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***In vivo* quantification of intraventricular hemorrhage in a neonatal piglet model using an EEG-layout based electrical impedance tomography array**

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Abstract

Intraventricular hemorrhage (IVH) is a common occurrence in the days immediately after premature birth. It has been correlated with outcomes such as periventricular leukomalacia (PVL), cerebral palsy and developmental delay. The causes and evolution of IVH are unclear; it has been associated with fluctuations in blood pressure, damage to the subventricular zone and seizures. At present, ultrasound is the most commonly used method for detection of IVH, but is used retrospectively. Without the presence of adequate therapies to avert IVH, the use of a continuous monitoring technique may be somewhat moot. While treatments to mitigate the damage caused by IVH are still under development, the principal benefit of a continuous monitoring technique will be in investigations into the etiology of IVH, and its associations with periventricular injury and blood pressure fluctuations. Electrical impedance tomography (EIT) is potentially of use in this context as accumulating blood displaces higher conductivity cerebrospinal fluid (CSF) in the ventricles. We devised an electrode array and EIT measurement strategy that performed well in detection of simulated ventricular blood in computer models and phantom studies. In this study we describe results of pilot *in vivo* experiments on neonatal piglets, and show that EIT has high sensitivity and specificity to small quantities of blood (<1 ml) introduced into the ventricle. EIT images were processed to an index representing the quantity of accumulated blood (the ‘quantity index’, QI). We found that QI values were linearly related to fluid quantity, and that the slope of the curve was consistent between measurements on different subjects. Linear discriminant analysis showed a false positive rate of 0%, and receiver operator characteristic analysis found area under curve values greater than 0.98 to administered volumes between 0.5, and 2.0 ml. We believe our study indicates that this method may be well suited to quantitative monitoring of IVH in newborns, simultaneously or interleaved with electroencephalograph assessments.

Keywords

electrical impedance tomography; quantification; hemorrhage; neonatal; EEG-electrode layout

Introduction

Approximately 30% of premature infants weighing less than 1500 g in the United States will have an intraventricular hemorrhage (IVH). The risk is inversely related to gestational age and birth weight, with 45% of very low birth weight infants (500–750 g) developing a severe IVH (Volpe 2001). Although the incidence of IVH has decreased over the last 2 decades, the magnitude of the problem has not changed, due to an increase in the survival rates of premature neonates who represent a high-risk population for IVHs (Perlman and Volpe 1987, Kiely and Susser 1992, Guyer *et al* 1998, Guyer *et al* 1999). IVH 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 origin of IVH is usually the sub-ventricular zone, a site of on-going stem cell production in the developing brain. IVHs are graded from I to IV based on the degree of hemorrhage using a system first developed by Papile *et al* (Papile *et al* 1978). The original staging system was developed using CT scans but has been adapted for many years to cranial ultrasonography with a recent modification by Volpe (Volpe 2001). 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 outcomes (Alderliesten *et al* 2013, Noori *et al* 2014, Garton *et al* 2016). Adverse neurodevelopmental sequelae include cerebral palsy, seizures, and hydrocephalus requiring a shunt, blindness, deafness, and cognitive impairment (Goldenberg and Jobe 2001, Hintz and O'Shea 2008).

Although the clinical consequences are severe, little is known about the exact etiology of IVH. 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. IVH is rarely present at birth; 50% occur within the 1st day of life and up to 75% within the 1st 3 d of life.

Neonates with IVH may present with a wide variety of clinical symptoms which can vary from readily apparent to clinically silent (Harcke *et al* 1972, Ballabh 2010). Because neonates may present with slight or subclinical symptoms of IVH, and IVHs have an impact on long term neurologic problems, most premature neonates undergo cranial ultrasonography at 7 d of life, a time in which >90% of hemorrhages will have occurred. These studies identify the hemorrhage in a retrospective fashion and in many neonates the hemorrhage may have occurred well before the study. Some neonates considered at high risk of IVH will be monitored frequently using ultrasound. However, cranial ultrasound's ability to detect smaller hemorrhages (grade II) is much lower than detecting larger hemorrhages (Mack *et al* 1981, Babcock *et al* 1982). Further, ultrasound cannot be used in a monitoring mode. A monitoring strategy is appropriate if early detection is required, or for investigations of the etiology of IVH. 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 (Sadleir and Tang 2009).

