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Detection of Intraventricular Blood using EIT in a neonatal piglet model

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***Abstract*—We have developed a sensitive EIT protocol for detection of intraventricular bleeding. A common model of human neonates is the neonatal piglet. We used our method to test the sensitivity of our method and device to small amounts of blood-like fluid injected near the left and right ventricles of a piglet cadaver. Comparing blood-like fluid detection in open an closed piglet skulls, we found that we could detect amounts of blood less than 0.5 ml, which is smaller than that required for our target of detecting grade II intraventricular hemorrhages in human neonates.**

I. Introduction

We are interested in detection and imaging of intraventricular hemorrhage (IVH) in premature neonates. Approximately 30% of premature infants weighing less than 1,500 g will have an IVH. The risk is inversely related to gestational age and birth weight, with 45% of infants 500–750 g developing a severe IVH [1]. Intraventricular hemorrhage originates in the germinal matrix, an area of the developing brain that contains fragile blood vessels. Immature blood vessels in this highly vascular region of the brain, combined with poor tissue vascular support, predispose premature infants to hemorrhage. The region of the bleed is the site of on-going stem cell production in the developing brain. IVHs are graded from I-IV based on the degree of hemorrhage using a system developed by Papile et al. [2]. The original staging system was developed utilizing CT scans but has been adapted for many years to cranial ultrasonography with a recent modification by Volpe [3]. A grade I hemorrhage represents bleeding isolated to the subependymal area. When this hemorrhage extends to the ventricles and the blood from the hemorrhage occupies 10–50% of the ventricle, it is classified as a grade II hemorrhage. Grade II hemorrhages account for 40% of IVHs. The bleed may become severe enough to occupy >50% of the ventricle producing dilation of the ventricles (Grade III). Large IVHs are associated with unfavorable neurological outcome. Adverse neurodevelopmental sequelae include cerebral palsy, seizures, and hydrocephalus requiring a shunt, blindness, deafness, and cognitive impairment. Although the clinical consequences are severe, little is known about the exact etiology of IVH. As mentioned previously, many physiologic disturbances have been associated with IVHs through retrospective studies but exact cause-effect relationships between these parameters (hypotension, PDA, pneumothorax, etc.) do not exist.

A. Clinical manifestations and therapies

IVH is rarely present at birth; 50% occur within the 1st day of life and up to 75% within the 1st 3 days of life. Neonates with IVHs present clinically in one of three ways [3]. Neonates may have a "catastrophic syndrome" characterized by an acute deterioration with apnea, pallor, metabolic acidosis, hypotension, bulging fontanel, seizures, and decreased muscle tone. A second presentation, "salutatory syndrome", presents with subtle alterations in the level of consciousness, apnea, and subtle neurologic symptoms which may be consistent with many ailments such as infections. In the final presentation, the clinically silent syndrome, neonates may have no clinical symptoms. This last presentation may account for as much as 50% of IVHs. Because neonates may present with subtle and undetected features of IVH and IVHs have an impact on long term neurologic outcomes, premature neonates undergo cranial ultrasonography at 7 days of life, a time in which >90% of hemorrhages will have occurred. These studies identify the hemorrhage in a *retrospective* fashion and in many of these neonates, the hemorrhage may have occurred well before the study. In addition, it may be important to intervene in treating IVHs early and cranial ultrasounds ability to detect smaller hemorrhages (grade II) is much lower than detecting larger hemorrhages [4]. The variation in clinical presentation and need to intervene early further stresses the need for a simple to interpret device that can monitor and detect IVHs in real time.

Management for IVHs is mainly supportive and aims to support ventilation and replace blood volume. This task is currently somewhat difficult because such parameters as an ideal blood pressure for premature neonates are unknown. Anticonvulsants are administered when seizures arise. There is currently a lack of a specific brain therapy to limit the extent of hemorrhage. The development of such therapies underscores the need to detect an IVH in real time. The development of a simple to interpret, real time diagnostic tool would allow us to accomplish this task while providing relevant physiologic information, which occurs at the time of the hemorrhage. Serial lumbar punctures or placement of a permanent ventroperitoneal shunts may be required to relieve posthemorrhagic hydrocephalus subsequent to confirmed grade III IVH [5]. We currently use indomethacin

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treatment in an attempt to limit severe bleeding, but its value is uncertain. At present few therapies exist for treatment of IVH but early intervention is necessary to provide supportive care. As treatments become available, early warning of IVH becomes crucial.

