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A prototype device for non-invasive continuous monitoring of intracerebral hemorrhage

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Abstract

A prototype for a non-invasive, real-time, monitoring device was developed to detect changes in the brain secondary to disease or injury such as intracerebral hemorrhage (ICH). The eventual goal is a non-invasive, real time sensor that can alert the clinician to alterations in the comatose patient's brain resulting from hemorrhage, seizure or stroke. In this work, a 400 MHz electromagnetic (EM) signal was transmitted with an antenna (T), incident on a 'brain gel' in vitro ICH model, and received by a receiving (R) antenna. Changes in the received signal were found to be induced by the presence of blood. The received power (P_R) was found to be a linear function of the cross sectional area of blood, as measured normal to the incident wave. In addition, the sensor was able to detect as little as 1 mL of blood in this 1000 mL in vitro model.

Keywords

Stroke; Intra-cerebral hemorrhage; Microwave tomography; Brain monitoring; Hematoma expansion

1. Introduction

Intracerebral hemorrhage (ICH) is a devastating form of acute stroke, and is responsible for substantial mortality and morbidity in the U.S. and elsewhere. It accounts for roughly 2 million strokes per year, and is increasing in incidence secondary to the aging of the population overall (Qureshi et al., 2009). Current therapy is focused on therapies such as improved blood pressure control, reversing anticoagulation, and optimizing intensive care unit (ICU) management (Elijovich et al., 2008). However, there is increasing recognition that hemorrhage growth after the initial injury is an important prognostic indicator, with those patients exhibiting earlier and larger hematoma expansion having poorer outcomes overall (Davis et al., 2006).

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GJS, OA, and JC are co-inventors on patent application –10738-186 which covers some of the technology discussed in this work.

The recognition that hemorrhage expansion and/or re-bleeding in ICH patients is clinically important has led to several studies of hemostatic agents such as recombinant factor VII as a potential therapy in this disease. Recently Mayer et al. (2005) studied the use of recombinant Factor VII in a dose escalation phase IIa trial in 399 ICH patients. They found less hematoma expansion in those receiving factor VII and lower mortality and morbidity, as compared with control patients. This led to a phase III trial (Mayer et al., 2008) which also showed that treated patients had less hematoma expansion, but did not demonstrate improved mortality and morbidity. Others have suggested the use of combined factor VII and prothrombin complex concentrate as a therapy for warfarin induced ICH (Sarode et al., 2012). In addition, surgical intervention trials centered on hematoma evacuation have shown mixed results in outcome for such patients, and trials are ongoing (Mendelow et al., 2011). Overall, hematoma expansion and/or re-bleeding are important markers for both prognosis and could be targets for future therapies in this disease.

Currently, the detection and characterization of ICH is provided by various neuro-imaging modalities. While non-invasive techniques such as computed tomography (CT), magnetic resonance imaging (MRI) and catheter angiography can assist with the diagnosis and monitoring of acute cerebral hemorrhage, they require specialized equipment and personnel, substantial time, and likely require the patient to be transported to the radiology suite to obtain results (Kidwell et al., 2004; Murai et al., 2007; Zhu and Poon, 1997). In addition, some of these techniques are invasive requiring intravenous (IV) dye or the use of vascular catheters to accomplish the study. It is clear that there is a clinical need for a non-invasive, point-of-care, continuous monitoring device that can alert the caregiver to changes in the ICH for use in current diagnosis and treatment, and for future therapeutics.

In this work, we demonstrate the capability of a 400 MHz EM based device to detect an experimental ICH in a brain tissue simulating gel model. This frequency lies in the FCC authorized ISM (Industrial, Scientific and Medical) bands. The eventual goal is the development of a non-invasive EM based device to safely monitor brain injured ICH patients.

2. Materials and methods

2.1. Brain-mimicking gel

A brain mimicking gel was made using the methods of Zhou et al. (2007). First, 0.75 grams of chemical grade NaCl were added to 1 L of filtered deionized water. Fifty six grams of commercial unflavored gelatin (Kroger, Cincinnati, Ohio) were mixed into the 1 L of 0.75 g/L saline solution using a hot plate with a magnetic stirrer to ensure consistent concentration throughout the gel. After the gelatin had dissolved, the gel was cooled at room temperature, and placed in a 4°C refrigerator to solidify overnight.