Blood has a distinct conductivity from other body tissues (Nyboer *et al* 1950, Geddes and Baker 1967, Faes *et al* 1999, Hoetink *et al* 2002), therefore EIT should be very sensitive to the appearance of free blood in the head. Furthermore, unlike magnetic resonance imaging (MRI), computed tomography (CT) and even ultrasound, EIT can be used in continuous monitoring mode and thus can be used to alert clinicians of the onset of bleeding (Sadleir and Tang 2009, Bera 2015).

In previous papers (Sadleir and Tang 2009, Sadleir *et al* 2009, Tang *et al* 2010, Tang and Sadleir 2010, 2011) we described promising results in numerical simulations and phantom experiments. We found that an 16-electrode layout based on the electroencephalograph (EEG) 10–20 layout, combined with a measurement strategy that involved applying a sequence of current patterns with all return paths over the anterior fontanel (the ‘Cz pattern’) was superior to other patterns considered. The use of standard EEG locations also allows for simultaneous EEG and EIT monitoring. We also observed that the image-derived measures of conductivity anomaly quantity, location and resolution were either improved or stable using this measurement pattern in conjunction with a spherically-shaped reconstruction model. A schematic showing the electrode locations and numbering used in the Cz pattern is shown in figure 1 (left).

To validate the quality of our method, we describe here experiments performed with this measurement protocol using a neonatal piglet model. Piglets have been chosen as animal models in many studies (Aquilina *et al* 2007, Xu *et al* 2007, Jones *et al* 2008, Puiman and Stoll 2008, Wanjun *et al* 2008, Xu *et al* 2010, Aquilina *et al* 2012) because of the anatomical, physiological, immunological and metabolic similarities between piglets and human neonates.

Methods

In vivo animal procedures

The University of Florida Institutional Animal Care and Use Committee approved all procedures. Four one to two day old piglets were used in these experiments. Piglets were obtained from the University of Florida Swine Unit shortly before each procedure commenced and transferred to a specialized Piglet Neonatal Intensive Care Unit (PNICU). On arrival in the PNICU animals were weighed; their length was measured and their general health was assessed. At the start of the procedure the animal was placed prone on a heated pad on a mobile cart and 2–3% isoflurane was administered via mask. The scalp was cleaned and all hair at electrode locations was removed. Electrode locations were marked on the scalp with permanent marker. The piglet was then transferred to the surgical room, moved to a surgical table, and had placement of a pulse oximeter probe and a rectal probe for temperature monitoring. The piglet was turned supine, the umbilical vein was identified, and a 3.5 F umbilical venous catheter was inserted (Kendall, Argyle, NY). Two 3 ml aliquots of blood were removed from the umbilical catheter into heparinized syringes and placed on a rocker. After the blood was drawn, a Ringer’s Lactate solution with 5% dextrose was administered through the umbilical catheter at a rate of 5 ml h⁻¹. The piglet was then turned prone in preparation for EIT testing. One of two custom-made guides, one customized for the left ventricle and the other for the right (figure 2) was positioned on the scalp using the

right eye as an anatomical landmark. A stylet was used to mark the skin, the guide removed, and the scalp opened near this point. The guide was applied a second time and a stylet used to mark the entry point on the skull. A burr hole was then made using a bone drill (dia 12.5 mm). The guide was then positioned a final time and a coaxial introducer needle set (Cook Inc., Bloomington, IN) was used to introduce a polyimide cannula (0.05" inside diameter, 0.002" wall thickness, Cole-Parmer, Illinois, USA) a depth of approximately 14 mm so that its tip lay in the ventricle. Before completing the procedure, we confirmed CSF backflow in the injection catheter, which indicated that we had located the ventricle correctly. The catheter was then secured by using adhesive (Vetbond, 3M Global Headquarters, MN, USA) attaching it to the surrounding bone and the scalp incision was closed using suture. A blunt 16 G needle was connected to one 3 ml syringe and the syringe was inserted upright into a retort stand. The 16, 4 mm EEG electrodes (Biopac Systems Inc., Goleta, CA) were then attached to the head at the marked locations using either 10–20 electrode paste (Weaver and Company, Aurora, CO) or adhesive rings and electrode gel (Biopac Systems, Parker Laboratories Inc., Fairfield, NJ). EIT monitoring was commenced for a period of approximately 5 min to establish a baseline value and to allow confirmation that electrode contacts were stable and of sufficiently low resistance. EIT data were collected at 2 s intervals. Injection of 3 ml of blood was then commenced at a rate of either 0.5 ml/20 s, 0.5 ml/10 s, 0.2 ml/20 s or 0.5 ml/40 s (table 1). After the first 3 ml injection, another baseline measurement was taken (approximately 50 measurements or 100 s), following which a second 3 ml was injected using the same protocol as for the initial volume. The piglet was then turned supine while euthanasia was performed by exsanguination. Piglet brains were preserved in formaldehyde and sectioned after the experiment to confirm injection locations. Sectioning was performed by securing the brain in a graduated plastic frame, then slicing a series of coronal planes with thicknesses of 2–3 mm, using a 50 mm-wide square blade.

