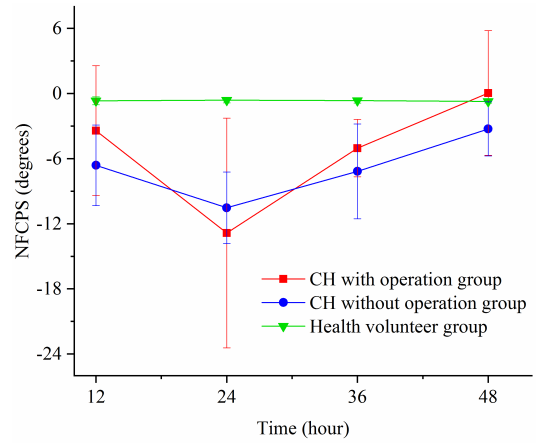

FIGURE 4. The mean ± sd change trends of NFCPS in the three groups.

The surgical group had the most drastic changes (-3.42 ± 6.0 degrees, at 12 h; -12.85 ± 10.58 degrees, at 24 h; -5.04 ± 2.65 degrees, at 36 h; 0.05 ± 5.74 degrees, at 48 h). The patients of the surgical group generally suffered from the worse conditions of bleeding. After craniotomy and hematoma removal surgery, the volume change of the cranial contents was much larger than that in other groups, resulting in a large change in the group's slope, which is consistent with the observations from CT images. Due to the individual differences of patients after craniotomy, as well as the difference in NFCPS between patients when the skull was no longer airtight, the standard deviation of the patients was as high as 10.58 degrees.

The change of the slope in the conservative treatment group was smaller than that in the surgical group (-6.61 ± 3.71 degrees, at 12 h; -10.53 ± 3.30 degrees, at 24 h; -7.17 ± 4.37 degrees, at 36 h; 3.27 ± 2.49 degrees, at 48 h). As shown in figure 5, the NFCPS variation amplitude in the conservative treatment group from 12h to 24h and 36h to 48h was also lower than that in the surgical group. Since the skull was completely sealed, the composition of the cranial contents in the conservative group had less dramatic changes than that in the surgical group. Although the brain edema appeared in the later stage, the treatment with cranial pressure lowering drugs, such as mannitol, slowed down the pathological process. As a result of the low expansion of the brain tissue and the small changes of cranial contents, the NFCPS had less variation.

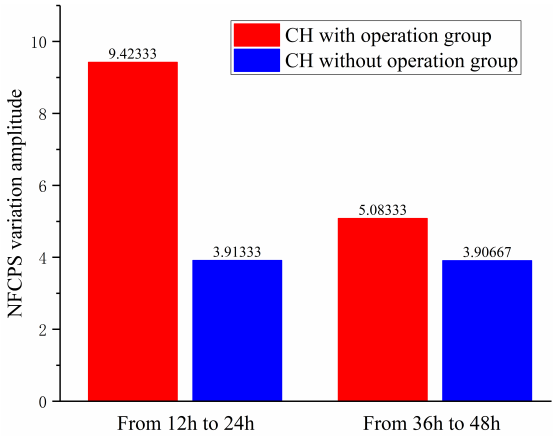

FIGURE 5. The NFCPS variation amplitude from 12h to 24h and 36h to 48h.

The results of the NFCPS changes in healthy volunteers, conservative treatment group and surgical group suggested that NFCPS can reflect the volume and composition changes of the cranial contents.

C. COMPARISON OF THE NFCPS AND CT IMAGES BETWEEN SURGICAL AND CONSERVATIVE TREATMENT GROUP

The NFCPS showed a downward trend first and then an upward trend in both the surgical and conservative treatment groups. However, considering the pathophysiological process of the cerebral edema under the two therapies described in

the above sections, we can infer that the pathological mechanisms in the surgical and conservative treatment group are different. In order to confirm this inference, the NFCPS and CT images of the surgical group and the conservative group at the same time points were compared.

