The detection of chronic cerebral hemorrhage in rabbits with magnetic induction

Jian Sun¹, Gui Jin¹, Mingxin Qin¹*, Zibing Wan², Jinbao Wang³, ChaoWang⁴, Wanyou Guo⁴, Lin Xu¹, Xu Ning¹, Jia Xu¹, Xianjie Pu¹, Mingsheng Chen¹ and Hongmei Zhao²

¹ College of Biomedical Engineering and Medical Imaging, Experimental Animal Center, Third Military Medical University, Gaotanyanzheng street 30, Shapingba district, 400030 Chongqing, China
² College of Life Sciences and Technology, Xidian University, Taibai South Road 2, 710126 Xi’an, China
Email: nksunj@126.com, qmingxin@tmmu.edu.cn
* Corresponding author.

Abstract. Chronic cerebral hemorrhage (CCH) in the brain is an important clinical problem that is often monitored and studied with expensive devices such as MRI and PET, which are not readily available in low economical resource parts of the world. We have developed a less expensive tool for non-contact monitoring of CCH in the brain. The system measures the phase shift between the electromagnetic signals on the two coils. CCH was induced in the brain of rabbits by stereotactic method. Intracranial pressure (ICP) and Electrocardiograph (ECG) of subjects were monitored for 1.5h. Signals were continuously monitored up to \( t = 1.5h \) at exciting frequency 10.7 MHz. From 0.8 to 2.4 ml of autologous blood was injected (each injection quantity of 0.8 ml, the interval time for 30 minutes). The results show significant phase shifts increase as a function of injection volume. ICP and phase shift were directly proportional to the related, while HRV were stable around 200 beats*min\(^{-1}\). Our system has high sensitivity that even 0.8 ml can also be detected. In this study, the curves of inductive phase shift are significantly related to ICP. This observation suggests that the method could be valuable, in
addition to continuous monitoring, also for early warning in emergency medicine and critical care units.

1. Introduction
In brain neurosurgery to date, deformation of the brain usually occurs due to the change of intracranial pressure, which can be caused by surgical intervention, medications received and acute cerebral hemorrhage [1]. The study of the cerebral hemorrhage is benefited from advances in medical imaging such as MRI and PET [2]. While advanced medical imaging techniques are extremely valuable in studying cerebral hemorrhage, the devices are expensive and not readily available either to patients or to researchers in areas with low economical resources [3, 4]. The goal of this study is to introduce a new inexpensive and valuable technology which could become a useful tool in research and clinical applications related to the study of brain injury in general and cerebral hemorrhage in particular.

The field of study relates to the electromagnetic properties of biological tissues. As shown by Tarjan and McFee [5], an electrode-less measurement of changing impedances in the human body can be achieved by measuring the effect of inducted eddy currents. It is established in the literature that different biological tissues have different electromagnetic properties and that it is possible to distinguish between different tissues on the basis of these properties [6]. The complex electrical properties of impaired tissue are substantially different from those of normal tissue, various non-invasive systems based on electro-magnetic measurements have been proposed for different medical applications [7, 8]. Magnetic induction tomography (MIT) has been studied as a potential tool for noninvasive detection of tissue oedema [7, 8, 9, and 10]. Also there are different approaches for detecting electromagnetic changes in tissue by non-invasive means [11]. Measuring changes in the electromagnetic properties of the tissue with two non-contact induction coils placed around the tissue could be used as an alternative technique for detection of the clinical changes in the tissue [12, 13]. While information is not in the form of an image it can produce temporal and even gross local information about changes in tissue [14], from non-invasive bulk measurements. In particular, detecting the change in the variable electromagnetic phase shift in time after the occurrence of a suspected clinical episode could serve as a first-order clinical warning to detect the presence and progression of change in tissue [11]. In this study, we show with experiments in the rabbit brain that the concept of non-invasive measurements of the electromagnetic properties of the brain can be used to detect the evolution of cerebral hemorrhage in the brain. The electromagnetic property we measure in this study is the change of electromagnetic phase shift in time in the brain. We describe here the fundamental principles, the device and show results obtained in the brain of cerebral hemorrhage rabbits.

