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TITLE: Novel Noninvasive Methods of Intracranial Pressure and Cerebrovascular Autoregulation Assessment: Seeing the Brain Through the Eyes

PRINCIPAL INVESTIGATOR: Mohamad Hakam Tiba, MD, MS

CONTRACTING ORGANIZATION: University of Michigan

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14. ABSTRACT

Traumatic brain injury (TBI) plays a major role in approximately 30% of injury related civilian deaths in the U.S. The Defense and Veterans Brain Injury Center (DVBIC) has reported over 34,000 moderate to severe combat-related TBI (CRTBI) since 2000, making it a major source of mortality and morbidity for the U.S. military between 2000 and 2016. The significance of such numbers becomes apparent with the military's increased focus on Prolonged Field Care (PFC) and prolonged damage control resuscitation (pDCR). PFC is field medical care, applied beyond doctrinal planning time-lines by a SOCM (Special Operations Combat Medic) or higher, in order to decrease patient mortality and morbidity, utilize limited resources, and provide sustained care until the patient arrives at an appropriate level of care.

One of the significant management strategies in the treatment of TBI is aimed at preventing secondary brain damage, which mainly manifests itself as brain ischemia and inflammation. Monitoring of intracranial pressure (ICP) and cerebral autoregulation (CAR) to optimize cerebral perfusion pressure (CPP) to a target and maintain cerebral blood flow (CBF) are the primary methods to prevent secondary injury and are the mainstays of current practice. In a recent study, Juul et al. has concluded that acute neurological deterioration is a powerful predictor of poor outcomes following TBI. The study showed that 29% of patients with acute neurological decline having an unfavorable outcome and the most powerful predictor of such neurological deterioration was the patient's measured ICP. Therefore, it is critical to be able to monitor and manage ICP as early as possible following TBI. Current guidelines of the Brain Trauma Foundation recommend the use of invasive ICP monitoring in patients who meet specific criteria, with the aim of achieving significant reduction in mortality in civilian centers.

Recently, physicians and healthcare providers began utilizing a more dynamic, patient-oriented optimization of CPP based on CAR. Autoregulation is considered one of the most important central nervous system auto-protective mechanisms. It is described as the ability of vessels to modulate their tone in response to changes in CAR is a complex process (critical in preventing secondary brain injury) often impaired after injury and has been shown to be a significant predictor of outcomes in patients with various acute neurological diseases, including severe TBI-related and ischemic injuries. Therefore, continuous monitoring of autoregulation may be beneficial as a means to enable optimization of CPP on a patient-by-patient basis. This represents a more precise and personalized approach to managing the CPP components (ICP and mean arterial pressure) as there is likely great variation in autoregulation ability among individuals and across injuries. Assessment methods such as Transcranial-Doppler (TCD), brain tissue oxygenation (ORx), hemoglobin saturation measured by near-infrared spectroscopy (NIRS), and Laser-Doppler flowmetry of CBF have been used in the past to assess cerebral autoregulation, but with mixed results. Such methods are problematic in PFC settings for a number of reasons, including the intermittent or invasive nature of the measure, the need for a high level of operator experience, and the lack of technology available in far-forward echelons of care.

Newer approaches to autoregulation monitoring, such as pressure reactivity monitoring (PRx, a correlation between mean arterial pressure and ICP), have proven to be independent predictors of outcome. PRx is calculated as the moving Pearson correlation coefficient between certain count of consecutive 5-10 second averages of mean arterial blood pressure (MAP) and ICP. Since PRx is calculated as a correlation, its values would range between -1 and 1, with positive values indicating impaired autoregulation (pressure-passive behavior of the arterial walls) and negative values indicating intact autoregulation (vascular bed with active vasomotor responses). However, PRx is frequently difficult to interpret due to noise in the signal, and would be difficult to apply in early echelons of care due to the requirement for invasive ICP and arterial blood pressure monitoring. In addition, because of the complexity of PRx calculation and the requirement for additional software, PRx monitoring has been limited to research-oriented academic centers. Therefore, there exists an unmet need for non-invasive, portable diagnostic tools for the early detection impairment of autoregulation and elevated ICP, prior to a potentially catastrophic clinical decline, in patients or injured warfighters who may require initiation of medical therapy and priority evacuation for neurosurgical intervention.

15. SUBJECT TERMS

TBI, Bioimpedance, ICP, Cerebrovascular Autoregulation, Ultrasound, cerebral blood flow, Optic Nerve Sheath, PRX, Non-invasive

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INTRODUCTION:

Traumatic brain injury (TBI) is a major public health problem both in the U.S. and around the world. One of the significant management strategies in the treatment of TBI is aimed at preventing secondary brain injury, which mainly manifests itself as brain ischemia and inflammation. Monitoring of intracranial pressure (ICP) and cerebrovascular autoregulation (CA) to optimize cerebral perfusion pressure (CPP) and maintain cerebral blood flow (CBF) are the primary methods to prevent secondary injury and are the mainstays of current practice. Care of moderate to severe combat-related traumatic brain injury (TBI) continues to pose enormous challenges sometimes compounded by the need to provide prolonged field care (PFC). Figure 1 shows the relationship between CPP and CBF. CBF is maintained consistent over a wide range of CPP.

TBI in the presence of other injuries requiring prolonged damage control resuscitation (pDCR) provides additional challenges. The austere, resource-constrained combat environment and lack of readily available diagnostic capabilities often lead to delayed recognition of the severity of TBIs, resulting in exacerbated damage and increased TBI-related disabilities. CA and ICP monitoring has been used in cases of civilian TBI-related injuries to optimize cerebral perfusion pressure and blood flow to prevent secondary injury. However, technologies currently available to monitor CA and ICP require invasive techniques and a high level of experience, while providing intermittent readings, making them impractical and unavailable in PFC and pDCR settings (Figure 2). Robust methods of noninvasive monitoring of CA and ICP would allow for early application by combat medics, first responders, emergency departments, surgeons, and critical care staff. The proposed project aims to utilize trans-ocular brain bioimpedance and optic nerve ultrasound in a novel manner to assess CA and ICP, utilizing the eye as a window to the brain.

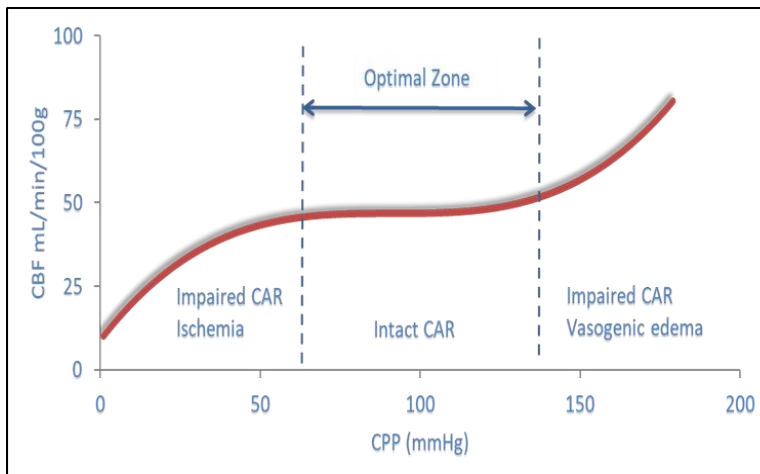


Figure 1. Relationship between cerebral perfusion pressure and cerebral blood flow

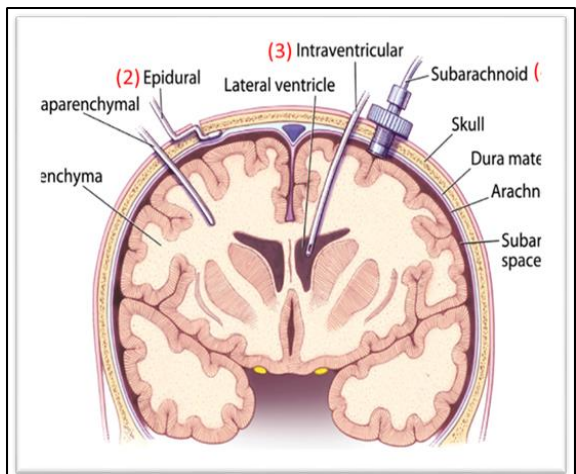


Figure 2. Different types of invasive methodology for ICP monitoring

KEYWORDS:

TBI, Bioimpedance, ICP, Cerebrovascular Autoregulation, Ultrasound, cerebral blood flow, Optic Nerve Sheath, PRx, Non-invasive

ACCOMPLISHMENTS:

What were the major goals of the project?

- **Major Task 1:** Evaluation of trans-ocular brain impedance (TOBI) in two swine TBI models.
- **Major Task 2:** Evaluation of trans-ocular brain impedance (TOBI) as an indicator of cerebral autoregulation in humans who are undergoing both invasive arterial blood pressure and ICP monitoring for brain injury.
- **Major Task 3:** Collection of ONS ultrasound videos for assessment of ICP in humans who are undergoing both invasive arterial blood pressure and ICP monitoring for brain injury. Months
- **Major Task 4:** Development of an ultrasound video analytic system to evaluate ONSD. Months

What was accomplished under these goals?

1. **Major Task 1:** Evaluation of trans-ocular brain impedance (TOBI) in two swine TBI models. *Months 0-36*
 - 1) Overall target: 5 animals (either model)/quarter
 - 2) Specific objectives:
 - a. IACUC approval: June 12, 2017
 - b. ACURO approval: August 11, 2017
 - 3) Animals use Data:
 - a. Species: Sus Scrofa Domestica
 - b. Total animal number used: 54
 - c. USDA pain category for all animals used: D
 - 4) Significant Results:

Methods: Forty-two animals have been used to date for this study using Model 1: Provocative maneuvers to manipulate cerebral blood flow (CBF) systemic blood pressure (MAP) and ICP, and twelve animals have been used to date for this study using Model 2: Blunt Trauma. A combination of maneuvers and injuries were performed including slow infusion of vasopressors (Norepinephrine) to increase MAP to ~ 140-160 mmHg, epidural hematoma by insertion of a Foley catheter into the epidural region and inflating the balloon, and lastly a slow systematic hemorrhage and crystalloid resuscitation.

All animals were intubated, anesthetized, and received the same surgical Instrumentation for monitoring and evaluation of:

- Invasive arterial blood pressure (MAP)
- Intracranial pressure (ICP)
- Cerebral blood flow (CBF)
- End tidal CO₂ (PetCO₂)
- Cerebral perfusion pressure (CPP)
- Pressure reactivity index (PRx)
- Ocular bioimpedance
- Laser Doppler flow (LDF)

- Transcranial Doppler flow (TAMEAN)

Injury and maneuvers:

- a. Vasopressor (norepinephrine) administration: Norepinephrine will be administered and titrated upward to increase MAP to ~ 140-160 mmHg. MAP will be maintained for 2-30 minutes while data is recorded. Afterward, norepinephrine solution infusion will be stopped and the animal's MAP will be allowed to return to near baseline level. The norepinephrine infusion procedure may be repeated up to three times.
- b. Epidural Hematoma: Simulation of an epidural hematoma was created using a 8F Foley catheter placed under the skull above the parietal cortex of the brain. Catheter's balloon will be inflated using a syringe pump and ICP was monitored with a target maximum pressure of 20-40mmHg. When the target ICP was reached, the pressure will be maintained for a period of 1-15 minutes. After the monitoring period, balloon will be deflated till ICP reaches baseline level.
- c. Systemic Hemorrhage: Approximate 40% of the animal's estimated blood volume will be removed to reach a mean blood pressure of 35-40 mmHg. Low pressure will be maintained for up to 60min then animal will be resuscitated with a combination of shed blood and normal saline to return blood pressure to baseline value.
- d. Combination of A-D above will be performed to simulate intracranial pathology and various concomitant injuries (systemic hemorrhage) and treatments (transfusion, vasopressor use).

Measurements of all physiological data and hemodynamics (MAP, ICP, CBF, CPP, as well as ocular impedance) will be recorded at baseline then at different intervals during maneuvers. At the end of all maneuvers and monitoring, animals will be euthanized under anesthesia and not allowed to recover. All non-invasive data was time stamped and matched with invasive data collected by the monitors described above. This allowed for temporal comparison of invasive and non-invasive data.

Data analysis: Using the data collected during the course of the provocative maneuvers model, we have developed several novel analytic tools for the assessment of the trans-ocular bioimpedance waveform as it relates to cerebrovascular autoregulatory parameters such as MAP, ICP, CPP, and CBF. One, we have been able to fully automate the quantification of the respiratory amplitude (dz) (Figure 3) in an effort to move to a continuous real-time analytic. Second, we have begun to assess the potential information available in the cardiac component of the bioimpedance signal in conjunction to the respiratory component. We have also investigated how the bioimpedance signal interacts with arterial blood pressure in an effort to create an analytic similar to the pressure-reactivity index (PRx).

In addition, we have developed a surrogate of the pressure reactivity index (PRx). PRx is calculated as the moving Pearson correlation between MAP and ICP with 1 second intervals. Positive PRx values may be indicative of impaired CA function. Similarly, our bioimpedance index (termed DZx) is calculated a moving Pearson correlation dz and MAP with one second interval similar to PRx. It is notable that DZx and PRx often move opposite one another due to the inverse relationship between dz and ICP.

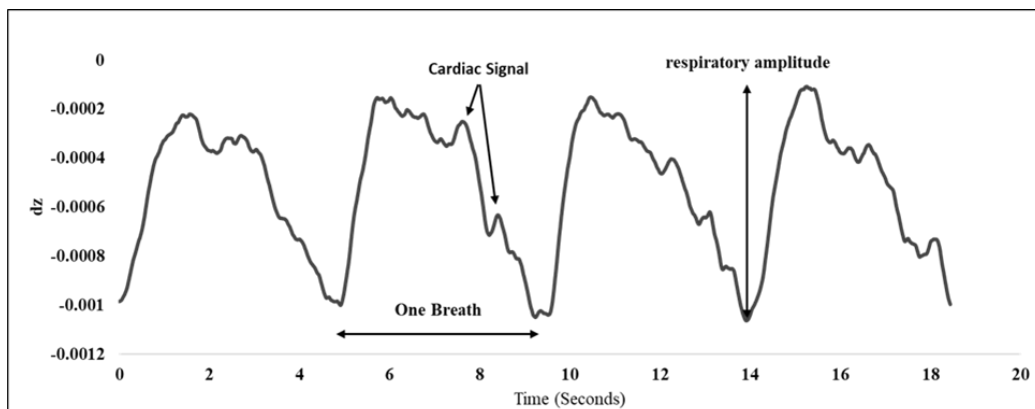


Figure 3: Respiratory-induced changes in trans-ocular brain bioimpedance. The figure shows four breaths. dz is calculated as peak to peak difference in the impedance signal.

Data Presentation: We have investigated the relationship between DZx, PRx, and CA, in two models of hemodynamics and CA perturbation, during hypertension due to vasopressors administration and during hypotension due to systemic hemorrhage

Relationship between DZx, PRx, and CA, during hypertension due to vasopressors

Data is presented in detail in **Manuscript: *Trans-ocular brain impedance index for assessment of cerebral autoregulation in a porcine model of cerebral hemodynamic perturbation***

PMID: 32666400 DOI: [10.1007/s10877-020-00556-1](https://doi.org/10.1007/s10877-020-00556-1)

Methods: Twelve Yorkshire swine were instrumented to continuously record ICP, MAP, and cerebral blood flow (CBF). TOBI was recorded by placement of standard ECG electrodes on closed eyelids and connected to a data acquisition system. MAP, ICP and CBF were manipulated utilizing an intravenous vasopressor challenge. TOBI indices (dz and DZx) were compared to the hemodynamic indicators as well as pressure reactivity index (PRx). Figure 4 shows the experimental design.