The final conductivity of the gel was similar to that of the human brain at 0.33 S/m (Kandadai et al., 2012). Sunaga et al. (2003) measured a permittivity (ϵ) of 49–50 for such gels using a similar recipe at 400 MHz. This value lies between the measured 400 MHz permittivity of gray matter of approximately 60 and white matter of approximately 40, as determined by Gabriel et al. (1996b).

2.2. ICH model

The in vitro ICH Model consisted of a blood filled cylindrical cavity in the center of the gel about 6 cm from the bottom. Thin stainless steel wire was used to cut through the gel, making a cap at about 8 cm from the bottom. Next, a plastic cylinder of the volume being tested (1, 3, 5, 10, or 20 mL) was inserted into the center of the gelatin and removed, thereby

removing that volume of gelatin. The cavity was then filled with human blood purchased from a commercial blood bank.

2.3. Radiofrequency setup using ICH model

The ICH model system (Fig. 1) was placed inside a $0.76 \times 0.84 \times 1.02$ m Faraday cage (Automate Scientific, Inc., Berkeley, CA) to reduce external noise in the system. A signal generator (Hewlett Packard, Palo Alto, CA; HP8657B) was used to generate a signal at a frequency of 400 MHz with constant amplitude of 1.5 V into an RF Amplifier (ENI, Rochester, NY; ENI607L). The amplifier output was connected to a transmitting antenna (Ramsey Electronics, Victor, NY; PCB Log Periodic WA5VJB) within the cage. Power received by a receiving antenna (Myers Engineering International, Inc., Margate, FL; SATCOM UL-3001-340-CF portable UHF) was measured by a spectrum analyzer (Hewlett Packard, Palo Alto, CA; HP8560E). The transmitting and receiving antennae were placed on a platform at the same level 0.15 m apart so that their highest point was 2/3 of the height of the gelatin. The platform was 0.22 m above the bottom of the cage. When the gel was present during an experiment, it was always placed in the same location between the transmitting and receiving antennae.

Spectrum data was collected onto a computer every 3 s using MATLAB (Mathworks Inc., Natick, MA; v.7.10.0.499). The received power was collected over a bandwidth of 10 MHz with the center frequency at 400 MHz. The received power spectrum was numerically integrated using a MATLAB routine to determine the received power (P_R). Ten measurements were made for three different experiments for each gel; the empty cage (control), the brain mimicking gel (gel), and the gel with the blood filled cavity (ICH). The mean and standard deviation was calculated for each experimental group. The human blood used in these experiments was purchased from a local blood bank.

2.4. Effects of antenna positioning, temporal bone and artificial cerebrospinal fluid (CSF) on received power (P_R) in the ICH model

In order to approximately quantify the sensitivity of the P_R measurements on relative antenna position, the relative percent difference in P_R as a function of distance between antennae was measured. The receiving antenna was moved relative to the transmitting antenna so that the distance between antennae ranged from 14 to 18 cm. The received power at the different distances was normalized to the received power value at 15 cm.

In addition, a piece of human cadaveric temporal bone was placed between the transmitting antennae and gel, in order to measure the approximate change in P_R with the presence of skull in addition to the gel. A total of 6 trials were performed in these measurements. Finally, in order to determine the approximate effects of cerebrospinal fluid on P_R in this model, artificial cerebrospinal fluid (aCSF) was manufactured according to the methods of Kehr et al. (2001), and 20 mL were placed in the gel cavity, as manufactured for the 20 mL blood experiments. The effect on P_R was determined for 3 trials of the aCSF.

2.5. Statistical analysis and modeling

SigmaPlot 11.0 statistical software was used for statistical analysis. Means and standard deviations of the data were calculated as needed. Student's paired *t*-test was used to determine the statistical significance of the difference between the ICH model and the gel alone, and a $p < 0.05$ was considered significant. MATLAB (Version R2010B, Mathworks, Natick, MA, USA) was used to perform calculations for the dielectric slab model.

3. Results

3.1. 20 mL ICH model data

P_R values were measured for gel only (gel) and for gel with blood (ICH) volumes of 20 mL (Fig. 2). The average value of $P_R(\text{gel})$ was 519 (14) mW (mean and standard deviation). The average value of $P_R(\text{ICH})$ for the 20 mL measurements was 537(15) mW. The difference was significant ($p < 0.001$).