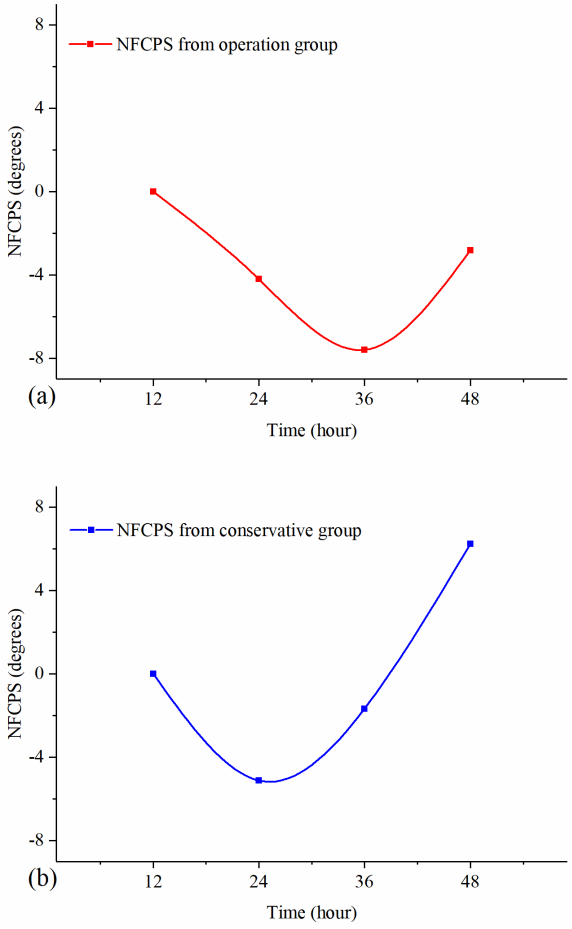

FIGURE 6. NFCPS from operation group and conservative group (a) The NFCPS of patient E00000005 at 12h, 24h, 36h and 48h after the surgery (b) At 12h, 24h, 36h and 48h, the NFCPS of patient C00000003 enduring conservative treatment.

The NFCPS and CT comparison results between operation group and conservative group were shown in Figure 6 and 7. For the patient E00000005, the NFCPS decreased 7.60 degrees in the period from 12 to 36 h after the surgery, as shown in Figure 6(a). The CT image at 11h revealed that after hematoma removal and bone flap decompression, the original intracranial hematoma position was filled with normal saline, the sulci and gyri were visible, and the ventricular area on the other side was enlarged due to the development of pressure difference. At 36 h, as a result of the open wound, the pressure inside the cavity resulted in expansion of the cavity volume. The pressure difference caused the swelling of the brain, and part of the brain tissue even spilled throughout the skull. This change led to the decrease of the overall brain conductivity.

The NFCPS of patient C00000003 in the conservative treatment group was shown in Figure 6(b). In the period

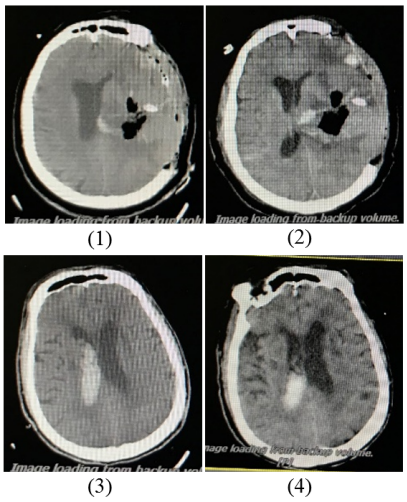

FIGURE 7. The CT images from operation group and conservative group. The CT images at 11h and 37h of patient E00000005 after the surgery are from (1) to (2) and the CT images at 12h and 84h of patient C00000003 enduring conservative treatment are from (3) to (4).

from 12 to 24 h reversal in admission, the NFCPS decreased 5.12 degrees. In contrast, the 12 h CT image showed that the right basal ganglia cerebral hemorrhage broke into the ventricle, and 75% of the right ventricle was occupied by the hemorrhage and then the hematoma began to clot slowly, corresponding to a decrease in conductivity and NFCPS. The CT images at 84 h showed that after a series of conservative treatments, the cerebral hemorrhage was slowly absorbed, and occupied only 50% of the right ventricle. Furthermore, the sulci and gyri were clearly visible, indicating slow changes in cranial contents. Blood began to absorb or liquate which may have caused the increase of the NFCPS.

The comparative analysis of the NFCPS and CT images of the surgical group and the conservative group confirmed that the pathological mechanisms leading first to a downward trend and then an upward trend of the NFCPS in the two groups are indeed different, which is consistent with the analysis of the relationship between the NFCPS and the cranial content change.