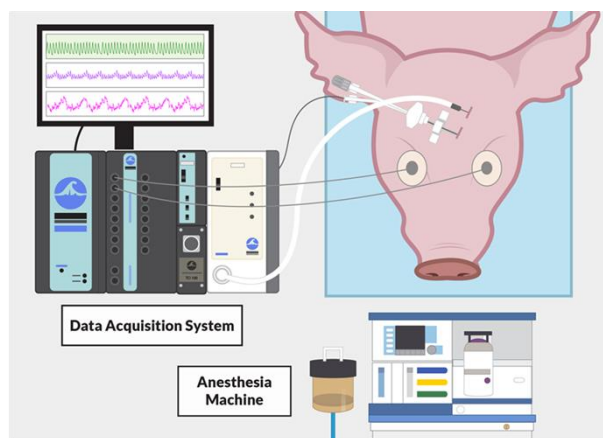


Figure 4. Modeling of the equipment used to measure the changes in a porcine model of cerebral autoregulation perturbation. Impedance, intracranial pressure, and laser Doppler flow are recorded using the data acquisition system which is stored on the computer.

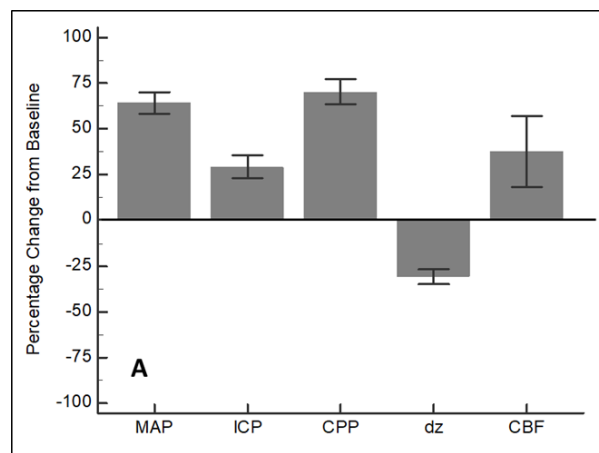


Figure 5: Percentage change from baseline of MAP, ICP, CPP, dz, and CBF during vasopressors challenge.

Results: During the vasopressor challenge, dz was highly correlated with ICP, CPP, and CBF ($r = <-0.49, p<0.0001$). ICP, CPP, and CBF had a mean percent increase (Standard Deviation) from baseline of 29(23.2) %, 70(25) %, and 37(72.6) % respectively while dz

decreased by 31(15.6) % (Figure 5). Receiver Operator Curve test showed high predictive performance of DZx when compared to PRx with area under the curve above 0.86, with high sensitivity and specificity (Figure 6).

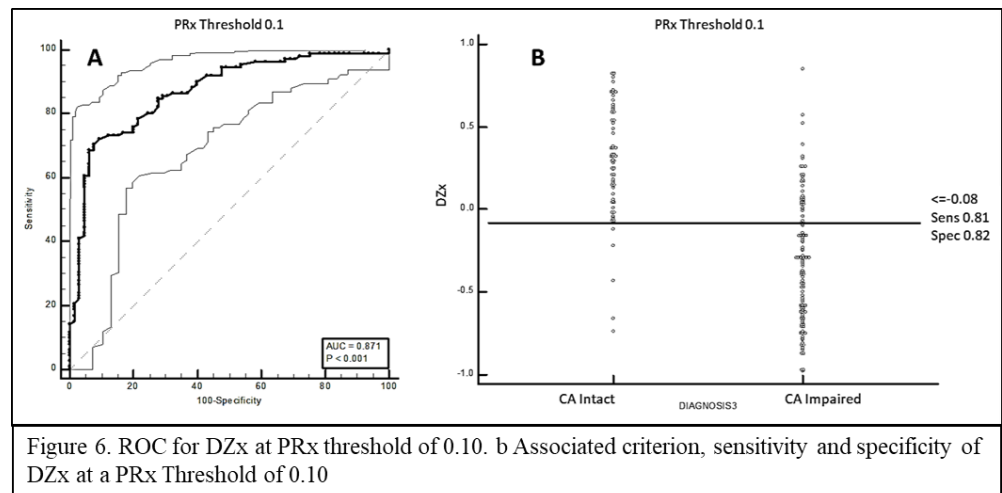


Table 1: lists Area under the Curve for DZx and its associated test performance metrics and criterion at different thresholds of PRx . DZx : Impedance Index. PRx : Pressure Reactivity Index

DZx	PRx Threshold > 0.3	PRx Threshold > 0.2	PRx Threshold > 0.1	PRx Threshold > 0
Sample size	177	177	177	177
Positive group	103 (58.19%)	107 (60.45%)	112 (63.28%)	114 (64.41%)
Negative group	74 (41.81%)	70 (39.55%)	65 (36.72%)	63 (35.59%)
Area under the ROC curve (AUC)	0.88	0.89	0.87	0.89
Standard Error	0.0251	0.0246	0.0276	0.0247
95% Confidence interval	0.835 to 0.933	0.845 to 0.942	0.817 to 0.925	0.842 to 0.939
Significance level P (Area=0.5)	<0.0001	<0.0001	<0.0001	<0.0001
Associated criterion	≤ -0.16	≤ -0.08	≤ -0.08	≤ -0.08
Sensitivity	0.82	0.81	0.78	0.79
Specificity	0.81	0.82	0.83	0.82
Positive Predictive Value	0.69	0.68	0.65	0.62
Negative Predictive Value	0.90	0.90	0.90	0.91
Positive Likelihood Ratio	4.3	4.4	4.5	4.4
Negative Likelihood Ratio	0.23	0.23	0.22	0.22

Relationship between DZx , PRx , and CA, during hypotension due to systemic hemorrhage

Data is presented in detail in **Manuscript: Trans-ocular brain impedance indices predict pressure reactivity index changes in a porcine model of hypotension and cerebral autoregulation perturbation**

Methods: Eleven Yorkshire swine were instrumented to record intracranial pressure (ICP), mean arterial pressure MAP, and cerebral blood flow (CBF). TOBI was recorded using ECG electrodes placed on the closed eyelids and measuring impedance (dz) in response to injecting 0.4 mA of current. MAP, ICP, and CBF were also measured (figure 4). Animals

were subjected to a controlled hemorrhage removing 34 (5.3)% blood volume over a duration of 26 (10) minutes. Hemorrhage was titrated to maintain a MAP above 30 mmHg and etCO₂ above 28 mmHg. PRx was calculated as moving Pearson correlation between MAP and ICP. TOBI indices were calculated as the amplitude of the respiratory-induced changes in dz. DZx was calculated as a moving Pearson correlation between dz and MAP. TOBI indices (dz and DZx) were compared to hemodynamic indicators and PRx. Sample waveforms are presented in figure 7.

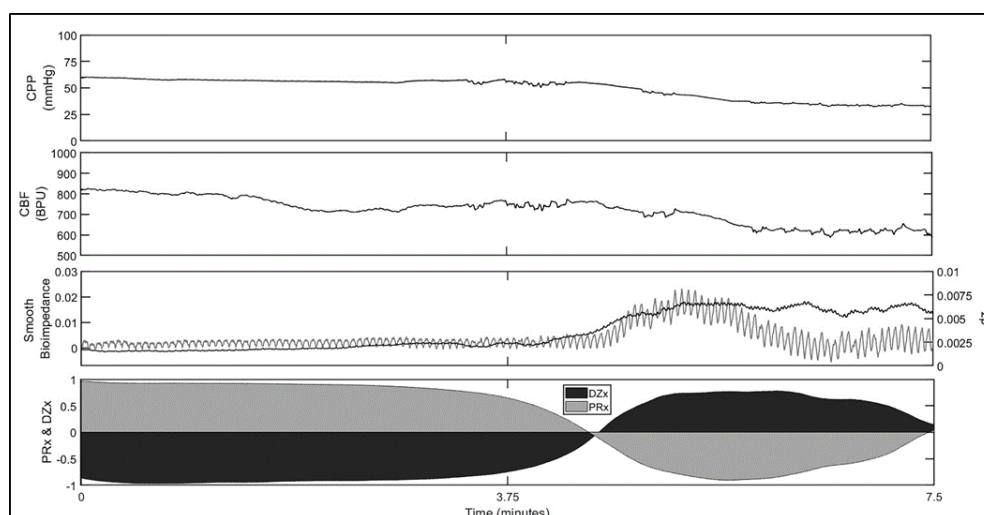


Figure 7: Longitudinal changes in MAP, CPP, CBF and dz during hemorrhage. “Smooth Impedance” panel show both respiratory signal as well as the dz (amplitude change) in solid line. MAP is mean arterial pressure. CPP is cerebral perfusion pressure. CBF is cerebral perfusion flow. dz is amplitude change in TOBI respiratory signal.

Results: dz was shown to be highly correlated with MAP, ICP, CPP, and CBF ($r = -0.823, -0.723, -0.813, \text{ and } -0.726$) respectively ($p < 0.0001$) (Table 2). During the hemorrhage period, CPP, and CBF had a mean percent decrease (Standard Deviation) from baseline of -54.2 (12.5)% and -28.3 (14.7)% respectively while dz increased by 277 (268)% (figure 8). Receiver operator characteristics (ROC) and precision-recall

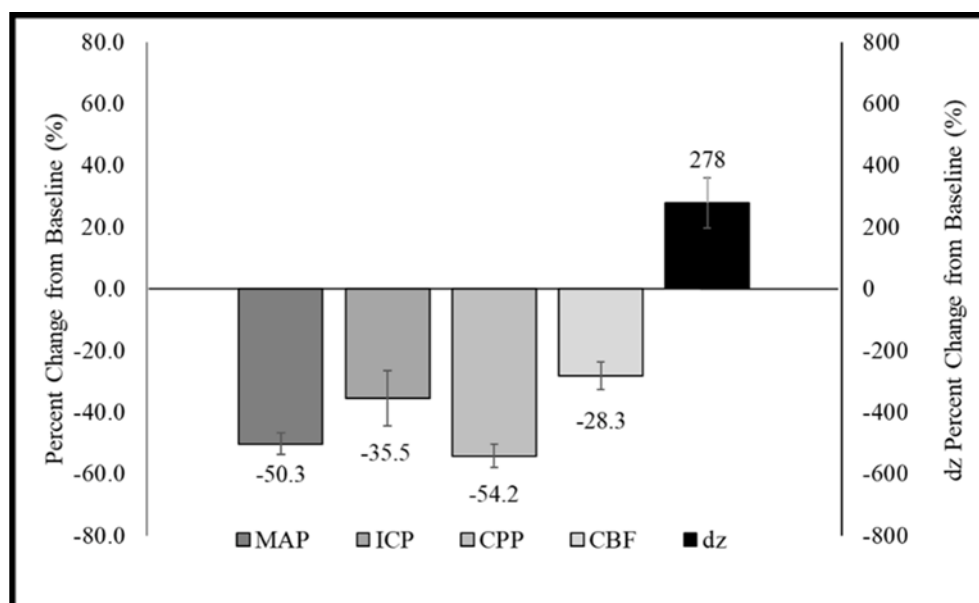


Figure 8: Percent changes during hemorrhage of MAP, ICP, CPP, CBF, and dz. MAP is mean arterial pressure. ICP is intracranial pressure. CPP is cerebral perfusion pressure. CBF is cerebral perfusion flow. dz is amplitude change in TOBI respiratory signal. dz change has been divided by 10 to fit the scale of the figure

curves (PRC) demonstrated high predictive performance of DZx when compared to PRx with area under the curve above 0.82 and 0.89 for both ROC and PRC respectively, with high sensitivity and positive predictive power (Table 3).

	<i>dz</i> vs. MAP	<i>dz</i> vs. ICP	<i>dz</i> vs. CPP	<i>dz</i> vs. CBF	CPP vs. CBF
Mean	-0.823	-0.723	-0.813	-0.726	0.867
Std. Deviation	0.1097	0.1911	0.1170	0.1432	0.1292
Std. Error of Mean	0.03306	0.05763	0.03528	0.04317	0.03897
Lower 95% CI of mean	-0.8962	-0.8509	-0.8912	-0.8219	0.7805
Upper 95% CI of mean	-0.7489	-0.594	-0.734	-0.6295	0.9542

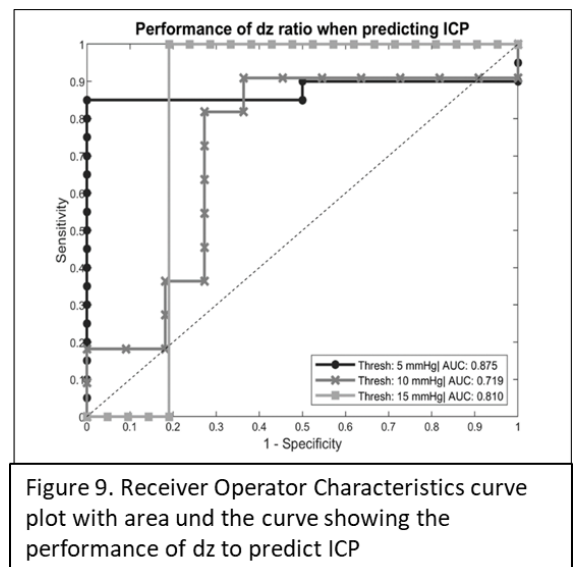
Table 2: Average Pearson correlations between *dz* and MAP, ICP, CPP, and CBF as well as between CPP and CBF. MAP is mean arterial pressure. ICP is intracranial pressure. CPP is cerebral perfusion pressure. CBF is cerebral perfusion flow. *dz* is amplitude change in TOBI respiratory signal.

	DZx at PRx Threshold (0)	DZx at PRx Threshold (0.1)	DZx at PRx Threshold (0.2)	DZx at PRx Threshold (0.3)
Number of values	10	11	11	11
ROC (AUC) Mean	0.852*	0.848*	0.829*	0.821*
Std. Deviation	0.1428	0.1375	0.1568	0.1500
Std. Error of Mean	0.04515	0.04145	0.04728	0.04523
Lower 95% CI of mean	0.750	0.756	0.724	0.720
Upper 95% CI of mean	0.955	0.941	0.935	0.921
Precision-Recall (AUC) Mean	0.928*	0.927*	0.895*	0.889*
Std. Deviation	0.0974	0.0962	0.1312	0.1389
Std. Error of Mean	0.03079	0.02901	0.03957	0.04189
Lower 95% CI of mean	0.858	0.862	0.807	0.796
Upper 95% CI of mean	0.997	0.991	0.983	0.982
Sensitivity	0.815	0.848	0.871	0.898
Specificity	0.673	0.571	0.559	0.510
PPV	0.856	0.831	0.795	0.783
NPV	0.553	0.611	0.637	0.693

Table 3 lists average AUC for DZx at different thresholds of PRx. PRx is pressure reactivity index. DZx is TOBI index. ROC is Receiver Operator Characteristics. AUC is area under the curve. CI is confidence intervals.

*Denotes and statistically significant value ($p < 0.0001$). $\alpha = 0.05$.

Furthermore, we have used our current baseline TOBI data in a cohort of 25 animals that are surgically instrumented to measure baseline ICP and MAP to test the utility of *dz* ratio in assessing ICP. A receiver operator curve analysis revealed a high performance of *dz* ratio when predicting ICP with AUCs between 0.72 to 0.88 at different threshold of ICP between 5 and 15 mmHg (Figure 9). In addition, using the hematoma maneuver data, *dz* and *dz*-calculated ICP were shown to be highly correlated to measured ICP with an average $r = 0.63$ ($p < 0.05$) (Figures 10). ROC curve yielded a highly predictive performance with an average AUC 0.775 ($p < 0.0001$). Figure 11 shows a representation of 9 animals to allow for clarity in the figure.



