Intracranial Pressure Noninvasive Comprehensive Detection System in Clinic

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Abstract
It is difficult to determine the widespread use invasive intracranial pressure monitoring methods on the account of its limitations in clinical application. Each intracranial pressure noninvasive measurement approach has its own principle restriction. As a consequence, its accuracy and constancy are not guaranteed. In order to ease this situation, this study proposes a new approach of implementing the comprehensive intracranial pressure monitoring system in clinic. This approach has achieved the integrated application of multiaxial axioms in intracranial pressure detection on the same instrument hardware platform through the synchronous acquisition and feature extraction of the multidimensional biomedical signal, based on the discussion on the fusion of human pathophysiological parameters associated with changes in intracranial pressure. This new approach has vast importance to improving the clinical feasibility and monitoring precision of noninvasive intracranial pressure measurement, and expanding its application in clinic, accordingly.

ABBREVIATIONS
ICP: Intracranial Pressure; FVEP: Flash Visual Evoked Potential; TCD: Transcranial Doppler; AAMI: The American Medical Instrument Promotion Association

INTRODUCTION
The degree and duration of intracranial hypertension, which is the primary cause of secondary brain injury, are relevant to the fraction surviving and extent of permanent dysfunction. In particular, intracranial pressure (ICP) would be rapidly lifted, provided that there is a little change in intracranial volume when it reaches the critical point of the intracranial volume-pressure curve. This would exacerbate brain displacement and cerebral hernia, causing central failure. Consequently, monitoring ICP in clinic is vital, which is the basis of taking precautions, controlling intracranial hypertension, and determining treatment options. Simultaneously, the clinical monitoring of ICP can provide an objective method to measure curative effects. However, ICP is currently not being monitored in a number of hospitals. The main reason of this phenomenon is that monitoring ICP is invasive, which not only has a risk of infection, but also needs professionals to carry it out and explain the clinical data [1]. Furthermore, due to the invasiveness of monitoring ICP, this approach is also costly.

A literature [2] reviewed 93 articles on ICP monitoring from 1985 to 2009, and pointed out that the application of invasive ICP monitoring in clinic was confined to neurosurgical intensive care units (ICUs) and some special hospitals, and that this invasive technique could not be widely applied in hospital, emergency rooms, outpatient services and accident scenes, even though ICP monitoring has been widely accepted due to its benefits in clinical application. Accordingly, the technique and equipment used for noninvasive ICP monitoring provides an excellent choice for improving the clinical value of ICP monitoring.

MATERIALS AND METHODS
The technique for noninvasive ICP monitoring was first reported in 1966, which was used to measure the ICP of neonates and infants whose fontanelle was not closed, but was inapplicable to older children and adults [3]. In the past years and decades, monitoring techniques have been developed by a substantial number of researchers, and these methods have one thing in common, it indirectly estimated ICP through variables that were related to ICP, but could be monitored more readily than ICP. Nevertheless, these techniques could not be widely applied in clinical at present, and the reasons might be as follows:

Imaging approaches (CT and MRI)
These methods can provide more abundant clinical information, and be used to evaluate hydrumcus, hemorrhage, intracranial lump, or ICP lifting more easily. Therefore, these techniques can partly replace invasive ICP monitoring [4]. However, signs of elevated ICP in CT or MRI are only qualitative indicators. In particular, when ICP is chronic or slowly elevated, and the brain has time for self-regulation, ICP measurements may not be accurate. In addition, the means of evaluating
ICP based on CT or MRI is inefficient and harmful to patients, because CT and MRI cannot be performed at the bedside, and requires patients to be delivered from the ICU to the imaging device, which is unrealistic. Moreover, CT detection is noninvasive but detrimental to human health, owing to the radiation from the CT scanner.