IV. DISCUSSION

The occurrence of cerebral hemorrhage and cerebral edema will disrupt the dynamic balance of brain parenchyma, CSF and brain blood in a closed skull. As the cranial contents increase, the CSF first compensates to maintain this balance. When the cranial contents are further increased, the compensatory capacity of the CSF reaches its limit, and then the nervous system maintains balance by regulating the cerebral blood volume. When the cranial contents continue to increase, and various physiological self-regulatory capacities reach saturation, the ICP will rapidly increase, and may lead to hernia and in severe cases to death. In 2016, we established a simple three-layer spherical model of cerebral hemorrhage and determined the variation trend of the overall

brain conductivity in the situation of acute cerebral hemorrhage [29]. However, such model does not take into account the effect of the clinical treatment leading to drastic change in the overall brain conductivity distribution. Under clinical conditions, such simple model of electrical conductivity and volume changes in the cranial content is no longer applicable, especially in patients who have undergone hematoma removal and bone flap decompression. On the basis of electrophysiological, pathophysiological and imaging evidence, in this study we fully considered different stages of cerebral edema development and two treatment methods after cerebral hemorrhage, thus totally improving the previous model. The NFCPS was analyzed at three postoperative time points to demonstrate the effectiveness of monitoring cerebral edema after basal ganglia hemorrhage.

At present, CT, MRI and other imaging techniques are commonly used in the diagnosis of cerebral edema in cerebral hemorrhage patients. However, the equipment required for such imaging techniques is too bulky and generally fixed. It is impossible to perform bedside real-time monitoring on patients, and the detection time resolution is very low. Hari Ramakonar et al. developed an ''imaging needle'' that can visualize nearby blood vessels in real time and applied this novel tool for the detection of cerebral blood vessels in vivo. Their research revealed that there indeed are a series of demands of a real-time method to achieve high time resolution, and thus provide timely guidance in both intraoperative and postoperative situations [36]. In 2017, Giraudet F compared the non-invasive measurement of the cochlear microphonic potential (CMP) phase to the ICP recorded invasively in a prospective series of patients with acute brain injury managed in a neuro-ICU. Whenever invasive monitoring cannot be performed, non-invasive CMP-based monitoring of the ICP might be beneficial to early management of brain-injured patients with initially preserved consciousness and to the diagnosis of neurological conditions [37]. However, abnormal transmission of sound through the middle ear must be ruled out as it may influence the CMP phase in an unpredictable manner. Bachmann MC introduced the characteristics, technical concepts, and clinical applications of EIT, which may allow better monitoring of lung function during acute respiratory distress syndrome (ARDS) [38]. Patients who enter the ICU are usually in a serious condition with rapid development. In some cases, traditional imaging methods cannot keep up with the development of the disease, which is likely to delay the appropriate treatment. The NFCPS measurement system designed in this work has many attributes, such as is small in size, low power requirement, simple operation and long-time operation to achieve real-time bedside monitoring. The comparative analysis of the NFCPS and CT images revealed that the NFCPS can also reflect the pathophysiological changes of the brain. The larger the intracranial space-occupying lesion, the greater the change in the NFCPS. In contrast, the smaller the intracranial space-occupying lesion, the smaller the change in the NFCPS. NFCPS technology focuses on the changes of cranial contents. Although, at present, it can neither distinguish cerebral hemorrhage and cerebral edema nor locate the lesion, it can monitor the known lesions and disease types targeted by the existence of imaging diagnostic information. Apparently, the NFCPS can be used as a reasonable supplement to imaging methods, such as CT and MRI. In addition, it is fully anticipated to help medical staff improve the treatment of patients with cerebral hemorrhage and cerebral edema, as well as reduce the mortality and disability rates.

In the surgical group, the brain tissue of most patients is given enough space to expand, while the ICP remains normal. Evidently, a single index of ICP cannot accurately reflect the occurrence and development of cerebral edema.