B. Electrical Impedance Tomography (EIT)

EIT [6] is a method of obtaining internal maps of conductivity distribution in the body that involves applying small electrical currents to the body and observing perturbations in the field patterns created by these currents as the conductivity distribution changes. Currents are applied via two electrodes of an electrode array (typically comprising 16 or more electrodes) and voltage measurements are made between certain pairs of the remainder of the array. This process is then repeated for many current patterns and voltage measurements. Three-dimensional reconstructions of the spatial distribution of conductivity are found by using a model that relates changes in measurements to locations of conductivity changes in a reference model. Electrode positions are informed by the overall geometry of the area under study (for example, spherical for the head, cylindrical for the trunk or limbs) and by the background conductivity distribution within the area of interest. In order to optimize the threshold of detection for IVH, it is important to determine an EIT measurement configuration that is capable of producing a good signal from blood appearing in the centre of the head, and that is configured to the anatomy of the neonate.

EIT was briefly tested to the detection of neonatal intra-ventricular hemorrhage in the late 1980s [7], [8], with a result showing detection of ventricular bleeding in one neonatal patient. However, artifacts significantly affected these data. Murphy et al. [8] found that breathing movements and variations in cerebral blood flow caused the largest signal artifacts - up to 1% variation in their baseline signal at a frequency of approximately 0.5 Hz. The other significant artifact was synchronous with heart electrical activity, causing a variation of about 0.1% in signals. Large artifacts due to movement of the infant were also encountered. Nevertheless, these early studies of IVH using EIT demonstrated the potential of EIT for this application.

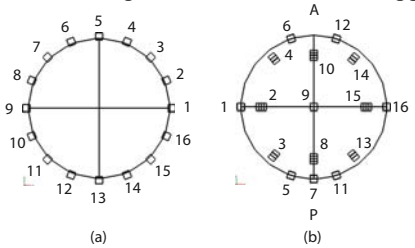


Figure 1 Three-dimensional spherical models showing (a) *Ring* and (b) *EEG* layouts.

More recently, researchers in EIT of the head have concentrated on the accurate detection of the position of epileptic foci, stroke and on functional studies, amongst other applications, and not on IVH [9]-[11]. Their studies typically used 31 electrode patterns based on the 10-20 EEG system, with collection of data from all available configurations. The first applications of EIT to the head used the *Ring* layout shown in Figure 1(a) [7], [8]. The main disadvantage of this method is that it cannot determine axial locations of anomalies. We analyzed the layouts shown in Figure 1 in terms of their *sensitivity* (amount of change in measured values per unit conductivity change) and *selectivity* (contribution of each region to total measurement) to the introduction of conductivity changes into the upper hemisphere of the imaged region, the areas shown in Figure 2(a). We found that although the *Ring* pattern had higher maximum sensitivity, the *EEG* pattern had generally higher selectivities. The *CzRing* pattern had significant negative sensitivities in the central region. Although selectivity was quite high in the ventricular regions of the realistic geometry head model shown in Figure 2(c) it therefore seemed unsuitable for use in this context. Most significantly, we found that the EEG pattern's sensitivity and selectivity were greatly increased when we assessed them using a model (Figure 2(b)) that incorporated realistic values for neonatal head conductivities [12]. In particular, the presence of the fontanel in combination with the EEG method strategy of injecting current through the Cz electrode produced much larger selectivity.

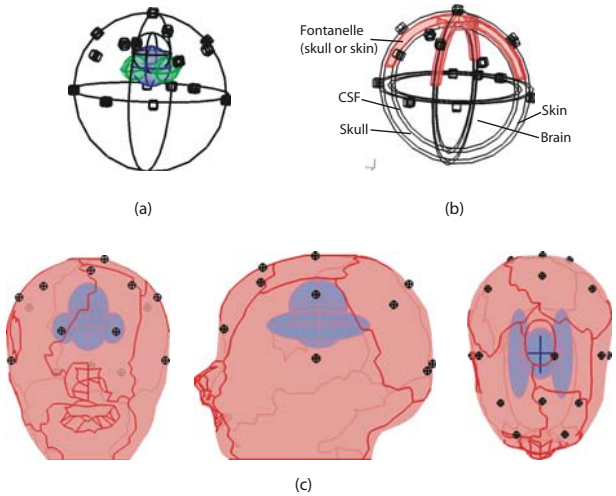


Figure 2 Three-dimensional EEG spherical models showing (a) central and lateral ventricle regions. The spheres each have relative radii of 0.25 and are centered at z = 0.33 and z=0.5. The elliptical lateral ventricle structures had relative radial locations of (x, y, z) = (-0.2, 0, 0.3) and (0.2, 0, 0.3) and semiaxes of 0.15, 0.44 and 0.15 in x, y and z axes respectively, (b) Layered spherical model with EEG layout. Conductivities used in the layered model were: CSF (1.3 S/m); Scalp (0.43 S/m); Skull (15 mS/m); Brain (0.127 S/m). The fontanel was either chosen as skull or skin. (c) axial, saggital and coronal views of realistic geometry model, showing ventricle and central structures.