3.2. ICH model and gelatin comparison

The average difference in received power (Δ) between the ICH model and gel increased with increasing blood volume (V), as shown in Fig. 3. The Δ values increased with ICH blood volume. Δ was found to be linear in the cross-sectional area of the blood in the gel (Fig. 3; $p < 0.001$; $R^2 = 0.98$)

3.3. Results of antenna positioning, temporal bone and artificial cerebrospinal fluid (CSF) on received power (P_R) in the ICH model

Overall, a change in the distance between the antennae of about 15 mm was required to observe a 3% change in received power, and this was found to vary linearly with the distance. Therefore, a change in antenna position of approximately 5 mm would be required to see a 1% variation in P_R . The presence of the temporal bone increased the received power by $2.1 \pm 0.4\%$ (mean and standard deviation) for 6 trials. The presence of 20 mL aCSF increased the received power $2.6 \pm 1.0\%$ for 3 trials.

3.4. Theory/calculation

Overall, the presence of blood in a brain-mimicking gel increased the transmitted power in this prototype pilot device. One can qualitatively understand this behavior by studying the transmission of a plane electromagnetic (EM) wave of angular frequency ω through a dielectric (Fig. 4) (Griffiths, 1999). In this model, an EM wave is normally incident on a semi-infinite dielectric slab of finite thickness d , and index of refraction n_s . It is also assumed that the wave is incident from air where the index of refraction is n_0 . The transmission coefficient T of the dielectric slab can then be written as (Griffiths, 1999)

$$\frac{1}{T} = \frac{1}{4n_0^2} \left\{ 4n_0^2 + \frac{(n_0^2 - n_s^2)(n_0^2 - n_s^2)}{n_s^2} \sin^2 \left(\frac{n_s \omega d}{c} \right) \right\} \quad (1)$$

where c is the speed of light in vacuum. Dividing through by the first term, simplifying, and inverting to solve for the quantity T yields,

$$T = \left\{ 1 + \frac{(n_0^2 - n_s^2)^2}{4n_0^2 n_s^2} \sin^2 \left(\frac{n_s \omega d}{c} \right) \right\}^{-1} \quad (2)$$

One can then make the physically reasonable assumption that

$$P_R = AT P_T \quad (3)$$

where P_R is the received power, A is a constant that contains the geometry of the model, and P_T is the transmitted power, which is held constant in these experiments. In addition, we also assume that the addition of blood effectively alters the overall index of refraction n_s in

the dielectric slab. Therefore, we can express the fractional change in the transmission coefficient as

$$\Delta T \equiv T(n_{\text{ICH}}) - T(n_{\text{Gel}}) \quad (4)$$

where n_{Gel} and n_{ICH} are substituted for n_s , and are the effective indices of refraction of the slab without or with blood respectively. The change in received power ΔP_R can then be calculated using Eqs. (3) and (4). First, one can write

$$\Delta P_R \equiv P_R(n_{\text{ICH}}) - P_R(n_{\text{Gel}}) = A P_T \Delta T \quad (5)$$

The fractional change in received power f can then be written as,

$$f \equiv \frac{\Delta P_R}{P_R(n_{\text{Gel}})} = \frac{A P_T \Delta T}{A P_T T(n_{\text{Gel}})} = \frac{\Delta T}{T(n_{\text{Gel}})} \quad (6)$$

such that the change in power is normalized to the received power in the gel configuration.

The quantity f can be calculated as a function of n_{ICH} for the physical conditions of the in vitro brain gel model used in this work. Specifically, the parameters used are; the EM RF frequency of 400 MHz, d (gel diameter) of 0.1 m, the angular frequency ω of $2.5 \times 10^8 \text{ s}^{-1}$, and n_{Gel} of 7.1 (Sunaga et al., 2003). One can then calculate f in Eq. (6) as a function of n_{ICH} . The reasoning for this calculation is that if the gel n is 7.1 and n for blood is 7.7 (Gabriel et al., 1996b), then introducing small volumes of blood into the gel would yield an effective gel $n(n_{\text{ICH}})$ of between 7.1 and 7.7.

Fig. 5 exhibits the results of this calculation; here f is plotted as a function of n_{ICH} which ranges from 7.1 to 7.7 as discussed. Note that for all values of n_{ICH} greater than n_{Gel} , f is positive, i.e. introducing blood into the gel increases the received power in this model. Qualitatively, the results of this model agree with the experimental results seen above.