**Flash Visual Evoked Potential (FVEP) method**

This method achieves noninvasive ICP detection through the relationship between ICP changes and latency changes in the second negative wave (N2) of FVEP. This method was studied in 1986 [5-8]. At present, noninvasive ICP devices based on FVEP have been used in clinic [9]. However, FVEP for noninvasive ICP monitoring has the following main problems: individual differences are large, and the stability and repeatability of the waveform is not ideal. In addition, FVEP is very sensitive to anesthetics, and attention should be focused on the stability of the physiological and pharmacological state. The current literature is based on the linear relationship between FVEP N2 wave latency and ICP changes, but the critical point in the intracranial volume-pressure curve should be a turning point. Thus, ICP is linearly related to the FVEP before the critical point. On account of the power function between ICP and FVEP, it is possible to realize the noninvasive detection of ICP through the relationship between ICP changes [10].

**Transcranial Doppler (TCD) method**

ICP is generated by heart cycle fluctuations and cerebral blood pressure impacted by breathing, and its waveform consists of pulsed waves and respiratory waves. TCD is used to study cerebral blood flow fluctuations. Therefore, ICP fluctuations and the TCD study of cerebral blood flow theory are closely related. A number of literatures have established models between TCD hemodynamic parameters and ICP [11-14], but there is no well-recognized formula to quantify ICP noninvasively with TCD. Most literatures have proposed to establish a relationship between hemodynamic parameters and the ICP model. Hence, at present, the application of TCD is mainly the qualitative reflection of changes in ICP.

Other methods such as the bioelectrical impedance method, near infrared spectroscopy, intraocular pressure, tympanic membrane shift, anterior halo pressure measurement, and mathematical model methods have been reported for the noninvasive detection of ICP [15-18]. Different noninvasive ICP detection methods have a certain scope of application, and changes in ICP present a comprehensive characterization caused by different factors. It is difficult to achieve accurate ICP values through only one noninvasive detection method or several parameters. In accordance with the provisions of the American Medical Instrument Promotion Association (AAMI), ICP monitoring equipment should be able to continuously output in a range of 0-100 mmHg, the accuracy in the range of 0-20 mmHg is within ± 2 mmHg, and the maximum error should be < 10% for more than 20 mmHg of ICP; while most of the existing methods could not meet the AAMI standard [2,19]. Thus, although noninvasive ICP detection techniques have been studied for a long time, and some methods have proven to be clinically valuable, studies on noninvasive ICP monitoring methods and devices that truly meet clinical application requirements are presently in the exploratory phase. It is key to find a high-precision and operational approach for noninvasive ICP detection in clinic.

A literature [20] has summarized the advantages and disadvantages of the invasive and noninvasive methods of ICP monitoring and the scope of its use in clinic, according to 130 literatures from 1783 to 2011. This literature pointed out the accuracy and stability of noninvasive ICP detection could not be guaranteed due to the impact of individual differences in patients. Noninvasive ICP detection equipment is uncommon in clinic, and could not effectively replace invasive detection methods in clinic. The realization of a high-precision noninvasive ICP detection model and its feasibility in clinical application should be based on the needs of the clinical application. Hence, more in-depth studies on noninvasive ICP detection methods and the mechanism of the internal changes of ICP should be performed through more extensive clinical data acquisition and effective noninvasive ICP detection methods.

**RESULTS AND DISCUSSION**

Based on clinical ICP in different elevated types, individual differences in patients, and the limitations of different noninvasive detection methods of ICP in clinical application, Zhong Ji et al., proposed a multi-parameter fusion method for the noninvasive detection of ICP [21]. On this foundation, they constructed a noninvasive ICP detection and diagnosis equipment through the comprehensive application of FVEP and hemodynamic parameters with TCD, and applied it to clinical use. Clinical application revealed that the device can better overcome the problems of accuracy and instability, and can be easy influenced by individual differences, when only a single noninvasive ICP detection method was applied. Compared with the invasive value, overall error can be controlled within 10%. However, due to the diversity of clinical diseases that cause intracranial hypertension, when the device is used to detect certain cases and certain patients, the errors are quite larger than invasive values, which do not meet the requirements of clinical application. In order to further improve the applicability of the noninvasive detection and diagnosis equipment of ICP in clinical application, on the basis of the model in reference [21], we further studied the model structure parameters.