Data acquisition

As in our previous modeling work, we used a 16-electrode EEG-layout array. The measurement protocol used is detailed in Tang *et al* (2010). The relationship between EEG electrode locations and electrode numbers is shown in figure 1 (left). There were 15 currents applied in the measurement protocol, such that each current passed through the electrode on the apex of the head (Cz) and one of the remaining 15 electrodes. For each current position, voltages between 'adjacent' electrodes (in terms of electrode numbering) were measured. This pattern produced 182 independent voltage measurements per cycle. Data were collected using a KHU Mark1 16-electrode EIT system provided by the Impedance Imaging Research Center (IIRC) at Kyung Hee University, Korea (Oh *et al* 2007). We chose to use a single frequency of 50 kHz and a constant current output of 1 mA. The in phase (resistive) data only were processed and used in reconstructions. The basic measurement setup used for both bench testing and animal experiments is shown in figure 3 of Tang *et al* (2010). An image showing electrodes attached to a piglet is shown in figure 1 (right). The polyimide catheter is also indicated in this image (red arrow).

Ten data sets were collected and averaged as a reference before injections commenced. During blood injections a timer added to the data acquisition software generated an audible tone that instructed the experimenter to begin each introduction. Blood injection times were

logged in a separate output file. Other notable events were logged in this file by the software in response to a user pressing an 'event register' button. The nature of other events was recorded manually.

Image reconstruction

In EIT difference imaging, conductivity perturbations are related to changes in boundary voltage measurements via a sensitivity matrix S (Murai and Kagawa 1985)

$$\Delta V = S \Delta \sigma \quad (1)$$

Here, ΔV denotes the temporal difference between differential voltages gathered from the head using the protocol, and $\Delta \sigma$ is the conductivity change corresponding to the voltage changes. The sensitivity matrix may be computed from a finite element model of the imaged domain (Sadleir and Tang 2009). We found that reliable representations of introduced anomalies were produced when the head was modeled as a homogeneous sphere (Tang and Sadleir 2011), and this model was used as the sensitivity matrix in the *in vivo* reconstructions presented here. Reconstruction can then be achieved by pseudo-inversion of (1). Because S is ill-conditioned, a truncated singular value decomposition method (TSVD) (Xu 1998) was used to regularize the pseudo-inversion of S in this study. Because the sensitivity within the imaged domain is always greater near surface electrodes and weaker in the interior (Oh *et al* 2009), deeper perturbations may be blurred or not detected in reconstructions. In this study, we applied a weighted minimum norm (WMN) method (Clay and Ferree 2002) to improve reconstructed image quality. In this method the equation relating measured voltage change to interior conductivity changes (1) is re-expressed as

$$\Delta V = S W W^{-1} \Delta \sigma \quad (2)$$

where W is a nonsingular matrix that has a well-behaved inverse W^{-1} . To choose such a matrix, we used the diagonal matrix:

$$W = \text{diag}(w_i) \quad (3)$$

where diagonal entries w_i were the inverse of the 2-norm of each column vector in S , thus normalizing the total sensitivity by the coefficients. This had the effect of making the matrix $S W$ less ill-conditioned than S alone (Sadleir and Tang 2009).

$$w_i = \left[\sum_{j=1}^{TM} S_{ij}^2 \right]^{1/2} \quad (4)$$

The inverse solution may be written as

$$\Delta\sigma = W(SW)^\dagger \Delta V \quad (5)$$

where $SW^\dagger$ is the Moore–Penrose pseudoinverse of SW .