It must be noted that this is only an approximate finding and there are substantial limitations on interpreting this result. First, the model assumes uniform, “plane wave,” behavior of the EM signal and the transmitted signal is only approximately a plane wave. In addition, the cylindrical geometry of the gel is substantially different than that of an infinite dielectric slab. Finally, the system is operating in the ‘near field’ EM regime whereby the dimensions of the system are much less than the wavelength of the EM signal λ ; this is known as the, ‘near,’ or, ‘static,’ EM zone (Jackson, 1975).

The above approximations are a concern, but likely do not significantly alter the applicability of the model to the results presented here. Although the transmitted signal is approximately a plane wave, this is a reasonable approximation for the work here as the transmitting and receiving antennae are aligned such that the sample blood collection is located at 0° in the primary lobe of the yagi antenna used here (Carr, 2001). In this configuration, the electric field ($\mathbf{E}$) is linearly polarized in the horizontal plane (see Fig. 1), and small variations in position or antenna alignment relative to the blood likely have little effect on the incident signal. This alignment also likely reduces the importance of diffraction of the incident signal due to the curvature of the cylindrical blood volumes used here. At 0° , $\mathbf{E}$ is approximately parallel to the interface of the cylinder with the gel (Fig. 4). Finally, in the ‘near zone,’ the electric and magnetic fields are quasi-stationary with no strong dependence on $\mathbf{r}$ (Jackson, 1975) with a harmonic time dependence at the RF signal frequency.

4. Discussion

In summary, a prototype 400 MHz RF based device was constructed to detect and monitor intra-cerebral hemorrhage. It was found that the presence of blood increased the received power, and that the device could detect a blood volume as small as 1 mL in a 1000 mL in vitro, “brain gel,” model. In addition, the change in received power ΔP_R was found to be linear with the cross sectional area of the blood, as measured normal to the incident RF signals. Finally, a dielectric slab model was devised that qualitatively explains the results.

The attenuation or enhancement of an EM wave depends on the nature of the media it is (Griffiths, 1999) interacting with. The interaction of an EM signal with biological tissues depends on the dielectric properties of tissues, number and depth of tissue layers, geometry of the tissue, the orientation and polarization of incident radiation, and the ratio of tissue size to wavelength (American Geophysical Union, 1979; Foster and Schwan, 1995; Gabriel, 1996; Lin and Bernardi, 1996; Polk and Postow, 1996). From an EM perspective, the magnetic properties of biological tissues are negligible. Hence, the main contributors to the EM properties of tissue affecting the interaction with EM radiation are the permittivity (ϵ) and conductivity (τ) (Foster and Schwan, 1995; Gabriel, 1996; Gabriel et al., 1996a).

In biological tissues, permittivity decreases as a function of frequency. The amount of dispersion depends on the tissue properties such as counterion relaxation at low frequencies (α dispersion), polarization of cell membranes and presence of smaller substructures (β dispersion), and permanent dipole moment of water and proteins in the tissue (γ dispersion). There is also tissue variability in the characteristic frequencies at which α , β and γ dispersion mechanisms are observed. Between 300 and 2000 MHz, a δ dispersion regime attributed to rotation of amino acids, partial rotation of charged side groups of proteins and relaxation of protein-bound water can be observed (Foster and Schwan, 1995; Gabriel, 1996; Gabriel et al., 1996b; Jaspard and Nadi, 2002; Jaspard et al., 2003).

Given that the eventual device will transmit RF radiation into the patients’ intra-cranial region, it seems reasonable to discuss the potential safety considerations of the technique. Current FCC guidelines suggest a maximum peak specific absorption rate (SAR) of 1.6 W/kg (Federal Communications and Commission, 2011) allowed to be incident on the human brain. Gandhi et al. showed that radiated powers of 121 mW and 310 mW are required for reaching the peak SAR values, at frequencies of 1900 MHz and 835 MHz (Gandhi et al., 2001). These values were estimated for cell phone antenna usage, with minimal air gap between the antenna and head. The same study also showed an increase in the steady state temperature of the brain of less than 0.1 °C after about 50 min of exposure at the 835 and 1900 MHz frequencies. Bernardi et al. (2000) showed that at a radiated power of 600 mW, the corresponding increase in the steady-state temperature after 50 min was still 20 times below the thermal tissue damage thresholds. Hence, by extrapolation, at the frequency studied in this work (400 MHz), and with the 1 cm air gap between each antenna and the brain gel, higher radiated powers can be tolerated before reaching the peak SAR value, or observing any appreciable temperature increases. Future prototypes can be designed to work at lower powers, and with pulsed radiation, as opposed to continuous radiation, so as to minimize a patient’s exposure to EM radiation.