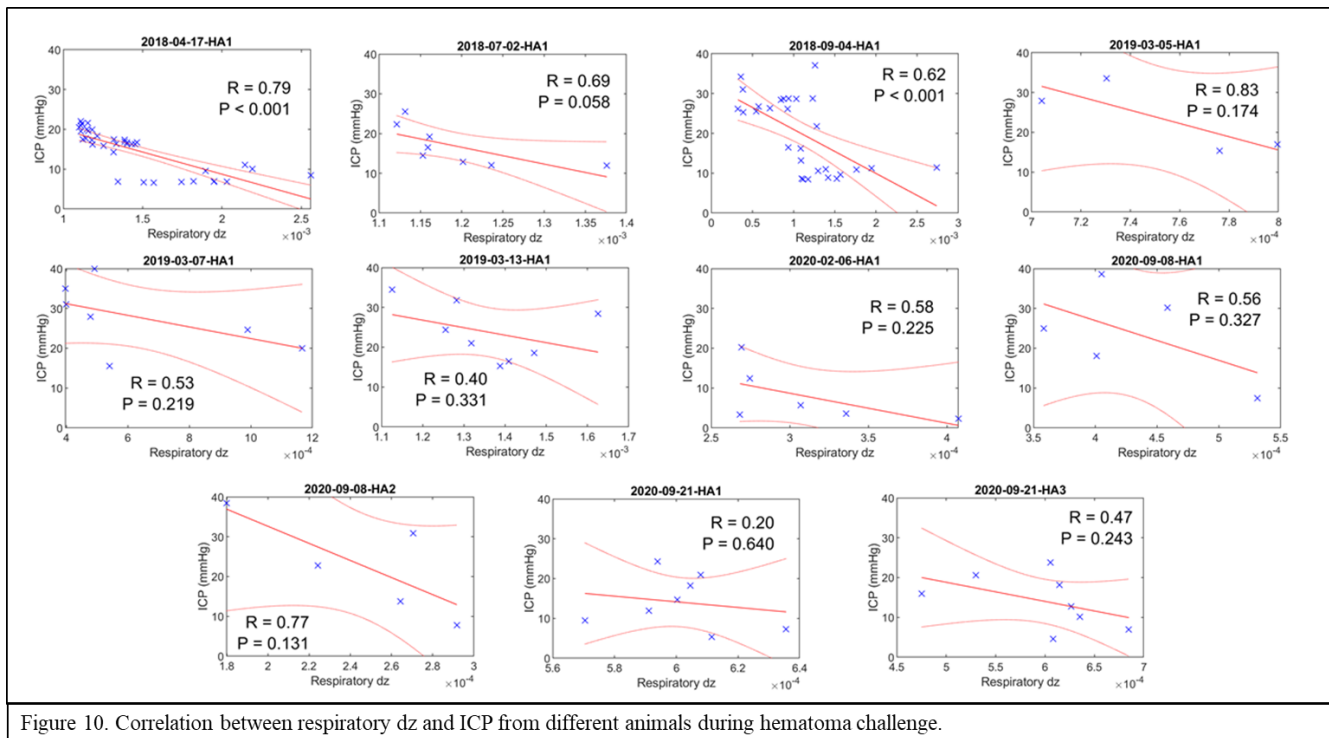


Figure 10. Correlation between respiratory dz and ICP from different animals during hematoma challenge.

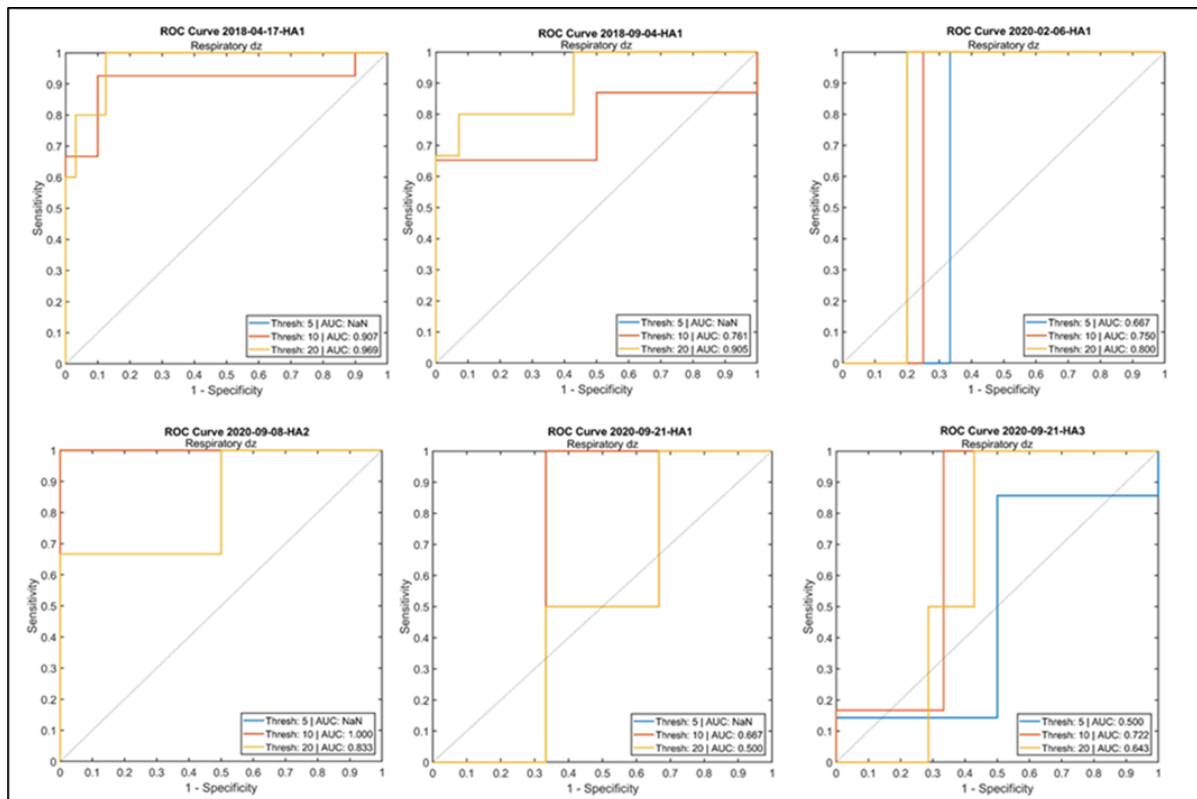


Figure 11. Receiver Operator Characteristics curve and Area Under the Curve for dz at different thresholds of Invasive ICP during a hematoma challenge.) and predicted (Calculated ICP) during a hematoma challenge

2. **Major Task 2:** *Evaluation of ocular impedance as an indicator of cerebral autoregulation in humans who are undergoing both invasive arterial blood pressure and ICP monitoring for brain injury. Months 0-36*

1. Specific objectives:

- a) IRB approval May 11, 2017
- b) HRPO approval September 22, 2017
- c) Total patient recruitment: 78 patients
- d) Annual patient recruitment: 12 patients

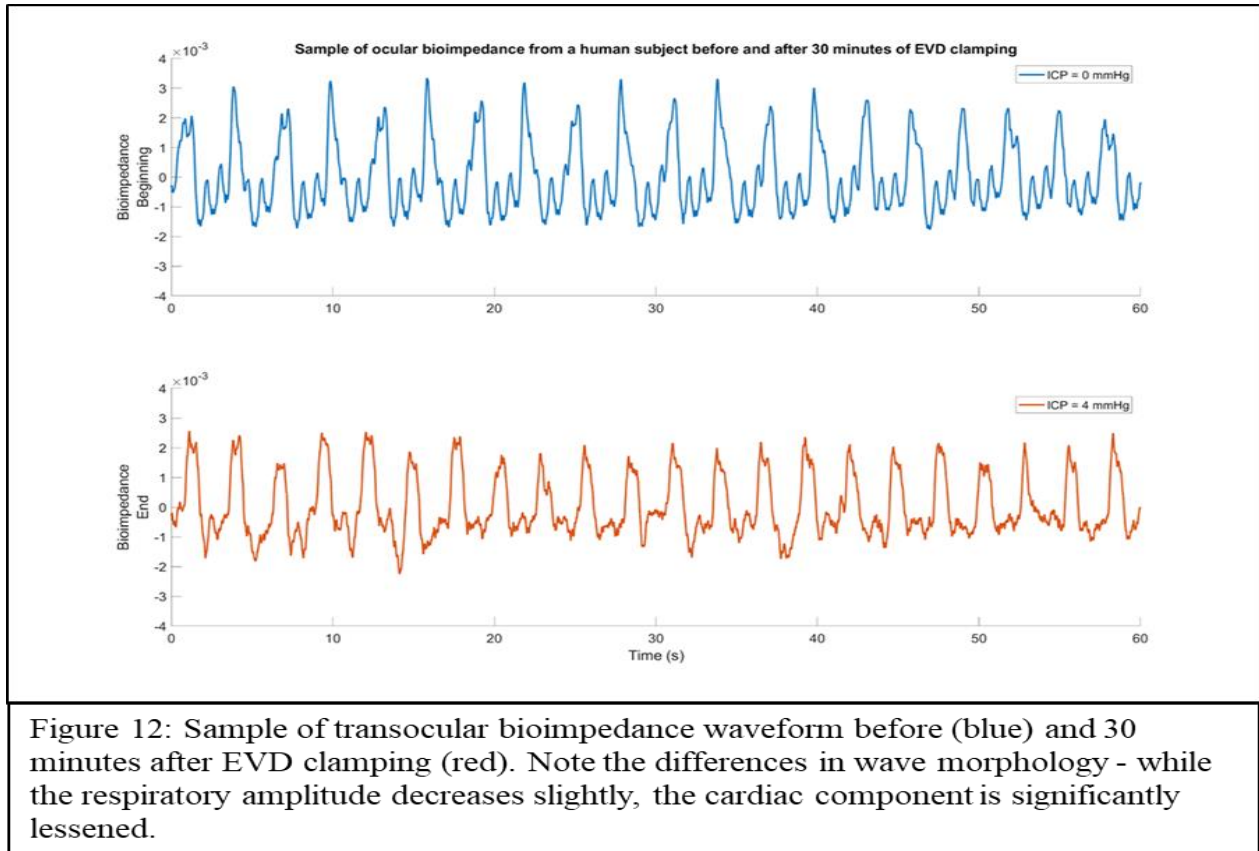
Patients who were admitted to the University of Michigan neurosurgery ICU or the trauma ICU with a ventriculostomy or an ICP monitor and arterial blood pressure monitoring were consented and enrolled into the study. In cases where the patient was unable to consent, the legally authorized representative consented on their behalf. A signed copy of the informed consent document was provided. Patients were admitted to the ICUs most commonly for subarachnoid hemorrhage (32 patients) but also for brain tumors (12), hematoma (4), hydrocephalus (6), trauma (3), meningioma (5), intracranial hemorrhage (4), cortical hemorrhage (2), dermoid cyst (1), compression of the brain stem (1), intraventricular hemorrhage (2), moyamoya (1), artery aneurysm (1), hypoxic ischemic brain injury (1), Cerebrovascular accident (1), and idiopathic Intracranial Hypertension (2). 38 females and 40 males were enrolled with an average (SD) age of 50.1 (15.9).

At a time when the physicians clamped the ventriculostomy as part of routine care, standard electrode patches (ConMed) were placed over the closed eyes of the patient and anchored at the nasal bridge, superior orbital rim, and the inferior orbital rim. Bioimpedance data was collected (Biopac Data Acquisition System) for 20-45 minutes while arterial blood pressures and ICPs were collected simultaneously. Starting January 4, 2019, the electrodes were changed from the standard electrodes to proprietary electrodes manufactured by In2Being Inc. and fitted onto a device resembling ocular glass wear only contacting the patient's eyelids. This setup has so far been tested on 34 patients with positive feedback for comfort, skill required for use, as well as signal integrity. This allows us to test on patients with orbital fractures and other facial traumas.

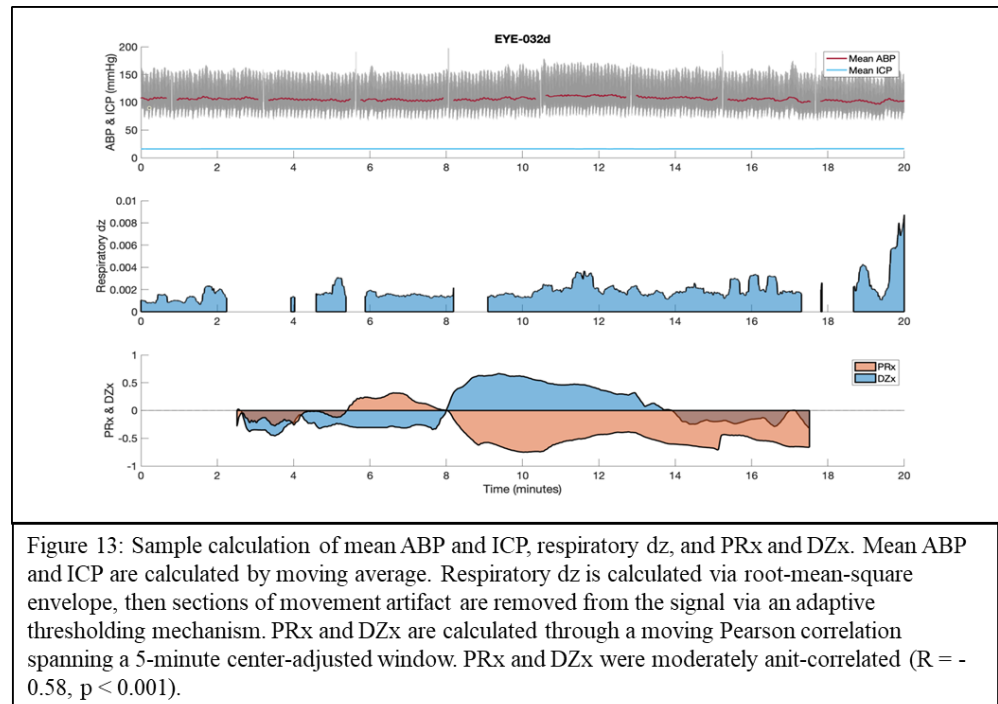
2. Significant results:

- a) Data analysis
- b) development of analytics for bioimpedance to current standard predictors of autoregulation

As with animals, the trans-ocular bioimpedance signal is largely composed of two frequencies of interest, relating to the respiratory and cardiac cycles. As expressed in the Q3 Quarterly Technical Progress Report, we have continued to investigate and refine our analysis of the cardiac component of the signal in conjunction with the respiratory oscillations to glean additional information from the signal. Figure 12 depicts a sample of the trans-ocular bioimpedance signal before and after 30 minutes of ventriculostomy clamping, during which ICP rose several points. Note the difference in wave morphology - the amplitude of the respiratory signal decreases slightly, and the higher-frequency cardiac component is significantly lessened. We've refined our analytic technique to quantify this change, using a root-mean-square envelope as it is more resistant to changes in respiratory rate, heart rate, and movement artifact.



Secondly, we have continued to analyze pressure-reactivity index (PRx) and our bioimpedance-driven analogue (DZx) in human subjects. Arterial blood pressure and ICP waveforms were extracted from the patient monitors through MCIRCC's data warehouse platform and aligned in time with the impedance data collected through our portable acquisition



system. A new artifact detection and removal process was developed, which uses an adaptive threshold to excise sections of noise due to movement and other sources of motion artifact which often occur in a clinical setting. This process allowed for the recovery of data that would otherwise be considered too noisy for PRx calculation.

As discussed above, PRx is the moving Pearson correlation between MAP and ICP, which may provide latent information about a patient's autoregulatory status. In the calculation of DZx, MAP is instead correlated against respiratory variability in the bioimpedance signal over a five-minute window. An example PRx and DZx calculation for one subject is reported in Figure 13 below. Note the inverse relationship between PRx and DZx, which occurs because the bioimpedance measure is inversely correlated with ICP.