We chose a truncation value of 50 based on L -curve inspection to regularize the pseudoinverse of SW . This truncation was used for all reconstructions in this study. Reconstructions of only the upper hemisphere were performed.

QI measures for each image were obtained by summing all voxel values, weighted by voxel volume, in an image, i.e.

$$QI = \sum_{e=1}^{NE} \Delta\sigma_i v_e \quad (6)$$

where NE is the number of voxels in the reconstruction model.

Data analysis

Isosurface images at half maximum (negative) conductivity changes were constructed. Only negative (i.e. less conductive) changes were displayed because as a consequence of blood's lower conductivity (ca. 0.67 S m^{-1} (Geddes and Baker 1967) with respect to cerebrospinal fluid (ca. 1.5 S m^{-1} , (Baumann *et al* 1997)) all images showed regions of decreased conductivity. We also computed QI values from all images collected before, during and after the injection period. The center of mass of the largest conductivity anomaly detected in each injection was also calculated for each data set as the quantity (x, y, z) , where

$$x = \frac{\sum_{i=1}^{NE} \Delta\sigma_i v_i x_i}{\sum_{i=1}^{NE} \Delta\sigma_i v_i}, \quad y = \frac{\sum_{i=1}^{NE} \Delta\sigma_i v_i y_i}{\sum_{i=1}^{NE} \Delta\sigma_i v_i}, \quad z = \frac{\sum_{i=1}^{NE} \Delta\sigma_i v_i z_i}{\sum_{i=1}^{NE} \Delta\sigma_i v_i}, \quad (7)$$

was determined for each isosurface anomaly. A linear discriminant analysis (LDA) and receiver operator characteristic (ROC) analysis were also performed on all data gathered for the four *in vivo* experiments.

Results

Experimental results

In some cases, data collection was truncated if the piglet became unstable during the procedure (piglet A). No data are presented here from second infusions as piglet condition became unstable during the second injection, possibly because of the increase in intracranial pressure (Aquilina *et al* 2012).

Histology

In the brain sections from piglet A (figure 3), clot formation was found primarily in the left ventricle with a small amount of blood in the right. The catheter path was found to be in the midline of the brain, which could explain the presence of small amount of blood in the right ventricle. The amount of clot did not occupy more than 50% of the left ventricle and was therefore consistent with a Grade II IVH. Backflow of blood was noted during injections on piglet B. In the brain sections from piglet B, the catheter path went directly into the left ventricle. The left ventricle contained a clot that filled the entire ventricle causing it to be grossly distended, which is consistent with a grade III IVH. No appreciable blood was found in the right ventricle. The brain sections from piglet C showed extensive clot formation that filled the entire right ventricle causing distension consistent with a Grade III IVH. The brain sections from piglet D revealed clot formation in the right ventricle which did not occupy more than 50% of the ventricle; findings consistent with a Grade II IVH. In piglet D, some clot formation was found in either the brain parenchyma or the inferior pole of the lateral ventricle.

Reconstructed image and QI data

Figure 4 shows the correlation between QI values and injected blood volumes for each piglet. QI data recorded over time (figure 4) showed a characteristic decrease that correlated well with injected blood volume. In two cases injection of a blood aliquot was consistent with a steep decrease in QI value (figure 4, piglet C, bottom left, and piglet D, bottom right). Values of QI were stable immediately preceding each injection. In piglet B, blood backflow was observed during the third injection of 0.5 ml. We believe this was caused by the relatively high injection speed of 0.5 ml/20 s used. The consequence on QI values can be observed in the curve in figure 4 (piglet B, top right).

Reconstructed isosurface images of *in vivo* data (figure 5) showed formation of less conductive anomalies in regions correlated with both the selected location of the injection (right or left ventricular guide) and histology. For piglet A, where injections were made in 0.2 ml increments, boluses appeared in both right and left ventricles, with the majority in the left side and the mean of all isosurface locations lying on the left side (table 1). For piglet B, conductivity changes were concentrated almost exclusively on the left side, with the mean location on the left. For piglet C, changes were observed in the right side with the mean locations on the right. For piglet D we observed conductivity changes appearing in both left and right ventricles, but with the majority deposited in the right hand side. From inspection of figure 5, volumes contained by isosurfaces were qualitatively similar in all cases with similar known injection volumes. In addition, the side on which conductivity anomalies appeared was consistent with the guide selected for use in each of the four experiments (table 1). In figure 6, the QIs obtained in each experiment are plotted against injected blood volume along with a linear fit of QIs against injected volume.