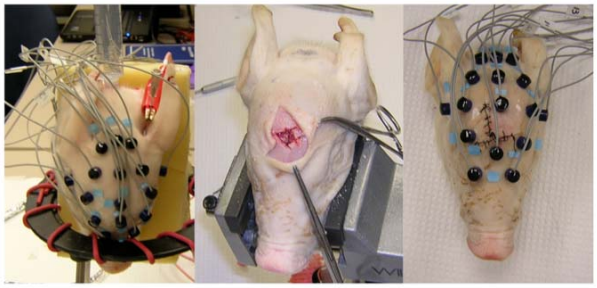
We tested all three methods using saline phantoms and blood-like anomalies [13]. Good reconstructions were created using both the *Ring* and *EEG* patterns, but processing of images to anomaly volumes was most reliable for the EEG based pattern.

Our model of choice in this study is the neonatal piglet, a commonly used analog of neonatal infants. In the sections below we describe measurements we performed on neonatal piglet heads to establish the feasibility of the *EEG*-based measurement method.

II. Materials and Methods

A. Piglet Preparation

Two female piglets were sacrificed by exsanguination at



(a) (b) (c)

Fig. 3. (a) Photograph of piglet held vertical in apparatus, with EEG electrodes attached. The syringe used to inject bloodlike fluid is shown at the central top of the image. (b) Artificial fontanel. (c) Open skull piglet showing replaced scalp and electrode placement.

approximately 1 week of age under a protocol approved by the University of Florida Institutional Animal Care and Use Committee. The sacrificed animals were decapitated and moved to our laboratory. Markings for locations of the sixteen electrodes of the *EEG* pattern were made on the scalp using scaled distance measurements from nasion to the mid point between the ears and left to right jaw distances. Sixteen 4 mm neonate EEG electrodes (Biopac Systems Inc. www.biopac.com) were then filled with electrode gel and fastened to the scalp with adhesive rings (Biopac Systems Inc.). A saline solution with the same conductivity as blood (0.67 Ωm) was made by dissolving salt at a concentration of approximately 3 g/l in water. In one piglet skull an artificial fontanel was created (Figure 3(b)). The procedure used for this was as follows. The scalp was laid open, avoiding electrode markings, and a cross-shaped hole was created with a Stryker bone saw at the intersection of saggital and coronal sutures. The scalp flap was then replaced and sutured in place (Figure 3(c)). Blood-equivalent saline was injected near the ventricles on left and right sides; in the case of closed skull measurements these measurements were made via the brain stem, in open skull measurements injections were made via the artificial fontanel. Injections were made in increments of 0.5 ml. In this bleeding case, increases in blood volume should result in decreases in measured impedances, as blood (0.67 S/m) has a higher conductivity than brain tissue (0.172 S/m) [14]. In an intact neonate, bleeding occurs into a cerebrospinal fluid (CSF) environment. CSF has a conductivity more than twice that of blood (1.8 S/m) [15] and therefore displacement of CSF by free blood should appear as an increase in impedance.

B. Measurement System and methods

Data was collected by a 16-electrode EIT system provided by the Impedance Imaging Research Center at Kyung Hee University, Korea [16]. This multi-frequency EIT system has a frequency range from 10 Hz to 500 kHz. We chose to use a single frequency of 10 kHz and a constant current output of 1 mA. Each 182-measurement data set took less than 1 s to collect.

C. Reconstruction and Processing

Data were gathered using the method detailed in [12]. Images were reconstructed by truncated singular value decomposition (tSVD) inversion of a sensitivity matrix calculated using a spherical finite element model. On inspection of an *l*-curve for the data we elected to use a truncation value of 50.

The quantity index (QI) is the integral of conductivity change over the image volume, that is

$$QI = \sum_{i=1}^{NE} \sigma_i v_i , \qquad (1)$$

where σ_i is the conductivity reconstructed into the i^{th} voxel, v_i is the volume of the voxel and *NE* is the total number of voxels. The QI is an excellent correlate of anomaly volume when anomaly contrast is high [19]. Isosurface images were made using a surface value of conductivity corresponding to the peak value in the image of the 0.5 ml injection.