Other achievements

1. Development of novel TOBI electrodes in collaboration with In2Being, LLC <https://www.in2being.com/>. The electrodes are fitted onto a 3D printed glasses with only the electrodes contacting patient's eyelids. This electrodes/goggles combination prototype has received positive feedback from patients for comfort and ease of application. This prototype will be used during patients testing in conjunction with Biopac system (Figure 14).
2. Development of a new prototype transocular brain impedance (TOBI) device in conjunction with Triple Ring Technologies <https://www.tripleringtech.com/>. The prototype is connected to two or four electrode that are placed on both eyelids. The prototype injects small electrical current (0.43 mA rms / 1.03 mA pp) at a frequency of 51 kHz. Triple Ring Technologies is currently working with In2being to join the two units together (Figure 15).
3. Development of a system for controlled cortical impact in large animals that is comprised of a voice coil actuator that uses an electromagnetic field to control the motion of the action piston along a linear vector. The piston velocity, depth of tissue impact and dwell time can be controlled with micrometer precision, which will allow us to produce highly accurate and repeatable impacts and, consequently, reproducible injuries. This new system is controlled by a laptop computer which provides a user-friendly interface that allows easy control of the impact parameters (Figure 16). (A disclaimer: Award funds were not used for the development of this device)



Figure 14. TOBI headset

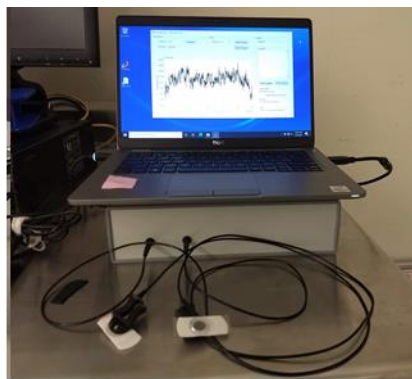


Figure 15. TOBI prototype.



Figure 16. TBI Impactor.

4. **Major tasks 3 and 4:** Collection of Optic Nerve Sheath (ONS) ultrasound videos for assessment of optic nerve sheath diameter (ONSD) in humans who are undergoing both invasive arterial blood pressure and ICP monitoring for brain injury (Months 0-36) and Development of an ultrasound video analytic system to evaluate ONSD. Months 6-36

1. Specific Objectives:

- IRB approval May 11, 2017
- HRPO approval September 22, 2017
- Total patient recruitment: **50** patients
- Annual patient recruitment: **3** patients
- Development of ultrasound analytic system
- Compare reading of automated ONSD with manual reading by clinicians

The optic nerve is part of the central nervous system surrounded by cerebrospinal fluid (CSF) and encased in a sheath (Figure 17). The sheath is continuous with the dura mater and diameter of this sheath changes rapidly with changing CSF pressure. It has been shown that ventriculostomy measurements of intracranial pressure (ICP) are correlated with Ultrasound (US) optic nerve sheath diameter (ONSD) measurements. Therefore, ONSD can be used as a non-invasive test for elevated ICP. However, manual ONSD measurement is cumbersome and prone to human error. An automated ONSD measurement can help physicians diagnose TBI patients faster and more accurately.

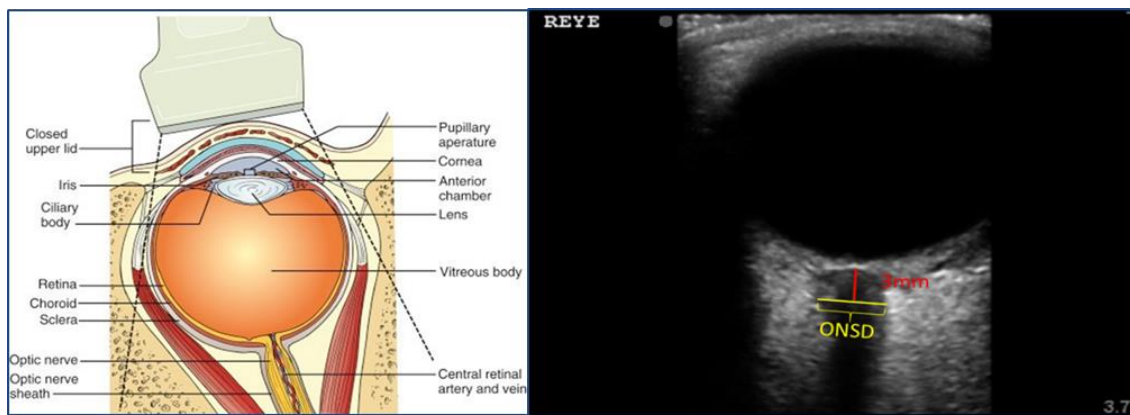


Figure 17: Gross anatomy and ultrasound image with the optic nerve sheath diameter (ONSD)

Method:

Here, we develop an automated algorithm using image processing techniques to analyze US images and calculate the ONSD in 3 mm posterior to the orbit/globe as shown in Figure 18. The schematic diagram of the proposed method is shown in Figure 9. Briefly, the steps are as follows:

- Determine lowest point in the eye
- Look for the ONS
- Go ~3 mm down the globe
- Determine outer sheath boundary within a region
- Determine the inner sheath boundary within a region
- Track the inner and outer boundaries over time

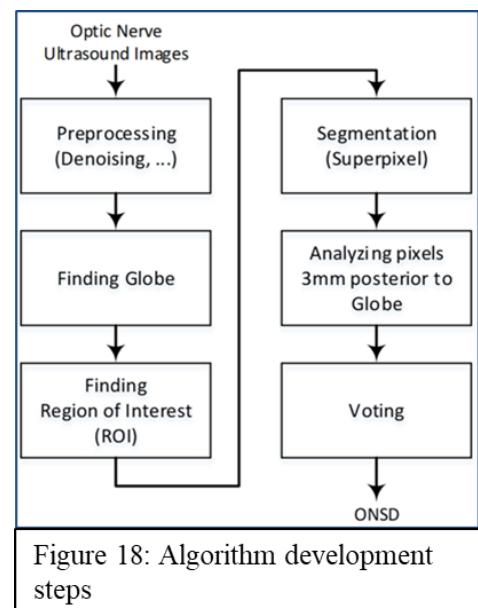


Figure 18: Algorithm development steps

Data Collection and Management: The following parameters were monitored for each patient throughout the experiment.

- ONSD using ultrasound (non-invasive); and
- Invasive ICP (invasive)

2. Significant results

a. Data analysis

- I. Pearson correlation between manual and algorithm assessment of ONSD
- II. Tukey mean-difference plot (Bland-Altman plot) (Manual and Algorithm)
- III. Intra-class correlation coefficient (ICC)
- IV. Student's *t*-test

b. Data Presentation

Fifty patients were recruited and tested from the neurological intensive care unit. The mean (SD) age was 51.08 (16.77) years and weight was 84.03 (26.95) kg. Thirty-four of the patients had sub-arachnoid hemorrhage or other spontaneous intracranial hemorrhage as their primary diagnosis, four patients had TBI, three had hydrocephalus, six had brain tumors, and three had other neurological conditions requiring intensive care. Forty-seven of the patients had an External Ventricular Drain and three had other invasive methods for measurement of ICP.

Ultrasound images of the optic nerve sheath from both eyes were obtained using an ultrasound unit with an ocular preset. Images were processed by two attending physicians to calculate ONSD manually. The images were processed as well using a novel computerized algorithm (described above) that automatically analyzes ultrasound images and calculates ONSD for both eyes. Algorithm-measured ONSD was compared to manually-measured ONSD using multiple statistical measures.

Results: Patients had a mean (SD) ICP of 13.9 (10.3) mmHg with a range between 6 and 57 mmHg. A *t*-test showed no statistical difference between the manual ONSD from left and right eyes ($p > 0.05$). Furthermore, a paired *t*-test showed no significant difference between the

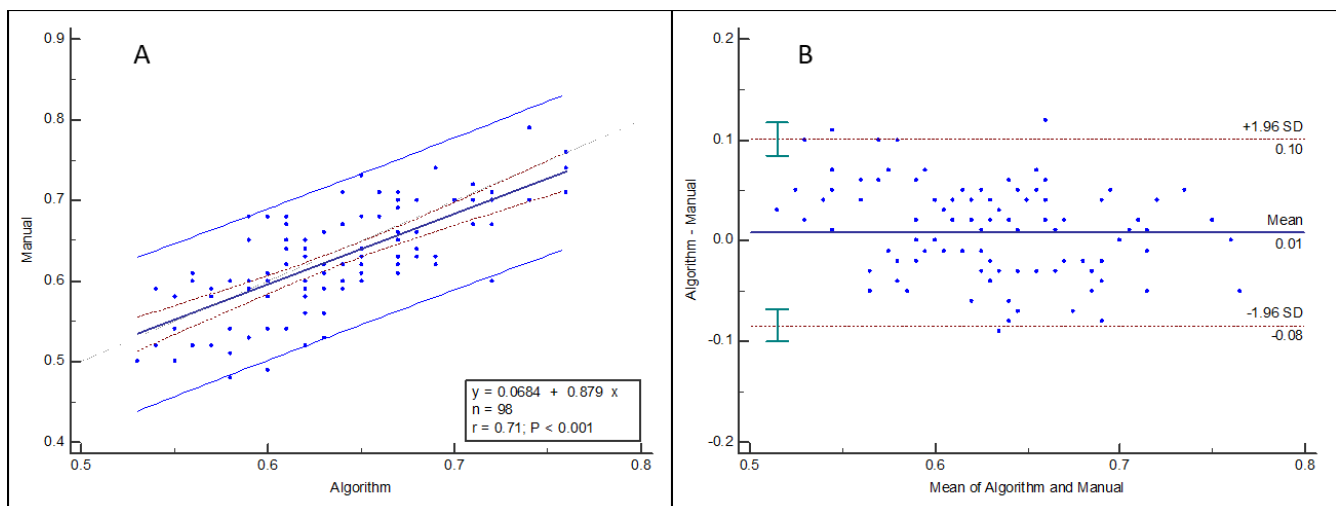


Figure 19: A) Regression of algorithm vs. manual ONSD measurements. B) Bland-Altman plot of algorithm vs. manual ONSD measurements. ONSD: Optic nerve sheath diameter.

manual and algorithm measure ONSD with a mean difference (SD) of 0.0085 (0.048) cm ($p>0.05$) and percentage error of difference of 5.98% ($p=0.15$). Agreement between the two operators was highly correlated ($ICC = 0.8$, $p=0.26$). Bland-Altman analysis between average (left and right) manual versus average (left and right) algorithm ONSD revealed Mean difference (SD) of 0.0085 (0.046) ($p = 0.303$; 95% CI: -0.084, 0.101) (Figure 19).

Receiver Operator Curve analysis of the algorithm ONSD at a threshold of 0.56 of manual ONSD yielded an AUC of 0.852 ($p<0.001$) with high sensitivity and specificity (Figure 20)

In order to find out if there is any correlation between ICP and ONSD we computed the Pearson and Spearman correlation coefficients between ICP and different ONSD measures such as the manual and algorithm measurement of left and right ONSD as well as the average of the left and right. See table 4 below.

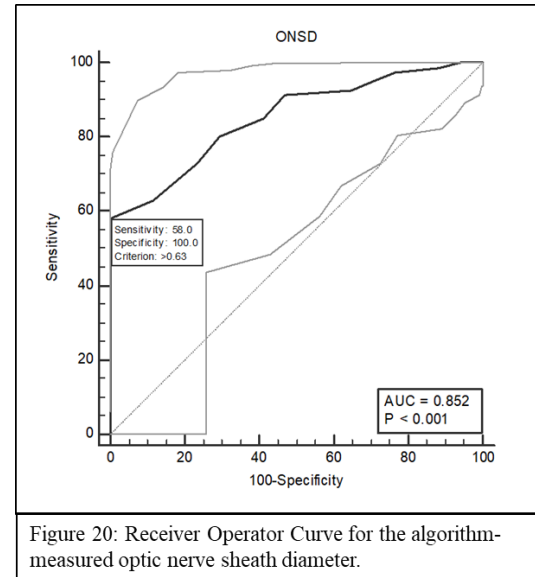


Figure 20: Receiver Operator Curve for the algorithm-measured optic nerve sheath diameter.

		Manual ONSD			Algorithm ONSD		
		Right Eye	Left Eye	Average	Right Eye	Left Eye	Average
Pearson Correlation	r	-0.1197	-0.1149	-0.1279	-0.1244	-0.1346	-0.1461
	95%	-0.3852 to	-0.3811	-0.3923 to	-0.3893 to	-0.3980 to	-0.4079 to
	CI	0.1641	to 0.1689	0.1560	0.1594	0.1494	0.1378
	p	0.4077	0.4269	0.3761	0.3892	0.3515	0.3112
Spearman Correlation	r	-0.001108	-0.03359	-0.0333	-0.005597	-0.06968	-0.03216
	95%	-0.2871 to	-0.3167	-0.3164 to	-0.2913 to	-0.3489 to	-0.3154 to
	CI	0.2851	to 0.2550	0.2553	0.2810	0.2208	0.2563
	p	0.9939	0.8169	0.8184	0.9692	0.6306	0.8245

What opportunities for training and professional development has the project provided?

Opportunity was provided for Dr. Reza Soroushmehr, a Research Fellow to present a conference paper at the 2019 *41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)* in Berlin Germany. Dr. Soroushmehr works with the PI and Co-I on development of automated algorithm to measure ONSD.

The conference paper was published online and can be found at

<https://ieeexplore.ieee.org/abstract/document/8856449>

Soroushmehr, R., Rajajee, K., Williamson, C., Gryak, J., Najarian, K., Ward, K. and Tiba, M.H., 2019, July. Automated Optic Nerve Sheath Diameter Measurement Using Super-pixel Analysis. In *2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)* (pp. 2793-2796). IEEE.

How were the results disseminated to communities of interest?

- A conference abstracts was submitted to the 2020 M Military Health Science Research Symposium (MHSRS) as well as several publications as detailed in the section “Other publications, conference papers, and presentations” below
- Successful submission of the annuals TBI data upload to The Federal Interagency Traumatic Brain Injury Research (FITBIR)

What do you plan to do during the next reporting period to accomplish the goals?

The activities in all major task areas will be continued for the duration of the next reporting period. We plan to continue animal testing using the provocative maneuvers and the blunt trauma TBI using the new impactor. Human subjects’ recruitment and testing will continue for the remainder of the project. Human subjects’ data collection will be collected using the latest iteration of the Trans-Ocular Bioimpedance prototype (TOBI), and compared to preliminary data for signal quality device validation. In tandem with collection, data analysis and signal processing will continue for the duration of the next reporting period. (Signal processing a validation of bioimpedance signal against autoregulation parameters such as MAP, ICP, or cerebral blood flow). Further development of ultrasound technique and algorithm for assessment of ONSD will continue for the duration of the project (Patients recruitment and algorithm validation). Data and project progress will continue to be divulged via presentations at scientific meetings both locally at the University of Michigan and nationally at the MHSRS and the Shock Society Meeting during the next reporting period. Lastly, scientific manuscript writing will begin this reporting period with a target of 2-4 publications in major scientific and clinical journals covering all major tasks outlined in the report.

- i. Continue testing animals both models 1 & 2
- ii. Continue patient recruitment
- iii. Continue patients testing using prototype
- iv. Further algorithm development for ONSD ultrasound
- v. Data analysis and signal processing
- vi. Data presentation (national and local
- vii. Manuscripts submission

IMPACT:

- a. **What was the impact on the development of the principal discipline(s) of the project?**

Nothing to report at this time as we are still in testing phase. However, we are expecting a high level of impact by the end of the project on the understanding of cerebrovascular autoregulation and its relationship to cerebral blood flow with the ability to monitor and track these events using transocular impedance that can be commercialized. We will also continue to assess ICP non-invasively using ONSD via ultrasound and an automated algorithm.

b. What was the impact on other disciplines?