Linear discriminant and ROC analysis

Linear discriminant and ROC analysis was performed on all data to substantiate our results. We performed a LDA on the QI data for the four *in vivo* piglets. The analysis showed that the diagnosis of bleeding had a 100% true negative rate, 24% false negative rate, 76% true

positive rate and 0% false positive rate (table 2). ROC analysis (figure 7) showed that the area under the curve was 0.9819, 0.9870, 0.9836 and 0.9848 for administered volumes of 0.5, 1.0, 1.5 and 2.0 ml respectively.

Discussion

Relationship between QI and injected volume

If increases in injected volume are imaged faithfully by the 3D system, we expect to observe a relation of the form

$$QI = p \times \text{volume} \quad (8)$$

in data from blood injections. There may be some offset, depending on system drift. Here, p is a constant value (with units of $\text{Sm}^2 \text{ml}^{-1}$) that depends on the conductivity of blood and may also vary depending on the reconstruction parameters chosen. It should be positive for appearance of more conductive material, and negative if fluid less conductive than the background brain tissue accumulates. Therefore, if blood displaces a more conductive background, we would expect to see a negative p value in QI data gathered during blood injections. This is in contrast to what we would expect if blood was injected directly into the parenchyma (Xu *et al* 2010), where the occult blood has a higher conductivity with respect to background brain tissue. From examination of figure 5, for the first three *in vivo* piglets (piglets A, B and C), we found $p_A = -1.9 \times 10^6$, $p_B = -1.3 \times 10^6$ and $p_C = -1.8 \times 10^6 \text{ Sm}^2 \text{ml}^{-1}$, and for piglet D we found $p_D = -1.4 \times 10^6$. Standard errors found in all slope calculations are shown in table 1. R^2 values were above 0.95 in all cases except for piglet B, where the R^2 value was 0.85.

With the measured voltage data, we could reconstruct negative conductivity changes at the corresponding locations, which further indicated that we had successfully injected blood into a more conductive CSF environment. This was confirmed by the coronal brain sections in figure 3.

Comparing p values between post mortem and *in vivo* experiments, we expected that *in vivo* the conductivity contrast should be the difference between blood and CSF, that is, around $0.67 \text{ S m}^{-1} - 1.3 \text{ S m}^{-1} = -0.63 \text{ S m}^{-1}$. In the post mortem experiment on the piglet injected with bloodlike saline (0.67 S m^{-1}) the contrast would be expected to be closer to $0.67 \text{ S m}^{-1} - 0.17 \text{ S m}^{-1} = 0.5 \text{ S m}^{-1}$, where 0.17 S/m is an estimate of brain conductivity (Tang *et al* 2010). Therefore, the expected ratio between $p_{in vivo}$ and $p_{postmortem}$ may be around -1.26 , while our result showed a ratio of around -1 . In the experiments where piglets were injected with CSF-like saline (1.3 S m^{-1}), conductivity contrast was $1.3 \text{ S m}^{-1} - 0.17 \text{ S m}^{-1} = 1.13 \text{ S m}^{-1}$. Therefore the expected ratio between $p_{in vivo}$ and p_{head} should be around -0.55 , while our result showed a ratio of around -0.3 . These underestimates may be due to use of an incorrect conductivity for brain tissue, CSF or both. However, it may also have been due to dilution of injected blood in CSF decreasing the overall contrast.

Linear discriminant and ROC analysis

The results found by the LDA were excellent, but represented analysis of conditions where nearly all data points involved bleeding. We believe our results would be less impressive if measured on subjects with unknown bleeding status. Similarly, the promising ROC curve data should be interpreted cautiously. A more extensive clinical trial involving continuous monitoring would establish a more realistic view of this method's performance.

Conclusion

We successfully introduced bleeding into the ventricles of neonatal piglets using a guide wire insertion technique. Images reconstructed using a spherical sensitivity matrix and a weighted TSVD algorithm showed conductivity decreases at the approximate locations where blood was injected. These images also produced a consistent linear correlation between quantification indices and the injected blood volumes. EIT findings were confirmed by postmortem examination of tissue. We successfully detected and quantified 0.5 ml blood injections in three piglets and 0.2 ml blood injections in one piglet. These promising results indicate that EIT applied using an EEG-like electrode layout might be useful to detect and quantify IVH in neonates. This electrode arrangement is also convenient for simultaneous or interleaved combined EIT and EEG monitoring, the combination of which may lead to increased sensitivity to events preceding bleeding activity and possibly an improved understanding of the etiology of neonatal brain injuries that lead to these events.