Most of the NFCPS data in this work were collected after surgery, and all 9 valid data sets showed a decreasing trend first and then an increasing trend. The standard deviation was large due to individual differences among the subjects. In the conservative group without surgery, the volume of the cerebral hemorrhage no longer expanded in the acute stage after hemostasis, and the hematoma slowly solidified. The small sample size in terms of patients receiving conservative treatment was limited by various reasons, including no life-threatening, too old, difficult for surgical treatment, etc. These patients spent less time in the ICU ward than those who may need surgery.

The NFCPS in both the surgical group and the conservative group showed the same trend. However, it was determined that they also have different pathophysiological mechanisms and involved different disease transformation processes. This difference in processes ultimately results in the dissimilar changes in the volume and composition of the cranial contents.

In addition, the decline in the NFCPS and the increase in the slope in the surgical group were larger than those in the conservative group. This is due to the generally large amount of bleeding of the surgical group, with an average of more than 53 mL, thus the hematoma clearance will reach more than 53 mL. The brain tissue undergoes spatial expansion with the existence of the skull bone window, resulting in a dramatic change in the volume and composition of the cranial contents. In the conservative treatment group, as a result of a rigid skull, the composition and volume changes of the cranial contents were small, resulting in a small slope of the NFCPS. Thus, the composition and volume of the cranial contents of the healthy control group remained basically stable. This again proves that the change of the NFCPS is associated with the change of the biological tissue volume and composition. In addition, the NFCPS monitoring results in this work provide an important reference for the changes of the overall brain conductivity in patients with cerebral hemorrhage after surgery and conservative treatment.

However, it is important to note, that this is only a preliminary observation experiment where the NFCPS technology is applied in clinical practice for the first time. Azabou E et al. examined the relevance of electroencephalographic reactivity (EEG-R) in patients with impaired consciousness

to determine the neurophysiological mechanisms involved. They found that whatever the etiology, patients with impaired consciousness featuring a reactive electroencephalogram were more likely to have a favorable outcome, whereas those with a nonreactive electroencephalogram were likely to have an unfavorable outcome. EEG-R is therefore a valuable prognostic parameter and warrants a rigorous assessment [39]. A combined multimodal assessment using these tests, such as to increase the accuracy of outcome prediction in patients with impaired consciousness, has been reported. Dunham CM analyzed 1,883 h of data and found that $StcO_2$ and BIS are associated with survival, good neurological outcome, ICP $\leq$20 mmHg, cerebral perfusion pressure (CPP) $\geq$60 mmHg, and CAP index $\leq$0.30 ($p \leq 0.001$). The independent associations of BIS, $StcO_2$, and ICP with outcome suggest that non-invasive multi-modal monitoring may be beneficial [40]. All our actions must meet the ethical requirements, and there must be no interference with the medical treatment at all. Therefore, during the two-month study, less than 20 samples that met the requirements of the group were collected. In the future, under proper guidance, we will increase the number of samples, improve the ergonomic sensors and monitoring devices, and achieve automatic and 24-h continuous measurement without affecting any medical treatment.

V. CONCLUSION

In this study, a non-invasive real-time monitoring system of brain edema for use in the neurosurgery ICU was established based on NFCPS technology. A total of 17 subjects (divided into a surgical treatment group, a conservative treatment group and a control group) were selected to perform real-time NFCPS monitoring of cerebral edema. A comprehensive investigation was conducted by combing NFCPS and CT imaging data. We inferred that the aforementioned factors (bleeding, swelling, cavity edema) successively control the volume and composition change of the cranial contents. It was also inferred that the overall brain conductivity may show a decreasing trend first and then a rising trend in patients suffering from hemorrhagic stroke. Furthermore, patients who underwent surgeries like craniotomy and hematoma evacuation faced a more complicated situation, just like the NFCPS data in our study showed, and thus warranted more detailed observation and monitoring.

This pilot research strongly shows the robust clinical feasibility of NFCPS in the non-invasive real-time monitoring of cerebral edema. In addition, the change in the characteristics of the overall brain conductivity in hemorrhagic stroke patients provides guidance for subsequent researches.

Ethics Approval and Consent to Participate

The study was performed in accordance with the Declaration of Helsinki and was approved by Ethics Committee of the First Affiliated Hospital of Third Military Medical University (Southwest Hospital, Chongqing, China). For all research involving human subjects, informed consent to participate in the study had be obtained from participants. Protocol number of the approval: AF/11/054.0. Registered 20 December 2016.

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