D. Quantification Targets

The typical volume of both human neonatal ventricles is about 10 ml, representing about 1.5% of the total head volume [17]. Thus, identification of Grade II bleeding in the neonatal human case constitutes detection of less than 2.5 ml of blood (0.4 % by volume). A study of neonatal piglets [18] revealed that typical ventricle volumes are actually very small, around 0.4 ml (about 0.2% by volume). In the neonatal piglet 0.4% of head volume constitutes about 2 ml. Thus, if our method can find less than 2 ml in this model we have a good indication that this method will be feasible in humans for detection of Grade II bleeding.

III. Results

The reconstructed isosurface images shown in Figure 4 show the progression of reconstructed data in the head as bloodlike saline was injected into the left side of the head. The reconstructions clearly show an anomaly on the left side that grows in size as more saline is added.

Plots of the quantity index derived from the image sequence as a function of added saline volume showed a linear dependence of QI on volume. The sensitivities (QI/ml) of injections on the left-hand and right-hand sides were somewhat different, which is most likely explained by differences in the relative locations of left-hand and right-hand side injections. The error bars on measurements (based on QI values calculated over several series) are small, constituting around 0.01 ml of blood.

Data for single injections of bloodlike saline into the skull of the open-skull piglet showed a potentially higher sensitivity, which would be predicted by our prior modeling data. However, as we could not directly determine the relative locations of the open and closed skull injections this difference may have been due to spatial variance of QI.

IV. Discussion

A significant difference between the changes monitored in this experiment and in an intact or in-vivo experiment is that

in this experiment we injected blood into the brain or into ventricular spaces, not into CSF. Therefore, there may be some difference in sensitivities (most likely a decrease) when blood is injected into highly conductive CSF. However, this experiment does establish that we can image and quantify amounts of saline constituting less than 100th of the total head volume in an anatomical environment very similar to that of a human neonate.

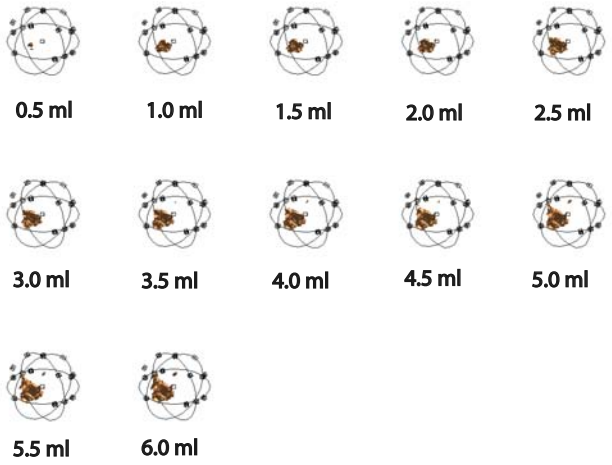


Figure 4 Isosurface plots of reconstructions of left side injections to the closed piglet skull. The three electrodes located together on the equator of the sphere at foreground right of each image are (left to right) electrodes O1, Oz and O2.

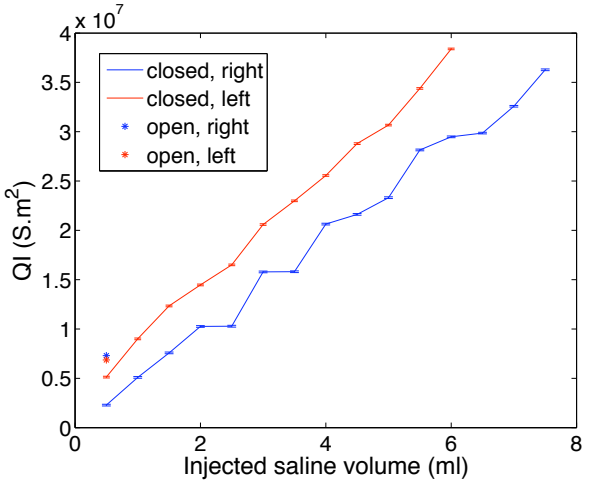


Figure 5 Quantity index as a function of injected volume of bloodlike saline.

One weakness of this experiment was that we were unsure where blood was placed inside the skull. A fundamental test of the method will be to assess the ability of the method to accurately locate anomalies. Before this experiment is repeated in vivo, we will construct a stereotactic device, derived from an MRI scan of a neonatal piglet, that will allow us to accurately target the ventricles and avoid administering blood intraparenchymally. Another issue that will be encountered in vivo is the potential interference with breathing and cardiac effects. We will attempt to remove these with cardiac gating of measurements and high pass filtering of breathing artifact. We believe that these results show promise for EIT as a method for identification and quantification of small amounts of blood in the brain of newborn human infants.

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