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Figure 1.
 (left) EEG locations and electrode numbering used in the ‘Cz pattern’ EIT measurement protocol used in this study, (right) Piglet with EEG electrodes attached. The polyimide catheter, sutured in place, is indicated with the red arrow.

Figure 2.

(A) Piglet used for MRI scan. (B) A coronal section of the piglet MRI head images showing the two lateral ventricles. (C) The injection guide designed to assist introducing the cannula into the ventricle. The numerical guide model constructed from the piglet head model, displayed in ProE (Needham, MA, USA). (D) The plastic guide made using a 3D printer. Both guides shown in (C) and (D) are for the left ventricle.

Figure 3.

Selected periventricular brain sections from piglets injected with blood. Each row shows a pair of adjacent sections collected from one piglet. Each section is labeled by the range and distance (mm) from the most rostral brain location. Left, right, superior and inferior directions are indicated on one image (top right). (Piglet A) Piglet A had a clot formation (indicated with red arrows) in the left lateral ventricle consistent with a Grade II IVH. (Piglet B) The left ventricle in piglet B was filled with a clot and grossly distended, consistent with a Grade III IVH. (Piglet C) The right ventricle of piglet C was filled with blood that

distended the ventricle and extended throughout the ventricular system, including the inferior pole. The finding is consistent with a Grade III IVH. (Piglet D) The right ventricle in piglet D contained a clot consistent with a Grade II IVH. Note the clot located either in the brain parenchyma or the inferior pole of the lateral ventricle for these sections.

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Figure 4.

QI values obtained from images (blue solid line) and injected blood volumes (red dashed line) as a function of time. (top left) Piglet A, (top right) piglet B, (bottom left) piglet C and (bottom right) piglet D. Blood administration rate for each piglet is noted on each plot. Red circles on QI plots show QI values corresponding to isosurfaces shown in figure 5.

Figure 5.

Isosurface plots of reconstructed blood anomalies at 0.5 ml increments from 0.5 to 3.0 ml, for each piglet. Plots for piglet A are at volumes of 0.4, 1.0 and 1.6 ml because blood was injected in 0.2 ml increments. Isosurfaces enclose half-maximum negative conductivity values found in each reconstructed image. (A) Piglet A, (B) piglet B, (C) piglet C, (D) piglet D.

Figure 6.
QI values and linear fits between QI value and injected volumes for piglet *in vivo* experimental data.

Figure 7.
ROC curves representing all *in vivo* piglet data.

Injection rates, guide placements, injected volumes, detected centers of mass (COM) with standard deviations, and observed QI slopes (p) in piglet procedures.

Table 1

Piglet	Injection rate	Guide placement	Volume injected	COM $\pm$	$p \cdot 10^{-6}$ ($\text{Sm}^2 \text{ ml}^{-1}$)
A	0.2 ml/10 s	Left	3 ml	(-0.25, 0.16, 0.30) $\pm$ (0.02, 0.07, 0.01)	-1.9 $\pm$ 0.16
B	0.5 ml/20 s	Left	3 ml ^a	(-0.26, 0.20, 0.19) $\pm$ (0.02, 0.08, 0.03)	-1.3 $\pm$ 0.26
C	0.5 ml/20 s	Right	3 ml	(0.42, 0.10, 0.16) $\pm$ (0.03, 0.03, 0.01)	-1.8 $\pm$ 0.15
D	0.5 ml/40 s	Right	3 ml	(0.35, -0.02, 0.33) $\pm$ (0.07, 0.07, 0.04)	-1.4 $\pm$ 0.096

^aBackflow observed during injection.

Table 2

LDA performed on all *in vivo* piglet QI data.

Number of observations and percent classified by QI data			
Bleed/diagnosis	Negative	Positive	Total
No bleed	250	0	250
	TN = 100%	FP = 0%	100%
Bleed	54	302	356
	FN = 15.2%	TP = 84.8%	100%
Total	304	302	606
	50.2%	49.8%	100%