2. Methods
2.1. Theoretical estimation

We have considered as a case study a cylinder of tissue of radius $R$ and thickness $t$, placed centrally and midway between an excitation coil and a detection coil spaced at a distance $d(t<<d)$. A sinusoidal current $I$, of angular frequency $\omega$, flows in the excitation coil and produce a magnetic field $B$. The magnetic field matches in phase a reference voltage ($V_r$) in the excitation coil. The non-magnetic cylinder has conductivity $\sigma$ and relative permittivity $\varepsilon_r$. The skin depth $\delta$ is assumed to be much greater than $t$, which means that the attenuation produced by the cylinder is small. We use spherical polar coordinates($r, \theta$) as shown in Figure 1.

![Figure 1](image1.png)

Figure 1. Magnetic field in a cylinder due to an excitation coil (shown in polar coordinates). The cylinder of radius $R$ and thickness $t$ is placed centrally and midway between a small excitation coil and a small sensing coil spaced a distance $d$. The cylinder has conductivity $\sigma_c$, relative permittivity $\varepsilon_r$ and is non-magnetic.

According to Griffiths et al [15], at a point $P$ in the cylinder model, the magnetic vector potential

$$\frac{\Delta B}{B} = \frac{(r_0^2)}{(r_0^2+R^2)} \left[ \frac{1}{r^2} \right] \left( \frac{\omega \mu_0 d^3}{16} \right)$$

The magnetic field and its perturbation can be obtained from the voltages induced in the detection coil, $V_i$ and $\Delta V_i$ [16]. Hence, $\frac{\Delta B}{B}$ can be defined in terms of the induced voltage in the detection coil [16] by

$$\frac{\Delta B}{B} = \frac{\Delta V_i}{V_i}$$
We define a constant $k$

$$k = \frac{\mu_0 \tau_d}{16} \left[ \frac{1}{r_0^2} - \frac{r_0^2 + 2R^2}{(r_0^2 + R^2)^2} \right]$$

(3)

Substituting (3) and (2) into (1), the phase of the total induced voltage $\theta_{Vi}$ in the detection coil with respect to the induced voltage by the primary magnetic field could be expressed as a function of frequency and electrical parameters in the cylinder between the coils [15]by

$$\theta_{Vi} = \arctg \left( \frac{\text{Im}(\Delta V)}{\text{Re}(\Delta V)} \right) = \arctg \left( -k_{\omega} \frac{\omega}{\sigma} r_0^2 \epsilon_0 \epsilon_r + 1 \right)$$

(4)

The phase of the reference voltage $\theta_{Ve}$ in the presence of the cylinder sample can be estimated from the following expression [11]

$$\theta_{Ve} = \arctg \left[ \frac{\text{Im}(Z_L + \Delta Z_L)}{\text{Re}(Z_L + \Delta Z_L)} \right]$$

(5)

Where $Z_L$ represents the impedance of the excitation coil. $Z_{out}$ represents the output impedance of the excitation source. The total change in phase shift ($\Delta \theta$) between the reference and induced voltages in the excitation and sensing coil, respectively, is given by the expression:

$$\Delta \theta = \theta_{Vi} - \theta_{Ve}$$

(6)

2.2. Surgical procedure.

A rabbit (3.8kg) were anaesthetized with urethane (25% , 5ml/kg) via ear vein. We establish the model of ACH by means of stereotactic method. The coordinates for the brain were determined using a standard atlas [17]. A short midline skin incision was made and the point for a stereotactic approach through the skull determined. The head was leveled in such a way that the bared Bregma was 1.5mm higher than Lambda. With the position of Bregma as a reference point, the coronal zero planes (AP$_0$) passed through the coronal suture. A$_1$ referred to the coronary plane which was 1 mm before AP$_0$, while P$_1$ was 1mm after AP$_0$. The scope of the internal capsule was between A$_5$ and P$_2$. We chose coronary plane P$_1$. Puncture point is on the right of the coronal suture(R=6mm) and after the sagittal suture (P$_1$, AP=1mm). A 1mm drill bit was twisted by hand to perforate the skull. A needle (d=0.7mm) was then introduced to the proper depth (H=13mm) and autologous blood slowly injected. From 0.4 to 5.2 ml of autologous blood was injected. RM 6280B biological signal collecting and processing system was used to measure the changes of ICP and APP of paracel [18] and HRV. As shown in Figure2, rabbits were operated to monitoring ICP, APP and HRV.
2.3. Experimental magnetic induction prototype
An experimental inductive setup was designed and constructed. The system consists of seven modules: signal generator, excitation coil, detection coil, phase detector, PC and biological signal collecting and processing part. A picture of the experimental set-up is shown in Figure 3.