Nothing to report.

c. What was the impact on technology transfer?

1. Provisional patent application "Automated Optic Nerve Sheath Diameter Measurement" was filed on July 23, 2019, and assigned Serial No. 62/877,539.
2. Provisional patent application (62/506,971) Ocular Impedance-Based System for Brain Health Monitoring. Submitted May 16, 2017 and converted on 5/16/18 to a PCT patent application. The PCT was later nationalized into several countries, including the US. The US application has been assigned the serial number that you provided (16/613/707)
3. TOBI Prototype developed by In2Being, LLC.
4. TOBI technology now exclusively licensed to New Vital Signs, Inc.
5. New Vital Signs, Inc. is engaged with a venture firm and a manufacturer (Triple Ring Technologies) to develop new generation prototypes for multisite clinical testing

d. What was the impact on society beyond science and technology?

The proposed work is envisioned to lead to development of technologies for noninvasive evaluation of CA and ICP. Such technologies are envisioned to be suitable for in-hospital and out-of-hospital setting in both the civilian and military setting and will allow for:

- 1) Early application by first responders and military medics for precision management of the severe TBI patient including providing optimal and personalized cerebral perfusion pressure as opposed to a range.
- 2) Rapid point of care diagnostic indicators of severity of TBI allowing for earlier intervention in more far forward echelons of care.
- 3) Improved outcomes by earlier detection of injury and prevention of secondary damage.
- 4) Greater uninterrupted continuum of care as casualties moves from lower to higher levels of care.
- 5) Reduction in the need for experienced personnel to perform the time consuming procedures necessary for invasive monitoring as well as elimination of associated complications.
- 6) Improved resource allocation by providing indications for invasive monitoring as well as earlier termination of such invasive monitoring (when they are indicated) by transitioning into noninvasive monitoring.

CHANGES/PROBLEMS:

e. Changes in approach and reasons for change

Nothing to report

f. Actual or anticipated problems or delays and actions or plans to resolve the

Clinical Recruitment: Due to the unforeseen consequences of COVID-19 pandemic, and in order to follow the state, local, and the University of Michigan executive orders, all human clinical research activities that are not related to COVID-19 have been completely halted by the University of Michigan Office of Research (UMOR) from March 16th, 2020 till September, 30th, 2020. During this period our clinical research staff steered the wheel toward data analysis and manuscript writing. UMOR then developed a 4-tiers activation plan, where this study was approved for tier 2, which allowed us to continue our clinical recruitment activities with the following restrictions:

To help mitigating the spread of COVID-19 among susceptible population, research staff were not allowed to approach the following populations for recruitment purposes:

- Patients 65 years or older (restriction left on September 30th, 2020).
- Immunocompromised patients.

These restrictions resulted in a decreased pool of eligible subjects, hence a decrease in recruited subjects for the study. We will continue to recruit for eligible patients at full capacity while following the previously mentioned policies and restrictions.

Pre-clinical testing: The COVID-19 epidemic resulted in a temporary ramp-down of all non-critical university functions, which included all research not directly related to COVID-19 which began March 13th 2020. We were unable to execute animal lab experiments. During the ramp-down several personnel (clinical coordinator and animal lab technicians) were voluntarily furloughed to conserve grant funds during the operational ramp-down. The furloughed personnel have returned to their full appointments on this project in July. Animal research reengagement began August 4th 2020. A 12-day temporary suspension of all non-essential research occurred following the 2020 Thanksgiving holiday strongly advised by the University of Michigan.

To mitigate the loss of time, a no-cost extension to this grant has been submitted and granted. Beyond the COVID-19 ramp down, no additional problems are anticipated.

g. Changes that had a significant impact on expenditures

Nothing to report

h. Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

1. **Significant changes in use or care of human subjects:** None to report
2. **Significant changes in use or care of vertebrate animals:** None to report
3. **Significant changes in use of biohazards and/or select agents:** None to report

PRODUCTS:

i. Publications, conference papers, and presentations

1. **Journal publications.**
Three publications:

- 1) Soroushmehr R, Rajajee K, Williamson C, Gryak J, Najarian K, Ward K, Tiba MH. Automated Optic Nerve Sheath Diameter Measurement Using Super-pixel Analysis. Annu Int Conf IEEE Eng Med Biol Soc. 2019 Jul;2019:2793-2796. doi: PMID: 31946473.
- 2) Rajajee V, Soroushmehr R, Williamson CA, Najarian K, Gryak J, Awad A, Ward KR, Tiba MH. Novel Algorithm for Automated Optic Nerve Sheath Diameter Measurement Using a Clustering Approach. Mil Med. 2020 Aug 22:usaa231. PMID: 32830251.
- 3) Tiba MH, McCracken BM, Leander DC, Colmenero CI, Cummings BC, Greer NL, Picton P, Williamson CA, Ward KR. Trans-ocular brain impedance index for assessment of cerebral autoregulation in a porcine model of cerebral hemodynamic perturbation. J Clin Monit Comput. 2020 Jul 14. PMID: 32666400.

Another manuscript has been submitted to *Neurocritical care* and is under review

Mohamad H. Tiba, Brendan M. McCracken, Danielle C. Leander, Carmen I. Colmenero, Nicholas L. Greer, Paul Picton, Craig A. Williamson, Kevin R. Ward. Trans-ocular brain impedance indices predict pressure reactivity index changes in a porcine model of hypotension and cerebral autoregulation perturbation

All publications and the manuscript will be provided in the appendices

2. **Books or other non-periodical, one-time publications.** Nothing to report
3. **Other publications, conference papers, and presentations.**
An abstract has been accepted for a poster presentation at the 2020 Military Health Science Research Symposium (MHSRS). The conference was cancelled to COVID-19.
 - **MHSRS-20-00687:** Mohamad Hakam Tiba, Brendan M. McCracken, Danielle C. Leander, Carmen I. Colmenero, Brandon C. Cummings, Nicholas L. Greer, Craig A. Williamson, Kevin R. Ward, MD. Trans Ocular Brain Impedance Indices for Assessment of Cerebral Autoregulation Post Traumatic Brain Injury.

The abstract will be included in the appendices

a. Website(s) or other Internet site(s)

1. <https://mcircc.umich.edu/tobi>
2. <http://newvitalsigns.bio/#technology>

b. Technologies or techniques

Development of a new prototype transocular brain impedance (TOBI) device in conjunction with Triple Ring Technologies <https://www.tripleringtech.com/>. The prototype is connected to two or four electrodes that are placed on both eyelids. The prototype injects small electrical current (0.43 mA rms / 1.03 mA pp) at a frequency of 51 kHz. Triple Ring Technologies is currently working with In2being to join the headset with the new prototype

c. Inventions, patent applications, and/or licenses

1. Provisional patent application “Automated Optic Nerve Sheath Diameter Measurement” was filed on July 23, 2019, and assigned Serial No. 62/877,539.

2. Provisional patent application (62/506,971) Ocular Impedance-Based System for Brain Health Monitoring. Submitted May 16, 2017 and converted on 5/16/18 to a PCT patent application. The PCT was later nationalized into several countries, including the US. The US application has been assigned the serial number that you provided (16/613/707)
3. TOBI technology is fully licensed to New Vital Sign <http://newvitalsigns.bio/#technology>

d. Other Products

Web based information

1. <https://mcircc.umich.edu/tobi>
2. <http://newvitalsigns.bio/#technology>

e. Research material (e.g., Germplasm; cell lines, DNA probes, animal models);

Animal TBI model developed for this project is now being utilized for testing beyond bioimpedance

Describe the Regulatory Protocols and Activity Status (if applicable).

1- Human Use Regulatory Protocols

TOTAL PROTOCOLS:

One human use protocol will be required to complete the Statement of Work

PROTOCOL(S):

TOTAL PROTOCOLS: 1

PROTOCOL (1 of 1 total):

Protocol [HRPO Assigned Number]: DM160225

Title: Novel Noninvasive Methods of Intracranial Pressure and Cerebrovascular Autoregulation Assessment: Seeing the Brain Through the Eyes

Target required for clinical significance:150

Target approved for clinical significance: 150

SUBMITTED TO AND APPROVED BY:

- IRBMED Initial Approval 7/2/15
- IRBMED Amendment to add retrospective enrollment 1/11/16
- IRBMED Amendment to add bioimpedance 8/12/16
- HRPO Initial Approval 5/11/17
- IRBMED Amendment to add DoD and edits to comply with DoD regulations 7/10/17
- IRBMED Amendment to add TCD 4/26/18
- IRBMED Amendment to add wearable 3/4/19
- IRBMED Amendment to add/ remove staff, consent changes for FITBIR wording 8/13/19
- IRBMED Amendment to add PZT 11/19/19
- IRBMED Amendment to add staff 1/20/20
- IRBMED continuing review report 10/21/19
- IRBMED Amendment to add staff 02/24/2020
- IRBMED Amendment to change consent form language to meet FITBIR requirements 09/04/2020

- IRBMED Amendment to add remote and electronic consent, add staff, and add head circumference 10/15/2020
- IRBMED Amendment to change contact information on the consent form 12/08/2020
- IRBMED Amendment add staff 12/16/2020
- IRB continuing review report 07/23/2020

STATUS:

- (i) Number of subjects recruited/original planned target: 78/150
 Number of subjects screened/original planned target: 78/150
 Number of patients enrolled/original planned target: 78/150
 Number of patients completed/original planned target: 67/150
- (ii) Report amendments submitted to the IRB and USAMRMC HRPO for review:
None
- (iii) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation:
None

2. Use of Human Cadavers for Research Development Test & Evaluation (RDT&E), Education or Training

No RDT&E, education or training activities involving human cadavers will be performed to complete the Statement of Work (SOW).

3. Animal Use Regulatory Protocols

TOTAL PROTOCOL(S):

One large animal protocol will be required to complete the Statement of Work

PROTOCOL(S):

TOTAL PROTOCOL(S): 2

PROTOCOL (1 of 2 total):

Protocol [ACURO Assigned Number]: **DM160225**

Title: **Noninvasive Methods of Intracranial Pressure and Cerebrovascular Autoregulation Assessment**

Target required for statistical significance: 66

Target approved for statistical significance: 66

SUBMITTED TO AND APPROVED BY:

- Protocol submitted to University of Michigan (UofM) IACUC on 5/2/2017
- Protocol approved by University of Michigan IACUC on 6/12/2017
- Protocol submitted to ACURO on 8/2/2017
- Protocol approved by ACURO on 8/11/2017- Protocol Expired 6/12/2020

PROTOCOL (2 of 2 total):

Protocol [ACURO Assigned Number]: **DM160225**

Title: **Noninvasive Methods of Intracranial Pressure and Cerebrovascular Autoregulation Assessment**

Target required for statistical significance: 66

Target approved for statistical significance: 66

SUBMITTED TO AND APPROVED BY:

- Protocol submitted to University of Michigan (UofM) IACUC on 3/6/2020
- Protocol approved by University of Michigan IACUC on 3/31/2020
- Protocol submitted to ACURO on 4/14/2020
- Protocol approved by ACURO on 5/29/2020

STATUS:

- We have used 10 animals this year to test the performance of bioimpedance during TBI and Provocative maneuvers. 4 animals were used in the blunt impact model and 6 were used in the provocative maneuvers model. Total use for years 1-3 in the project is 56 animals.
- Data from these experiments were specifically collected to assist with the characterization of new indices of autoregulation assessment (DZx) compared to PRx. Additionally, they will be used to further correlate ocular bioimpedance with cerebral blood flow, intracranial pressure, and transcranial Doppler.
- Fully automated data quantification methods and indices for assessment of cerebrovascular auto-regulatory function are continually being explored and developed.
- We have not encountered any administrative, technical, or logistical issues that may impact the performance or progress of our study.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**f. What individuals have worked on the project?**

Name:	Mohamad Hakam Tiba
Project Role:	<i>PI</i>
Researcher Identifier: (e.g. ORCID ID)	
Nearest person month worked	<i>3</i>
Contribution to Project:	<i>Project oversight. Oversight of all data collection and analysis</i>

Name:	Kevin Ralph Ward
Project Role:	<i>Co-I</i>
Researcher Identifier: (e.g. ORCID ID)	
Nearest person month worked	<i>1</i>
Contribution to Project:	<i>Oversight of data collection and analysis</i>

Name:	Brendan McCracken
Project Role:	<i>Research Staff, Laboratory Assistant Director</i>
Researcher Identifier: (e.g. ORCID ID)	
Nearest person month worked	<i>2</i>
Contribution to Project:	<i>Laboratory oversight, management, data collection, data analysis</i>

Name:	Danielle Leander
Project Role:	Research staff, Technician
Researcher Identifier: (e.g. ORCID ID)	
Nearest person month worked	2
Contribution to Project:	Animal lab duties, data collection, data analysis

Name:	Nicholas Greer
Project Role:	Research Staff, Technician
Researcher Identifier: (e.g. ORCID ID)	
Nearest person month worked	3
Contribution to Project:	Animal lab duties, data collection, data analysis

Name:	Kayvan Najarian
Project Role:	Co-I
Researcher Identifier: (e.g. ORCID ID)	
Nearest person month worked	1
Contribution to Project:	Development of a computer image analysis algorithm

Name:	Jonathan Motyka
Project Role:	Data Engineer
Researcher Identifier: (e.g. ORCID ID)	
Nearest person month worked	9
Contribution to Project:	Data Signal processing, data storage and analysis

Name:	Abdelrahman Awad
Project Role:	Research Staff, Clinical coordinator
Researcher Identifier: (e.g. ORCID ID)	
Nearest person month worked	6
Contribution to Project:	Patients' recruitment, data collection, data analysis

Name:	Brandon Clark Cummings
Project Role:	Research staff, Data engineer
Researcher Identifier: (e.g. ORCID ID)	
Nearest person month worked	1
Contribution to Project:	Data collection, signal processing and data analysis

Name:	Carmen Irene Colmenero
Project Role:	Research staff, Specialist
Researcher Identifier: (e.g. ORCID ID)	
Nearest person month worked	2

<i>Contribution to Project:</i>	<i>Animal lab duties, data collection, data analysis</i>
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<i>Name:</i>	Hasan Alam
<i>Project Role:</i>	<i>Co-I</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Nearest person month worked</i>	<i>1</i>
<i>Contribution to Project:</i>	<i>Oversight of data collection and analysis</i>

<i>Name:</i>	Venkatakrishna Rajajee
<i>Project Role:</i>	<i>Co-I</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Nearest person month worked</i>	<i>1</i>
<i>Contribution to Project:</i>	<i>Perform ultrasounds, medical consultation</i>

<i>Name:</i>	Craig A Williamson
<i>Project Role:</i>	<i>Co-I</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Nearest person month worked</i>	<i>1</i>
<i>Contribution to Project:</i>	<i>Perform ultrasounds, medical consultation</i>

<i>Name:</i>	Reza Soroushmehr
<i>Project Role:</i>	<i>Research Staff</i>
<i>Researcher Identifier: (e.g. ORCID ID)</i>	
<i>Nearest person month worked</i>	<i>3</i>
<i>Contribution to Project:</i>	<i>Development of a computer image analysis algorithm</i>

- a. **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Nothing to report

- b. **What other organizations were involved as partners?**

None

- c. **Other.**

Nothing to report

SPECIAL REPORTING REQUIREMENTS

- d. **COLLABORATIVE AWARDS:**

None

- e. **QUAD CHARTS:** Included with this report before the appendices

APPENDICES:

1. Abstract: MHSRS-20-00687: Mohamad Hakam Tiba, Brendan M. McCracken, Danielle C. Leander, Carmen I. Colmenero, Brandon C. Cummings, Nicholas L. Greer, Craig A. Williamson, Kevin R. Ward, MD. Trans Ocular Brain Impedance Indices for Assessment of Cerebral Autoregulation Post Traumatic Brain Injury.
2. Publication: Soroushmehr R, Rajajee K, Williamson C, Gryak J, Najarian K, Ward K, Tiba MH. Automated Optic Nerve Sheath Diameter Measurement Using Super-pixel Analysis. Annu Int Conf IEEE Eng Med Biol Soc. 2019 Jul;2019:2793-2796. doi: PMID: 31946473.
3. Publication: Rajajee V, Soroushmehr R, Williamson CA, Najarian K, Gryak J, Awad A, Ward KR, Tiba MH. Novel Algorithm for Automated Optic Nerve Sheath Diameter Measurement Using a Clustering Approach. Mil Med. 2020 Aug 22:usaa231. PMID: 32830251.
4. Publication: Tiba MH, McCracken BM, Leander DC, Colmenero CI, Cummings BC, Greer NL, Picton P, Williamson CA, Ward KR. Trans-ocular brain impedance index for assessment of cerebral autoregulation in a porcine model of cerebral hemodynamic perturbation. J Clin Monit Comput. 2020 Jul 14. PMID: 32666400.
5. Manuscript: Mohamad H. Tiba, Brendan M. McCracken, Danielle C. Leander, Carmen I. Colmenero, Nicholas L. Greer, Paul Picton, Craig A. Williamson, Kevin R. Ward. Trans-ocular brain impedance indices predict pressure reactivity index changes in a porcine model of hypotension and cerebral autoregulation perturbation. Under review by *Neurocritical Care*

Novel Noninvasive Methods of Intracranial Pressure and Cerebrovascular Autoregulation

Assessment: Seeing the Brain through the Eyes

DM160225 Prolonged Field Care Research Award



Co-PIs: Mohamad Hakam Tiba and Kevin R. Ward

Org: University of Michigan

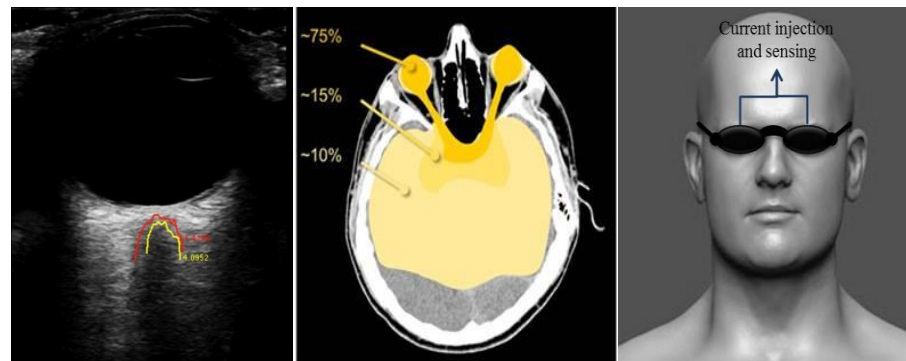
Award Amount: \$1,480,171

Study/Product Aim(s)

- Use non-invasive ocular electrical bioimpedance methodologies to track dynamic changes in cerebral blood flow (CBF) and associated changes in cerebrovascular autoregulation (CAR).
- Develop a computer image analysis algorithm and program capable of automating the analysis of images of the optic nerve sheath (ONS) obtained by ultrasound to evaluate intracranial pressure (ICP).

Approach

We will utilize two animal models concomitant with a clinical study. The animal models will include a swine TBI model of blunt trauma as well as a model designed to examine cerebral and systemic hemodynamics in response to various modulators of CBF. We will test ocular impedance as an indicator of cerebral autoregulation and ocular ultrasound videos for assessment of ICP in humans who are undergoing invasive arterial blood pressure and ICP monitoring for brain injury.



Ocular impedance and ocular nerve sheath ultrasound will be studied in both animals and humans with TBI

Timeline and Cost

Activities	CY	18	19	20	
Ultrasound video analytic and algorithm development					
Animal testing and recruitment of human subjects					
Development of big data platform					
Data analysis and report					
Estimated Budget (\$K)		\$507,353	\$482,327	\$490,491	

Goals/Milestones

CY18 Goal – Validation and system development

- Start validation of ocular impedance in both animals human subjects
- Collection of ONS ultrasound videos for assessment of ICP in humans
- Development of Ultrasound video analytic and algorithm
- Data Analysis and development of big data platform

CY19 Goals – Validation

- Continue animal testing, patients recruitment for both ocular impedance and ultrasound. As well as development of Ultrasound video analytic and algorithm
- Big data platform, data Analysis, reports and presentations

CY20 Goal – Validation, Final reports and presentations

- Continue animal testing, patients recruitment for both ocular impedance and ultrasound. As well as development of Ultrasound video analytic and algorithm
- Big data platform, data Analysis, final reports and presentations
- Development of a transition plan for future trials

Comments/Challenges/Issues/Concerns: A no-cost extension has been granted due to COVID-19

• Budget Expenditure to Date: \$1,412,996

Updated: (07.14.2020)

Trans Ocular Brain Impedance Indices for Assessment of Cerebral Autoregulation Post Traumatic Brain Injury

Mohamad Hakam Tiba, MD, MS^{1,5}, Brendan M. McCracken, BS^{1,5}, Danielle C. Leander, BS^{1,5}, Carmen I. Colmenero, BS^{1,5}, Brandon C. Cummings, BS^{1,5}, Nicholas L. Greer, BS^{1,5}, Craig A. Williamson, MD, MS^{3,4,5}, Kevin R. Ward, MD^{1,2,5}

¹Department of Emergency Medicine, University of Michigan, Ann Arbor, Michigan

²Department of Biomedical Engineering, University of Michigan, Ann Arbor, Michigan

³Department of Neurological Surgery, University of Michigan, Ann Arbor, Michigan

⁴Department of Neurology, University of Michigan, Ann Arbor, Michigan

⁵Michigan Center for Integrative Research in Critical Care (MCIRCC), University of Michigan, Ann Arbor, Michigan

Introduction: Cerebrovascular autoregulation (CA) is an auto-protective mechanism where vessels auto-modulate their tone in response to changes in cerebral perfusion pressure (CPP) as means to maintain constant levels of cerebral blood flow (CBF). CA is a significant predictor of outcome in patients with various neurological diseases, including severe TBI. Monitoring CA is beneficial for patient management to mitigate secondary brain injury and enable optimization of CPP. Current technologies and metrics used to assess CA such as the pressure reactivity index (PRx) are invasive, associated with potential complications, and late to obtain. In this study, we report a novel impedance indices utilizing a trans-ocular brain impedance (TOBI) methodology to provide non-invasive, effective, and continuous assessment of CA.

Hypothesis: Impedance indices will track changes in PRx and hemodynamics, and assess CA with high precision.

Methods: Yorkshire swine were instrumented to record intracranial pressure (ICP), mean arterial pressure (MAP), and CBF. TOBI was recorded using ECG electrodes placed on the closed eyelids. MAP, ICP, and CBF were manipulated utilizing a vasopressor challenge. Norepinephrine was titrated to reach a MAP of 150mmHg and induce increase in ICP, indicating the loss of CA. High MAP was maintained for 15 to 30 minutes followed by the titrated reduction or cessation of the infusion. PRx was calculated as moving Pearson correlation between MAP and ICP. TOBI indices were calculated as respiratory-induced amplitude change in Impedance (dz) and DZx which is a moving Pearson correlation between dz and MAP. TOBI indices (dz and DZx) were compared to hemodynamic indicators and PRx.

Results: During the vasopressor challenge, dz was highly correlated with ICP, CPP, and CBF ($r = <-0.49$, $p < 0.0001$). ICP, CPP, and CBF had an average percent increase (SD) from baseline at 29(23.2)%, 70(25)%, and 37(72.6)% respectively. While dz decreased by -31(15.6)% consistent with increased CBF. Receiver Operator Curve test showed high predictive performance of DZx compared to PRx at different thresholds (0 to 0.3) with an area under the curve above 0.86.

Conclusion: Impedance indices appear to track changes in PRx and hemodynamics that affect CA. TOBI might be a suitable less invasive PRx-surrogate to monitor and assess autoregulation.

Disclaimer:

This study is supported by a Department of Defense grant award W81XWH-18-1-0005. MHT and KRW are Co-inventors of the technology. A Provisional patent application (62/506,971) Submitted May 16, 2017.

Learning Objectives:

- 1- Describe Dynamic relationship between cerebrovascular autoregulation, cerebral perfusion pressure and cerebral blood flow.
- 2- Describe new and novel impedance indices to assess cerebrovascular autoregulation.
- 3- Describe ocular brain impedance changes during Interventions that manipulate levels of cerebral perfusion pressure, cerebral blood flow, and intracranial pressure.

Automated Optic Nerve Sheath Diameter Measurement Using Super-pixel Analysis*

Reza Soroushmehr, Krishna Rajajee, Craig Williamson, Jonathan Gryak,
Kayvan Najarian, Kevin Ward, Mohamad H. Tiba

Abstract— The optic nerve is a part of the central nervous system surrounded by cerebrospinal fluid and is encased in a sheath. Changes to the cerebrospinal fluid due to injury, tumor rupture and so on can increase intracranial pressure (ICP) and can result in changes in the sheath diameter. Measuring the changes in the sheath can be done through ultrasound imaging with which the optic nerve sheath diameter can be measured. Since this approach is non-invasive, it would reduce the cost for patients and healthcare if sheath diameter could be used as a predictor of increase in ICP. However, the manual measurement of the nerve sheath diameter is very time consuming and could be affected by human errors. In this paper we propose an image processing approach in which the optic nerve sheath diameter is measured automatically. In our proposed method, we first denoise images and then detect the region of interest using a simple line integral method. After that by analyzing super-pixels we measure the diameter. We compared the results of the proposed method with manual measurements from two experts and achieved the average percentage of error of 5.48%.

I. INTRODUCTION

The optic nerve sheath is an anatomical extension of the duramater, the outermost and most substantial meningeal layer of central nervous system, and the subarachnoid space around the optic nerve is continuous with the intracranial subarachnoid space and is surrounded by cerebrospinal fluid (CSF) [1-3]. The diameter of this sheath changes rapidly with changes in CSF pressure that can result from or result in brain injury [1]. The CSF pressure can increase the intracranial pressure (ICP) whose elevation degree and duration are correlated with patients' outcomes [4]. Therefore, ICP monitoring can provide important information for patients' management and treatment and hence can improve the mortality and morbidity rates of patients with brain injuries. This is also a standard tool for management of brain injured patients. However, as an invasive monitoring device, ICP monitoring can cause complications such as intracranial haemorrhage, dislocation, breakage of the fiberoptic cable and monitor-related infection [5]. Moreover, direct measurement of ICP, especially for patients with minor brain injury, is an unrealistic and aggressive requirement [6]. Therefore, the objective of some clinical trials and research studies is to replace the ICP monitoring with a non-invasive measurement [7-9]. Since it has been shown that ventriculostomy measurements of intracranial pressure are correlated with

ultrasound (US) optic nerve sheath diameter (ONSD) measurements, ONSD can be used as a non-invasive test for elevated ICP [6]. However, manual measurement of ONSD is tedious, time-consuming, and subject to human errors. Therefore, an automated measurement method not only can avoid many possible errors, but it can also make a large clinical study that requires the measurement, feasible. In order to measure the diameter automatically, we first need to segment the ultrasound images. A number of methods have been proposed for ultrasound image segmentation [10-12]. Nobel and Boukerroui [10] review ultrasound image segmentation methods developed for applications such as left ventricle segmentation, breast cancer, prostate cancer, obstetrics and gynecology and vascular disease. They also review state-of-the-art ultrasound segmentation techniques in terms of methodology. They refer to the techniques used for segmentation where they use different information such as image features (e.g. gray level distribution, intensity gradient, phase and texture), shape and temporal prior for those containing image sequences. In our proposed method we also use the temporal information and calculate the diameter in all the images in the video sequence and then we vote among all the measurements to reduce the measurement's error. Liu *et al.* [11] refer to some challenges facing the ultrasound image segmentation such as low signal to noise ratio (SNR), low contrast and blurry boundaries and propose an active contour model based on the level set method to segment breast ultrasound images. They propose an energy function based on level set approach using differences between the estimated and the actual probability densities of different regions' intensities. The minimum of the function is calculated using partial differential equation and is used for segmenting the images. In our method we use a denoising method to increase the SNR. In a recent research study, Xu *et al.* [12] propose an ultrasound image processing method for breast tumor segmentation. They used images from 21 subjects where they have 250 slices for each subject to train and test a convolutional neural network (CNN). They use an 8-layer CNN which has 3 convolutional layers, 3 pooling layers, one fully connected (FC) layer, and a softmax layer and achieve accuracy, precision and recall above 80%. In our research study, the consecutive images in a sequence are very correlated/similar to each other and the number of subjects is small. Therefore, we use traditional image processing techniques to calculate the diameter instead

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R. Soroushmehr and J. Gryak and K. Najarian are with the Department of Computational Medicine and Bioinformatics and also the Michigan Center for Integrative Research in Critical Care (MCIRCC), University of Michigan, Ann Arbor, MI, 48109, U.S.A.

M.H. Tiba and K. Ward are with the Emergency Medicine Department and also the Michigan Center for Integrative Research in Critical Care (MCIRCC), University of Michigan, Ann Arbor, MI, 48109, U.S.A.

K. Rajajee, C. Williamson are with the Department of Neurological surgery and Neurology and also the Michigan Center for Integrative Research in Critical Care (MCIRCC), University of Michigan, Ann Arbor, MI, 48109, U.S.A.

of using convolutional neural networks. The rest of the paper is organized as follows. In Section II, we describe the details of the method which includes preprocessing (denoising the images and finding the region of interest), segmenting images using a super-pixel approach, calculating the diameter in each image and voting among all the measurements. In Section III, we show the experimental setup and present the results of the proposed method and compare the results with ground truth. Finally, in Section IV we conclude the paper.

II. PROPOSED METHOD

The goal of this study is to develop an automated method using image processing techniques to measure the optic nerve sheath diameter from ultrasound images. This diameter is measured 3mm behind the globe as shown in Figure 1.

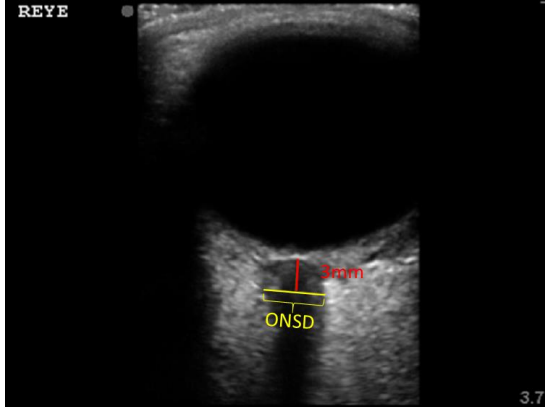


Figure 1: An ultrasound image with the optic nerve sheath diameter (ONSD)

The schematic diagram of the proposed method is shown in Figure 2.