In the analysis of multidimensional physiological parameters of clinical patients with intracranial hypertension, the following were found:

1. Acute intracranial hypertension progression is rapid. Intracranial hypertension causes serious symptoms and signs. Vital signs have acute changes, including blood pressure, respiration, pulse and temperature;
2. Acute intracranial hypertension can be complicated by neurogenic brain edema. Some scholars have considered that intracranial hypertension cause sympathetic excitation, which result in systemic vasoconstriction and an increase in cardiac output. A large volume of blood is forced into the lower resistance of the pulmonary circulation system, producing pulmonary edema;
3. Decreased cardiac output can leading to a decrease
in ICP and cerebral perfusion pressure, which is an important cause of brain damage;

(4) Positive end expiratory pressure can increase ICP, reduce intracranial venous flow and returned blood volume. Therefore, increased ICP and cardiac output reduction (low blood pressure) would lead to lower cerebral perfusion pressure.

Therefore, in addition to vital changes in intracranial hypertension (the cardiac hemodynamic index), cardiac output is a significant factor that affects changes in brain perfusion pressure. Accordingly, changes of hemodynamic parameters and cardiac function indexes can provide doctors with more sufficient information for further analyzing ICP levels, and assessing the physiological and pathological status in patients.

On the basis of the multi-parameter model described in reference [21], the cardiac hemodynamic parameters in patients are detected and added into the model, when ICP was detected by the noninvasive ICP detection equipment.

The established framework model of multi-parameter fusion for the noninvasive integrated evaluation of ICP:

\[ V_{\text{ncp}}(t, \text{Diseases}) = F(t, \text{ABP, Disease, feature parameters}, \ldots) + \Delta_s \]  

Where \( V_{\text{ncp}} \) is the noninvasive measurement value of ICP, and the selection of its computational model is related to the causes of changes in ICP in patients (Diseases); \( F \) is a function that reflects the relationship between \( V_{\text{ncp}} \) and each detection parameter, which depends on many interrelated factors, including time \( t \), arterial blood pressure \( \text{ABP} \), cerebrospinal fluid compliance, the status of cerebrovascular automatic regulation function, individual factors related to the patient (such as gender, age and body weight etc.), various pathological information and feature parameters recorded in the signal database. In addition to FVEP latency with flash stimulation and cerebral hemodynamic parameters with TCD described in reference [21], the cardiac hemodynamic parameters measured using the impedance method were also added; \( \Delta_s \) is the systematic error affected by a series of factors, such as individual differences, hardware system of the instrument platform, errors caused by model simplification, and input parameter errors, which would be compensated by the change in test result after the system platform is constructed. The individual factors, such as gender, age, body weight, will affect the flash visual evoked potential latency time and hemodynamic parameters etc., which will affect the detection value of noninvasive intracranial pressure; the intracranial pressure increased levels caused by different types of diseases are different, they may be acute, sub-acute or non-acute. Only for acute intracranial pressure rise, the noninvasive intracranial pressure detection methods have high detection accuracy and reliable, and have a good consistency of the invasive detection value of ICP.

Furthermore, in order to simplify the structural complexity of the model and equipment, using the multiple linear regression equation as the \( F \) function in equation (1), and the sensitivity analysis model of each parameter was established by using the multi-parameter sensitivity analysis method [21]:

\[ \frac{d}{dt} S_j = \sum_j \frac{\partial F}{\partial S_j} S_j + \frac{\partial F}{\partial p_j} \]  

Where \( S_j = \frac{\partial x}{\partial p_j} \) denotes the sensitivity of the \( j \)-th parameter corresponding to the \( i \)-th disease, and \( x \) denotes various diseases causing the increased ICP discussed in this project; \( p \) denotes the parameters associated with increased ICP; \( F \) denotes the non-linear model function applied for the \( i \)-th disease. The final model of noninvasive ICP detection is shown in equation (3).

\[ V_{\text{ncp}}(t, \text{Diseases}) = A \times T_{m1} + B \times \left( BP_m - BP_m \times \frac{V_d}{V_m} - 14 \right) + C \times CO + \Delta_s \]  

Where \( A, B \) and \( C \) are model structure coefficients of noninvasive ICP detection model associated with the type of disease; \( T_{m1} \) is the N2 characteristic wave latency obtained with the flash visual evoked potential (FVEP) method; \( BP_m \) is the average blood pressure based on the input values of systolic pressure and diastolic pressure; \( Vd \) and \( Vm \) are the cerebral hemodynamic parameters detected by TCD; \( CO \) is the patient’s cardiac output obtained by impedance detection method.