2.3.1 Signal generator
The function generator was implemented by a signal generator, which supplies a signal $I \cos(\omega t)$ of approximately 5v at 10.7MHz. The range of output power from the excitation source is 1.5~33dB. The frequency stability is the order of magnitude of $10^{-4}$, the distortion reaches $10^{-2}$~$10^{-4}$ and the SNR is 30~60dB in the excitation source.

2.3.2 The coils
The excitation and detection coils were coaxially placed. Both coils were ten turns with radius $r = 5$ cm. The distance between coils was $d = 11$ cm. To avoid inductive pickup the leads of the coils were twisted. The excitation coil induces a current in the detection coil by magnetic induction and an
inductive phase shift as a function of the electrical properties of the rabbit brain.

2.3.3 Phase detector
The phase detector includes the band-pass filter, amplifier, AD, FDGA, DSP, flash memory and LCD. The phase detector can be calibrated and the temperature drift and the noise can be eliminated by calibration software. The parameters of our phase detector are as follows: the range of the phase measurement: 0~180°, the phase precision: 0.05°, the range of gain: -10~35dB, once measurement time: 3~7s. The 12h data measured can be saved in the phase detector.

2.3.4 Biological signal collecting and processing part
The data processing part (6280C, Chengdu Instrument Factory) was controlled by a personal computer.

2.4. Experimental design.

![Figure 4 Work flow diagram](image_url)

Figure 4 shows a work flow diagram of the experimental prototype. ICP, APP, ECG and phase shift were synchronously collected for the comparison of measured results. In a typical procedure, baseline data were taken after the surgical procedure (t = 0). Signals were continuously monitored for 1.5h. Autologous blood was injected from 0.8 to 2.4 ml (Each injection quantity of 0.8 ml, the interval time for 30 minutes). When each 0.8ml blood was injected, the phase detector measured the phase shift for 30 minutes and got 500 data. We choose 10 stable and continuous measurements of phase shift before
next injection. ICP, APP and HRV were processed according to the 10 measurements of phase shift. And then each data set was averaged.

The values of the phase shift changes were recorded with respect to baseline measurements taken after the procedure. Experimental excitation and detection coils are coaxially placed around the brain cavity of the rabbits. In all the experiments the coils were placed in such a way that the brain cavity was centered between the excitation and detection coils. Changes in phase shift as a function of the injection volume were recorded. The fundamental hypothesis in this study is that the changes in phase shift measured with the detection coil will be representative of the changes in electrical conductivity of the brain.

The Animal Experiments and Ethical Committee of the Institution approved all experimental protocols and the care of animals was carried out in accordance with the Declaration of Helsinki and IASP guidelines [19, 20].

3. Results and discussion

![Graph](image-url)

**Figure 5.** Relationship curves of intracranial pressure and inductive phase shift from rabbit brain hematoma model

Figure 5 showed relationship curves of ICP, APP, HRV and phase shift from rabbit brain hemorrhage model at exciting frequency 10.7MHz.

Along with the increase of injection quantity, the changes of phase shift also increased. The phase shift curve’s slope was stable. Our study told us magnetic induction theory was reliable, and our system can detect a small amount of bleeding in the brain. ICP were directly proportional to phase shift, while HRV were stable around 200 beats*min⁻¹. So the changes of phase shift reflected the
changes of ICP.

Figure 5 also showed the change rate of ICP and phase shift were not identical. Reasons are as following: First, the collection of ICP and phase shift is not completely in sync. Second, manual injection brought error. Third, injection intervals were short (only for 30 minutes), so CBF (cerebral blood flow) and CSF (cerebrospinal fluid) regulatory function were not considered. As compared to this, CBF was reduced both around the hemorrhage and in the surrounding brain, and this change was strongly volume-dependent and was not accompanied by significant alterations in CPP [21]. Fourth, the animal moved in the experimental process. In future we must optimize our system to ensure synchronous collection and use injection pump to avoid artificial error.

Also we may take long term monitoring up to 12h above. The coils inductance and electrical conductivity of rabbit brain were not calculated. Due to time restrictions, sample number was too small and had no control group. Further development aims at contrast research.