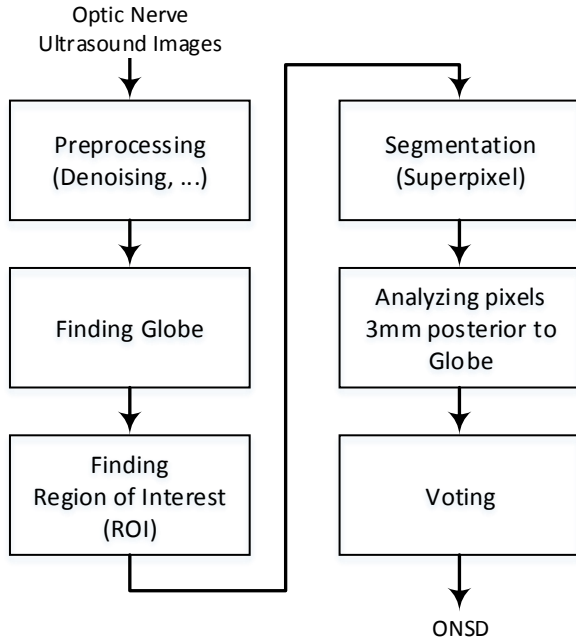


Fig.2: Schematic diagram of the proposed method

In the first stage of the proposed method, we perform preprocessing in which we crop images using Digital Imaging

and Communications in Medicine (DICOM) attributes that specify the location of the entire scan containing the nerve sheath and the retinal detachment. We also denoise images using a technique called image guided filtering [13] which is an edge-preserving method. In the following we briefly describe this method.

Suppose that the filtering input image and guidance image are shown as P and I respectively. The images are divided to overlapped windows with radius of r and following coefficients are computed in each window:

$$\begin{aligned} a_k &= \frac{cov_k(I, P)}{var_k(I) + \varepsilon} \\ b_k &= \bar{p}_k - a_k \bar{I}_k \end{aligned} \quad (1)$$

where k is the window index, $\bar{I}_k$ and $\bar{p}_k$ are average of intensities in k^{th} window in noisy and guidance images respectively. Also ε is called regularization parameter that determines the edge-preserving property of the filter. The filtered pixel q_i is the average of $a_k I_i + b_k$ in all the windows that cover q_i . cov and var functions compute the covariance and variance respectively

After denoising images, we find the region of interest (ROI) which only contains the nerve sheath by analyzing the image integral. This is done through calculating the summation of pixel values in each column and each row separately. Suppose that the denoised image is an $N \times M$ image shown as I_d . We analyze the following one dimensional signals.

$$v(n) = \sum_{m=1}^M I_d(n, m) \quad \text{for } n = 1, \dots, N \quad (2)$$

$$h(m) = \sum_{n=1}^N I_d(n, m) \quad \text{for } m = 1, \dots, M \quad (3)$$

The v signal (i.e. the yellow curve in Fig. 3 which is a result of vertical line/column integral) has two main peaks, Max_1 and Max_2 , corresponding to the brighter regions and a local minimum between these peaks corresponding to the dark region inside the sheaths.

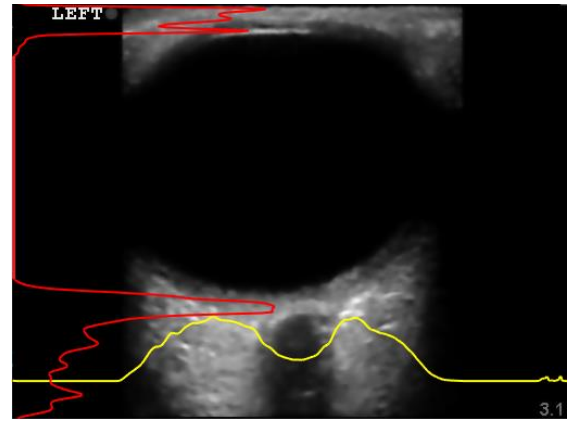


Figure 3: Vertical line and horizontal line integrals for finding the globe point and the region of interest (ROI)

The h signal (i.e. the red curve in Fig.3 resulting from horizontal line/row integral) is used to identify the globe point. In this figure, the v and h signals are superimposed on the image. We use the peaks of v to identify the borders of the ROI.

Suppose that the minimum of the v signal is g th element of the signal. This value corresponds to the column where we can find the globe.

$$g = \underset{Max_1 \leq i \leq Max_2}{argmin} v(i) \quad (4)$$

After finding the globe point and the ROI, we use a super-pixel segmentation technique called simple linear iterative clustering (SLIC) [14] to segment each image to super-pixels. This method partitions an image to homogenous regions based on spatially localized k -means clustering technique. The image is first partitioned to non-overlapped blocks/tiles and the center of each tile is used as an initial parameter for clustering. After that the center of each tile is refined and also its shape is modified in an iterative process using Lloyd algorithm [15]. The modified shape is called super-pixel. Finally, in a post processing stage super-pixels are analyzed in terms of their areas and small ones are excluded from the results.

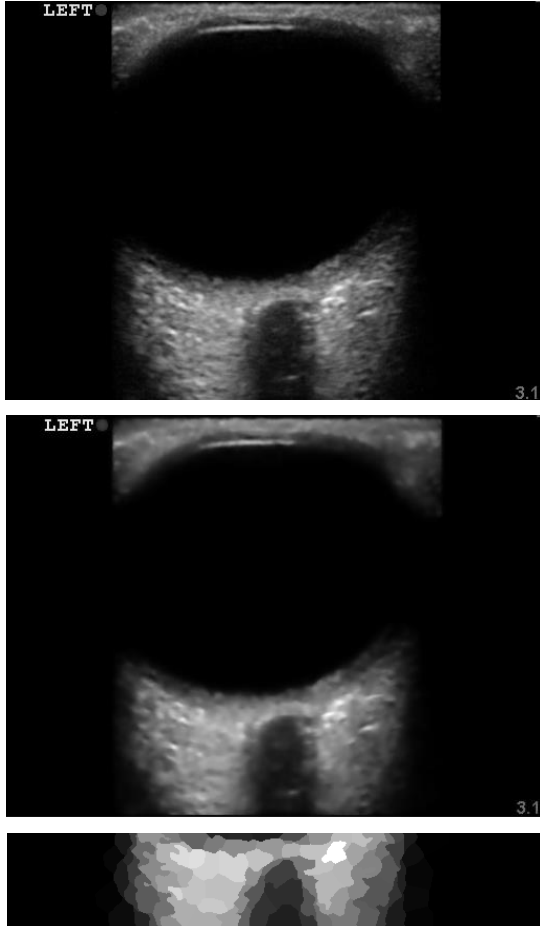


Fig. 4: The top image is the raw image, the middle image is the denoised image and the bottom image is the result of the SLIC algorithm on ROI.

Suppose that the output of this method is called I_s and the row which is 3mm below the globe is r_{3mm} th row of I_s . It should be mentioned that as the size of each pixel can be extracted from DICOM metadata, we can easily find the row which is 3mm below the globe. We analyze the peaks and also derivatives of this row to calculate the ONSD. As can be seen in figure 5, the minimum super-pixel value is at the globe point. As the derivative is calculated by subtracting each value from the previous one, we find the positive peaks after the globe point and negative peaks before the globe point from the derivate curve to find the border of nerve sheath and hence to calculate the diameter (i.e. ONSD).

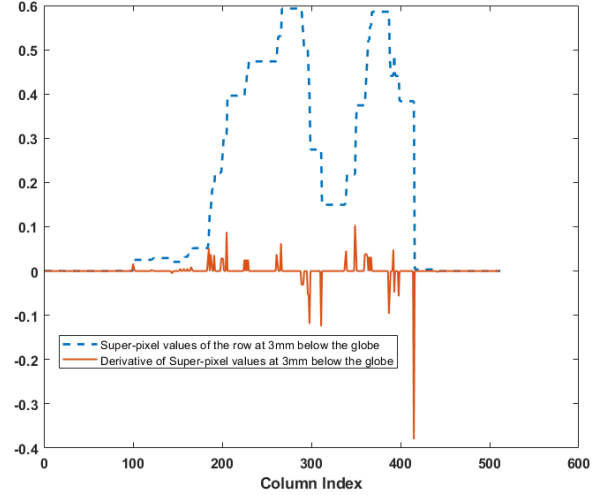


Fig. 5: Superpixel values of the r_{3mm} th row below the globe and also the derivatives of that row in one of the ultrasound images.

We repeat this process for all the images in the ultrasound video and then we vote among all the values by calculating their median.

III. EXPERIMENTAL RESULTS

We implemented our proposed method in MATLAB 2018b and applied it on 50 de-identified videos of 25 traumatic injured patients. These patients were admitted to the University of Michigan health system and for each patient we have ultrasound images of both eyes. We compared the results of the proposed method with ground truth measurements which are measurements from two experts. We also calculated the correlation between two experts' measurements. It should be noted that the individuals performing the manual measurements were blinded to each other's measurements as well as the algorithm measurement. We calculated the average error between the proposed method and the ground truth using Eq. (5).

$$e = \frac{1}{n_u} \sum_{k=1}^{n_u} \left| 1 - \frac{ONSD_1(k)}{ONSD_2(k)} \right| \times 100 \quad (5)$$

In (5), n_u is the number of ultrasound images. Also, $ONSD_1$ and $ONSD_2$ are the ONSD measurements from two sources. For instance, for comparing the results of the proposed method with the ground truth, $ONSD_1$ and $ONSD_2$ are the algorithm results and the average of two experts' measurements respectively. Moreover, for comparing two experts' measurement, $ONSD_1$ and $ONSD_2$ are the

measurements from each expert. The average percentage of error between the results of the algorithm and the average manual measurements is 5.49%. This error is 4.8% for two experts' measurements. The difference between these two errors show that the proposed algorithm can calculate the ONSD accurately. We also calculated the mean square error using Eq (6) where $\|\cdot\|_2$ is the norm-2.

$$MSE = \frac{1}{n_u} \|ONSD_1 - ONSD_2\|_2 \quad (6)$$

The MSE between the algorithm results and the average of two experts' measurements is 0.0018 while the MSE between two experts' measurement is 0.0016. Moreover, we calculated intraclass correlation coefficient (ICC) which shows the similarity between two quantitative measurements [16]. The ICC between the algorithm results and the average between two experts' measurements is 0.70 while the ICC between two experts' measurement is 0.87. These comparisons indicate strong correlation between the proposed method's results and the ground truth.

IV. CONCLUSION

Even though intracranial-pressure monitoring is a standard care for severe traumatic injured patients, using such invasive devices might be associated with worsening of survival and there might be complications following the placement of ICP sensors. Therefore, a non-invasive monitoring can prevent secondary complications. It has been shown that there is a correlation between the ICP elevation and the optic nerve sheath diameter. In this paper, we proposed an automated method to calculate this diameter using image processing techniques. We first denoised images and identified the region of interest using a simple method and then applied a super-pixel segmentation method. After that we analyzed the row which is 3mm below the globe to measure the diameter of the nerve sheath. This was done by performing derivative of that row and finding its peaks. We compared the results of the proposed method with the average of two experts' measurements and achieved the percentage error of 5.49%, mean square error of 0.0018 and ICC of 0.70 while these values between two experts' measurements were 4.6% and 0.0016 and 0.87 respectively. In our future studies we will run the method on more videos and also calculate the correlation between the ONSD and the elevated ICP.

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Novel Algorithm for Automated Optic Nerve Sheath Diameter Measurement Using a Clustering Approach

Venkatakrishna Rajajee, MBBS^{*,†,¶}; Reza Soroushmehr, PhD^{‡,¶}; Craig A. Williamson, MD, MS^{*,†,¶}; Kayvan Najarian, PhD^{‡,§,¶}; Jonathan Gryak, PhD^{‡,¶}; Abdelrahman Awad, MD^{§,¶}; LTC Kevin R. Ward, USAR, MC^{§,¶}; Mohamad H. Tiba, MD, MS^{§,¶}

ABSTRACT

Introduction:

Using ultrasound to measure optic nerve sheath diameter (ONSD) has been shown to be a useful modality to detect elevated intracranial pressure. However, manual assessment of ONSD by a human operator is cumbersome and prone to human errors. We aimed to develop and test an automated algorithm for ONSD measurement using ultrasound images and compare it to measurements performed by physicians.

Materials and Methods:

Patients were recruited from the Neurological Intensive Care Unit. Ultrasound images of the optic nerve sheath from both eyes were obtained using an ultrasound unit with an ocular preset. Images were processed by two attending physicians to calculate ONSD manually. The images were processed as well using a novel computerized algorithm that automatically analyzes ultrasound images and calculates ONSD. Algorithm-measured ONSD was compared with manually measured ONSD using multiple statistical measures.

Results:

Forty-four patients with an average/Standard Deviation (SD) intracranial pressure of 14 (9.7) mmHg were recruited and tested (with a range between 1 and 57 mmHg). A t-test showed no statistical difference between the ONSD from left and right eyes ($P > 0.05$). Furthermore, a paired t-test showed no significant difference between the manually and algorithm-measured ONSD with a mean difference (SD) of 0.012 (0.046) cm ($P > 0.05$) and percentage error of difference of 6.43% ($P = 0.15$). Agreement between the two operators was highly correlated (interclass correlation coefficient = 0.8, $P = 0.26$). Bland–Altman analysis revealed mean difference (SD) of 0.012 (0.046) ($P = 0.303$) and limits of agreement between -0.1 and 0.08 . Receiver Operator Curve analysis yielded an area under the curve of 0.965 ($P < 0.0001$) with high sensitivity and specificity.

Conclusion:

The automated image-analysis algorithm calculates ONSD reliably and with high precision when compared to measurements obtained by expert physicians. The algorithm may have a role in computer-aided decision support systems in acute brain injury.

The ability to monitor and manage intracranial pressure (ICP) is critical for the effective management of patients with

traumatic brain injury (TBI).¹ An ICP above 20 mmHg associated with a 3-fold higher risk of a neurologic deterioration in TBI.² The guidelines of the Brain Trauma Foundation recommend the use of invasive ICP monitoring in severe TBI, defined by a Glasgow Coma Scale < 9 .³ The use of ICP monitoring in severe TBI may be associated with a significant reduction in mortality in civilian centers.^{4,5} Furthermore, several studies have also demonstrated that military personnel with combat-related TBI who receive early aggressive intervention, including timely decompressive surgery in the setting of intracranial hypertension, can in fact have good outcomes.⁶⁻⁹ Current ICP monitoring modalities require invasive techniques that carry the risk of complications such as intracranial hemorrhage, dislocation, breakage of the fiber-optic cable, and device-associated infection^{10,11} Furthermore, the use of such techniques requires a high level of skill found only in specialized centers and thus significantly limit the ability to provide early precision interventions to victims of TBI.

Ultrasonographic measurement of the optic nerve sheath diameter (ONSD) is emerging as an effective non-invasive technique to assess ICP.^{12,13} The optic nerve sheath (ONS)

*Department of Neurological Surgery, University of Michigan, Ann Arbor, MI 48109-5338, USA

†Department of Neurology, University of Michigan, Ann Arbor, MI 48109-5316, USA

‡Department of Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, MI 48109-2218, USA

§Department of Emergency Medicine, University of Michigan, Ann Arbor, MI 48109-2800, USA

¶Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI 48109-2099, USA

¶Michigan Center for Integrative Research in Critical Care (MCIRCC), Ann Arbor, MI 48109-2800, USA

Presented as a poster at the 2019 Military Health System Research Symposium, Kissimmee, FL; MHSRS-19-01121.

The views expressed in this paper are those of the authors and do not necessarily represent the official position or policy of the U.S. Government, the Department of Defense.

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is a continuation of the brain's dura mater, whereas the subarachnoid space around the optic nerve is continuous with the intracranial subarachnoid space. Characteristics of the ONS, as well as blood flow to the eye, are known to be affected by changes in ICP and cerebral blood flow, potentially allowing the eye to serve as a window into the brain.¹²⁻¹⁴ Studies have shown that an increase in ICP results in distension of the retrobulbar ONS within seconds.¹⁵ We have shown previously that measurement of ONSD using ocular sonography is an accurate, noninvasive technique for the detection of intracranial hypertension when performed by an experienced operator with high sensitivity and specificity.^{14,16} However, manual calculation of ONSD is time-consuming, and subject to human errors leading to high variability in the measurement. The significant variation seen in the optimal ONSD threshold for identification of high ICP across several studies greatly limits the practical application of this technique at the bedside.¹² Much of this variation in the optimal ONSD threshold is likely related to technique, with variation in the margins used to define the ONS on acquired ultrasound images resulting from different operators.