Others have suggested the use of biological modification of EM fields to image structures in a technique known as microwave tomography (MT). Meaney et al. (1996) constructed a prototype microwave imaging system utilizing EM frequencies ranging from 300 to 700 MHz, and were able to localize electrical phantoms constructed from agar, distilled water, and a fat/bone phantom in an in vitro model. Similarly, Fhager et al. (2012) imaged dielectric targets in both distilled water and a lossy saline solution using an array of

monopole antennae. In addition, there have been some early studies on the use of MT in breast imaging (Bourqui et al., 2012).

Recently, Karanasiou et al. (2004) used microwave radiometry at 3.5 GHz to passively image changes in brain temperature in volunteers. In their work, an ellipsoidal cavity was constructed such that a microwave receiving antenna was placed at one focus, and the subject's head at the other. The cavity was moved in 3 dimensions so that various regions of the subject's brain were interrogated by the receiving antenna. They were able to resolve about 1% changes in microwave temperature between the right and left brain hemispheres induced by the presence or absence of noxious stimuli (subject's hand immersed in cold water). Although promising, this technique exhibited a small signal to noise ratio, and would be cumbersome in the clinical environment. However, the concept is quite promising, and lends credence to the approach taken in the current work.

Overall, there has been little or no translation of MT into the clinical realm, as discussed by Bolomey and Jofre (2010). Most of the efforts have been devoted to imaging which requires substantial microwave antenna sensitivity, complex post-signal processing, and substantial computer calculation. In contrast, the technique discussed here uses the RF signal to determine overall changes in the electrical properties of the interrogated biological tissue. As such, it is much simpler than most applications for MT, and will likely be easier to implement as an active monitor of changes in brain activity in the clinical environment.

A major limitation of the current work is that the results were obtained in a very simple in vitro model. Real brain tissue has substantial spatial variations in dielectric constant, and there are multiple tissue planes that can scatter, reflect, and alter any incident EM signal. In addition, the geometry of the blood samples used bears little resemblance to those that actually occur in hemorrhagic stroke. However, the overall technique is promising and certainly merits further investigation and in vivo study.

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highlights

- ▶ We demonstrate a prototype device to monitor intracerebral hemorrhage.
- ▶ This device is tested in an in vitro brain gel model.
- ▶ It can detect as little as 1 mL of blood in this model.
- ▶ This technique could be developed as a non-invasive sensor of brain status.

Fig. 1. Experimental set-up showing the prototype and the ICH model. The transmitting antenna is on the left and the receiving antenna is denoted on the right. The measurements were performed in a gauss cage to improve the signal to noise ratio.

Fig. 2. Comparison of received power for gel only and 20 mL ICH model. The average received power for the 20 mL experimental ICH measurements was 537 mW, for the gel only case was 519 mW. The difference in received power was significant ($p < 0.001$, Student's paired t -test).

Fig. 3. Average power differences between ICH and control for 1, 3, 5, 10, and 20 mL versus cross sectional area of the experimental blood collection. The error bars are the standard deviations for the data. The average power values vary linearly with the blood volume area ($R^2 = 0.98$).

Fig. 4. Schematic of the dielectric slab model for the received power calculations. This model assumes that the incident EM signal is a plane wave propagating along z with wavevector $\mathbf{k}$. Here, $\mathbf{E}$ and $\mathbf{E}'$ are the electric field vectors for the transmitted and received signals respectively. Note that both have linear polarization. The gel sample is approximated as a slab of thickness d , but infinite in the x and y directions.

Fig. 5. Fractional change in received power (f) as a function of index of refraction (n_{ICH}) for the Dielectric Slab model. The index of refraction for the gel alone n_{Gel} is assumed to be 7.1. For comparison, n_{Blood} is approximately 7.7. For values of n_{ICH} between these two, f is positive, or the received power increases with the presence of blood in the gel.