Through this model, the correlation among the clinical diagnoses of the disease, physiological and pathological parameters and the noninvasive detection values of ICP is established. Then, the model is trained by invasive ICP measuring values. Based on this, a balanced treatment of the completeness of the model and the complexity of the equipment structure are taking place, and it is expected that the precision and stability of the clinical ICP can be further improved under the premise of simplifying the structure of the device.

The detection platform of the multi-dimensional biomedical signal and physiological parameters shown in Figure (1) is constructed based on the final multi-parameter noninvasive ICP detection model.

In this system, FVEP, TCD and impedance hemodynamic parameters (ICG) were used to collect the physiology-pathological information associated with changes in brain pressure on the same instrument platform. The corresponding feature parameters are extracted by the signal processing methods as feature parameters in the equation (3). The patient’s information including the disease, gender, age, weight, blood pressure are input directly through the information management input port of the system to show the individual differences in the patient’s information in equation (3). High-precision and clinically adaptable brain pressure and cerebral perfusion pressure are obtained through the system platform to collect multi-dimensional physiological and pathological information, and for multi-parameter fusion analysis and diagnosis.

According to CFDA medical equipment clinical trial requirements, the clinical trials were carried out in Southwest Hospital and Daping Hospital of the Third Military Medical University in Chongqing, China. Firstly, the clinical trial protocol was determined and approved by those two hospitals’ ethics committee. Then, the clinical cases were screened. The subjects for clinical testing must be the patients whose intracranial pressure should be detected invasively in clinic, and noninvasive
measurement of intracranial pressure was conducted after informing patients with informed consent.

A total of 80 cases were selected from the two hospitals, 50 cases in Daping hospital and 30 cases in Xinan hospital, including 54 males and 26 females. The patients' age ranged from 18 to 81 and the average age was 52.51 years old. The patients have not neurological disorders, cataracts, blindness and fundus hemorrhage et al. The cases causing acute intracranial pressure increased consisted of 11 intracranial injury cases, 38 cerebral hemorrhage cases, 17 hydrocephalus cases and 14 intracranial tumor cases.

Among the 80 cases, the invasive intracranial pressure values of 50 patients were immediately measured by lumbar puncture after the noninvasive intracranial pressure values were detected by the device shown in Figure (1); Another 30 patients' intracranial pressure values were invasively detected by the ventricle puncture method, while the noninvasive intracranial pressure values were obtained by the device. The noninvasive intracranial value of every subject was the average of 3 consecutive tests. The test results were shown in Table (1). The mean relative error between noninvasive intracranial pressure and invasive intracranial pressure is 8.26%, which is less than 10% and meets the clinical requirements.

The system has a medical device product registration certificate from CFDA. Furthermore, this system can be used in neurosurgery and the intensive care unit, or any other situation where ICP is needed to be detected. This system provides a noninvasive and feasible method to understand a patient’s brain pressure situation.

**CONCLUSION**

Although the non-invasive method of monitoring ICP has been studied for a long time, and some of these existing devices can meet clinical needs to a certain degree, the accuracy and stability of these devices cannot be well-guaranteed due to the diversity of diseases which, bring about the rise of ICP and its complicated operation. In addition, it can reduce the pain of patients and put an end to intracranial infection. Thus, it has vital significance on research and the development of new comprehensive noninvasive ICP detection systems, increasing the clinical adaptability of this method to achieve accurate, convenient, dynamic, inexpensive and noninvasive ICP monitoring, and to allow its widespread application in clinic.

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