This was an early experiment and had many drawbacks. But this was the first study to reveal the relationship between the ICP and change of phase shift by animal experiment. A comparison of the analytical and experimental results with respect to others’ previous studies [12, 13] suggests that various physiological conditions in the brain such as oedema and ischaemia can be distinguished through the analysis of the inductive phase shift change at specific frequencies. In this study, the curves of inductive phase shift are significantly related to ICP. This observation suggests that the method could be valuable for early warning in emergency medicine and critical care units in addition to continuous monitoring.

4. Conclusion
Measuring the magnetic induction phase shift changes as a function of time after brain injury has the potential for being a simple method for early and non-contact detection of the occurrence and progress of cerebral hemorrhage in the bulk of brain. This technique could be useful in both research and clinical applications in particular for low economical resources areas of the world. This is a preliminary study and much more research remains to be done to confirm these observations. Although the experimental evidence provided in this study has relevance to the clinical case, the cerebral hemorrhage formation in clinical practice is a more complex process than the experimental model evaluated in this study.

5. Acknowledgments
This work was supported by Foundation of Third Military Medical University and National Natural Science Foundation of China (61072254).

6. References
[1] Lighthall W J 1988 Controlled cortical impact: a new experimental brain injury model J.
Neurotrauma. 5 1–15

[2] Chelsea S. Kidwell, Julio A. Chalela, Jeffrey L. Saver 2004 Comparison of MRI and CT for Detection of Acute Intracerebral Hemorrhage JAMA. 292(15) 1823-1830

[3] Otten D M, Onik G and Rubinsky B 2004 Distributed network imaging and electrical impedance tomography of minimally invasive surgery Technol. Cancer Res. Treat. 3 1–10

[4] Granot Y, Ivorra A and Rubinsky B 2008 A new concept for medical imaging centered on cellular phone technology Plos.One. 3 2075

[5] Tarjan P and McFee R 1968 Electrodeless measurements of the effective resistivity of the human torso and head by magnetic induction IEEE Trans. Biomed. Eng. 4 266–78

[6] Foster K R and Schwan H P 1989 Dielectric properties of tissues and biological materials: a critical review CRC Crit. Rev. Biomed. Eng. 17 25–104

[7] Al-Zeiback N S 1993 A feasability study of in vivo electromagnetic imaging Phys. Med. Biol. 38 151–60

[8] Korjenevsky A V and Cherepenin V A 1997 Magnetic induction tomography J. Commun. Technol. Electron. 42 469–74

[9] Korjenevsky A V and Cherepenin V A 1999 Progress in realization of magnetic induction tomography Ann. N. Y.Acad. Sci. 873 346–52

[10] Griffiths H 2001 Magnetic induction tomography Meas. Sci. Technol. 12 1126–31

[11] Gonzalez C A 2009 The detection of brain ischaemia in rats by inductive phase shift spectroscopy Physiol. Meas. 30 809–819

[12] Gonzalez C A and Rubinsky B 2006 A theoretical study on magnetic induction frequency dependence of phase shift in oedema and haematoma Physiol. Meas. 27 829–38

[13] Gonzalez C A and Rubinsky B 2006 Detection of brain oedema with frequency dependent phase shift electromagnetic induction Physiol. Meas. 27 539–52

[14] Rojas R, Rubinsky B and González C A 2008 The effect of brain hematoma location on volumetric inductive phase shift spectroscopy of the brain with circular and magnetron sensor coils: a numerical simulation study Physiol. Meas. 29 S255–S266

[15] Griffiths H, Steward W R and Gough W 1999 Magnetic induction tomography—a measuring system for biological materials Ann. New York Acad. Sci. 873 335–45

[16] Scharfetter H, Casañas R and Rosell J 2003 Biological tissue characterization by magnetic induction spectroscopy(MIS): requirements and limitations IEEE Trans. Biomed. Eng. 50 870–80

[17] Sawyer CH, Everett JW, Green JD 1954 The rabbit diencephalon in stereotaxic coordinates. J Comp Neurol. 101 801-824

[18] WJ Jing 2007 Study on the model building of internal capsule hemorrhage and the changes of intracranial pressure and discharge of vagus nerve in rabbits shanxi medical journal 361
[19] Helsinki 1996 Declaration of Helsinki Br. Med. J. 313 1448–9

[20] Zimmermann M1983 Ethical guidelines for investigations of experimental pain in conscious animals Pain. 16 109–10

[21] Fredric P. NATH, F.R.C.S., et al 1986 Early hemodynamic changes in experimental intracerebral hemorrhage J Neurosurg. 65 697-703