In this paper, we present the results of ONSD measurements obtained by developing a novel computer image-analysis algorithm using image-processing techniques to automatically measure the ONSD from ultrasound images. Such an algorithm is envisioned to standardize measurement of the ONSD and to minimize operator-dependent variability. We hypothesize that algorithm-measured ONSD will be an effective technique to replace manually measured ONSD.

METHODS

This research has been conducted under approval of the University of Michigan Institutional Review Board. Patients or their legally authorized representatives were consented for the study. Forty-four patients were recruited and tested from the neurologic intensive care unit. The average (*standard deviation* [SD]) age was 49 (16) years and weight was

85 (26) kg. Twenty of the patients had subarachnoid hemorrhage or other spontaneous intracranial hemorrhage as their primary diagnosis, five patients had TBI, four had hydrocephalus, nine had brain tumors, and five had other neurologic conditions requiring intensive care. Thirty-nine of the patients had an external ventricular drain, and five had an intraparenchymal probe for the invasive measurement of ICP.

Measurement of Optic Nerve Sheath Diameter

The sonographic measurements of ONSD were performed by a board-certified neurointensivist with training to perform and obtain the ultrasound images. Sonographic images were obtained using an M-Turbo Edge ultrasound unit and an L25 linear 13-6 MHz array transducer probe (SonoSite Inc., Bothell, WA, USA). Axial still images and videos were obtained from each eye using the following procedures. The ultrasound probe was positioned on the eyelid to obtain an image where the entirety of the globe and at least 2 cm of the ONS behind the globe are visible. Depth and then gain were adjusted as necessary to obtain the optimal image (Fig. 1A) with confirmation that the ONS is clearly visible on both sides of the optic nerve and that the margins of the ONS are clearly demarcated on both sides. Ten seconds of video were recorded. Next, a magnified image of the posterior globe and at least 2 cm of the optic nerve were obtained (Fig. 1B). Using calipers, the ONSD was measured at 3 mm into the optic nerve. Measurements were performed on both eyes. The manual assessment of ONSD was performed by two expert attending physicians. Both were blinded to the ICP values and each other's ONSD values.

Automated ONSD Measurement

This automated process utilizes multiple image-processing techniques, including denoising, region of interest detection by line integral calculation, and image segmentation by employing a clustering approach,¹⁷ to separate out components of interest (Fig. 2A and B). Using B-mode ultrasound images obtained by the attending physician, the novel

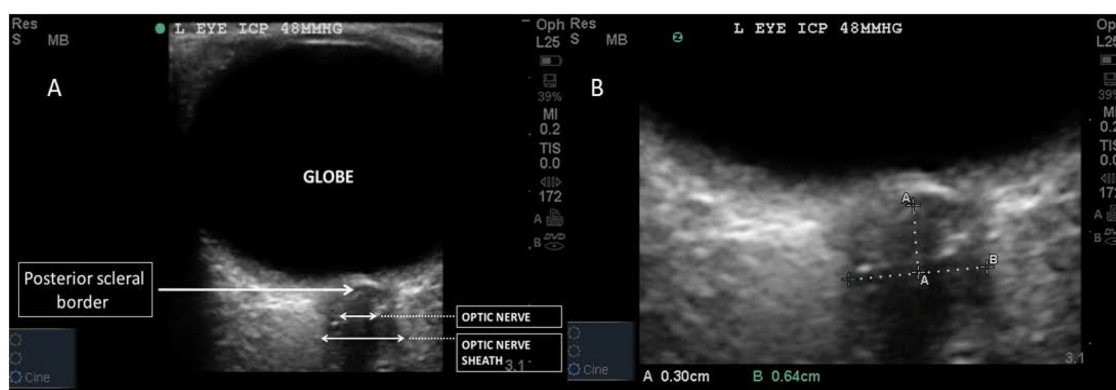


FIGURE 1. (A) Ultrasound image of globe, optic nerve, and optic nerve sheath. (B) Magnified image. Caliper A demarcates a point 3 mm behind the posterior scleral border and Caliper B measures the optic nerve sheath diameter.

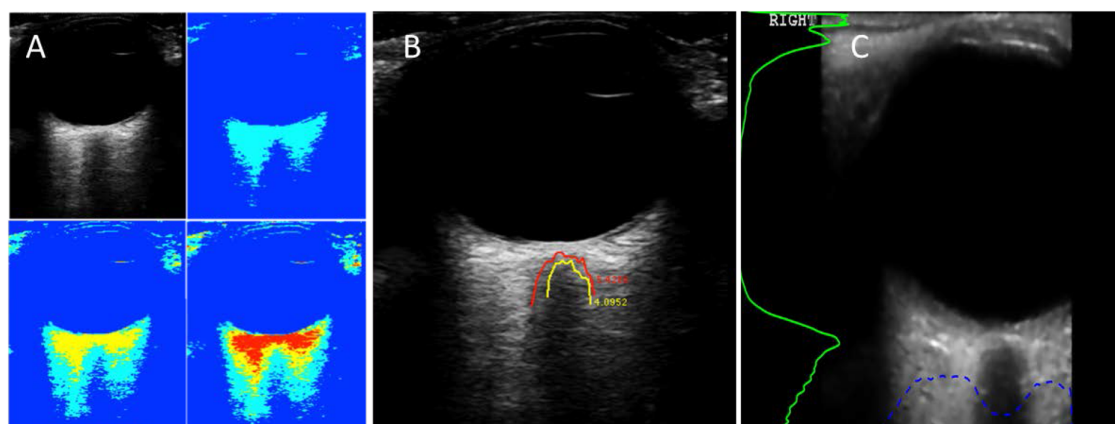


FIGURE 2. Multiple threshold image segmentation of optic nerve ultrasound (ONUS) Image. (A) ONUS image separated by multiple thresholds until the ONS region of interest (ROI) is isolated. (B) Inner and outer diameter of the ONS found in the ROI. (C) Vertical line integral (dashed blue line) and horizontal line integral (solid green line) for finding the globe point and the ROI.

algorithm first denoises images using a technique called image guided filtering,¹⁸ after which the region of interest (Fig. 2C)¹⁹ containing only the nerve sheath is found by analyzing the image integral. The algorithm then separates the ONS from both surrounding tissue and the optic nerve itself, allowing for the inner and outer ONSD to be quantitatively assessed. With a single optic nerve ultrasound sweep through the eye, the maximum diameter can be found through a combination of independent edge detection in both axial and lateral directions. After performing the pre-processing, images are segmented using a clustering approach that combines neighboring pixels based on their intensities. The results of the clustered images are then used to calculate the derivative at 3 mm below the globe point. The globe point was also calculated based on the line integral analysis. The derivative values were used to find the edges and measure the ONSD. ONSD calculations were repeated on all images for each patient from which the median of the measurements was obtained. All of these steps were performed automatically.

Statistical Methodology

Descriptive statistics are presented as average and SD. Algorithm-measured ONSD was compared with manually measured ONSD by the two clinician experts. Interclass correlation coefficient was assessed for agreement between the two operators manually assessed ONSD. Pearson correlation and the correlation coefficient were used to allow for visual inspection across a range of values of algorithm and manual ONSD. Percentage error difference between the readings of two operators as well as the algorithm and manual ONSD were calculated. Tukey mean-difference plot (Bland–Altman plot) was used to assess agreement between the two, algorithm and manual ONSD. Limits of agreement were calculated with standard errors and 95% confidence intervals. Percentage of error between the results (operators and manual vs. algorithm), receiver operator curve (ROC), and area

under the curve (AUC) were used to assess algorithm's predictive performance. Statistical analysis was performed using MATLAB 2018b and GraphPad Prism 8.

RESULTS

Manual and algorithm ONSD measurements were obtained from 88 ultrasound video images (44 from the left and 44 from the right eyes). The average (SD) ICP from all patients was 14 (9.7) mmHg with a range between 1 and 57 mmHg. The average (SD) for manual ONSD from the left and right eyes was 0.64 (0.07) cm and 0.62 (0.067) cm, respectively. A t-test showed no statistical difference between the left and right eyes ($P > 0.05$). Furthermore, average (SD) combined (left and right eyes) manual and algorithm ONSD was 0.63 (0.067) and 0.64 (0.055) cm, respectively. A paired t-test showed no significant difference between the two measurements (manual and algorithm) with a mean difference (SD) of 0.012 (0.046) mm ($P > 0.5$) and percentage error of difference of 6.43% ($P = 0.15$). In addition, the two measurements were highly correlated ($r = 0.734$, $P < 0.0001$) (Fig. 3A). Agreement between the two operators for the manual reading was highly correlated with an interclass correlation coefficient of 0.8 ($P = 0.26$) and a percentage error of 4.74% ($P = 0.26$). A Bland–Altman analysis revealed mean difference (SD) 0.012 (0.046) ($P = 0.303$) and limits of agreement between -0.1 and 0.08 (Fig. 3B). The ROC analysis yielded an AUC of 0.965 ($P < 0.0001$) at an ONSD threshold of 0.56 mm with 0.86 and 1.0 sensitivity and specificity, respectively (Fig. 4).

DISCUSSION

Several recent studies have been conducted with promising results demonstrating the predictive value of ultrasonographic-assessed ONSD when compared to invasive measurement of ICP as well as its ability to identify the presence of elevated ICP in the setting of brain injury.^{12,13,20–22} The clinical utility of ONSD will lie in its use as a standalone device or as an additional diagnostic tool to alert for the

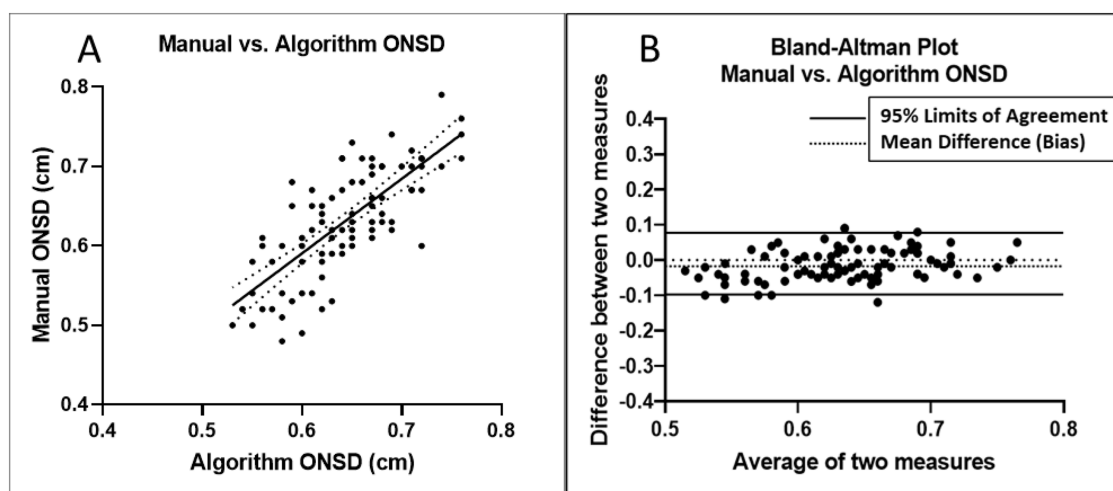


FIGURE 3. (A) Regression of algorithm vs. manual optic nerve sheath diameter (ONSD) measurements. (B) Bland–Altman plot of algorithm vs. manual ONSD measurements.

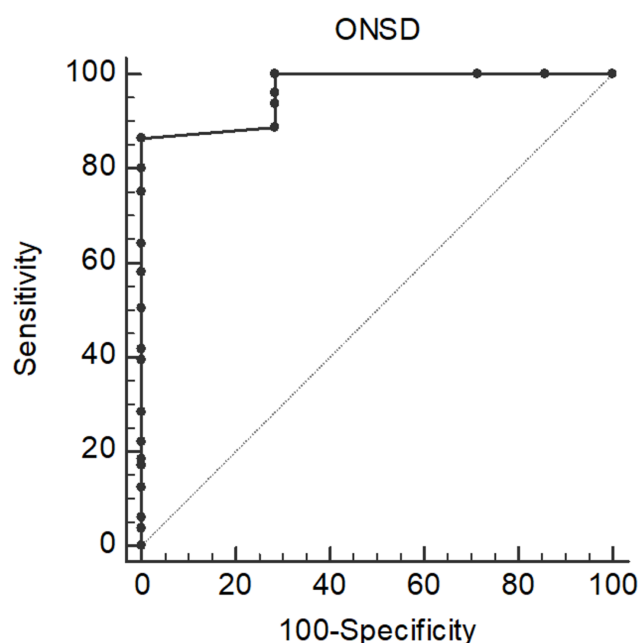


FIGURE 4. Receiver operator curve for the algorithm-measured optic nerve sheath diameter.

presence of elevated ICP, whenever invasive ICP is contraindicated or is not available.²²

Our previous studies comparing ONSD measurements to simultaneous invasive ICP measurements in a cohort of neurosurgical intensive care unit patients with TBI have demonstrated high predictive power of ONSD and identified an ONSD cutoff of >0.51 cm with high sensitivity and specificity, especially for the detection of ICP >25 mmHg.¹⁴ In addition, we have also demonstrated the feasibility of using ONSD to assess ICP in a resource-limited setting where invasive gold-standard monitoring was unavailable.²³ However, several studies have shown significant variation in the optimal ONSD threshold for the detection of high ICP (from 0.52

to 0.57 cm),^{12,13,21,24} which might limit the practical application of this technique at the bedside. Much of this variation in the optimal ONSD threshold is likely related to technique, with variation in the margins used to define the ONS on ultrasound images acquired by different operators. The ONS, visible as a linear, hypodense structure behind the eye can vary in its visualized dimension based on the angle and plane of insonation. Therefore, the development of a computer image analysis algorithm might lead to standardization of measurement of the ONSD and minimize operator-dependent variability. We have used our data to develop an automated image analysis and an algorithm to quantify changes in ONSD. The algorithm utilizes multiple image-processing techniques to separate out ONS from surrounding tissue and the optic nerve itself, allowing for the inner and outer ONSD to be quantitatively assessed.

A number of methods have been proposed for ultrasound image segmentation. Noble *et al.*²⁵ have reviewed ultrasound image segmentation methods developed for applications such as left ventricle segmentation, breast cancer, prostate cancer, obstetrics and gynecology, and vascular disease. They also reviewed state-of-the-art ultrasound segmentation techniques in terms of methodology. They refer to the techniques used for segmentation where they use different information such as image features (e.g., gray level distribution, intensity gradient, phase and texture), shape and temporal prior for those containing image sequences. In this study, we have utilized the methods described by Noble *et al.* (such as the temporal information) to calculate ONSD. In addition, we have used traditional image-processing techniques to calculate the diameter instead of using convolutional neural networks to reduce noise. Our results demonstrate that a computerized algorithm to process ultrasound images could be an appropriate methodology allowing for reliable assessment of ONSD removing the measurement error and uncertainty that comes from an operator's manual measurement. A robust methodology to

noninvasively monitor and assess ICP would allow for early application by healthcare providers and allow for precision management of severe TBI patients, providing optimal and personalized cerebral health management.

This study has several limitations. First, the ONSD measurements were done only once on each patient without a follow-up measurement to track changes over time. In addition, patients' ICPs were within the allowed range as dictated by the management plan. Second, some of the images suffered from challenges such as low signal-to-noise ratio, low contrast, and blurry boundaries. This was overcome by using image denoising and median calculation of ONSD measurements. Lastly, data were collected from 44 patients only, and may be underpowered to detect differences. Additional testing is warranted to further validate the technology. Of note is that the need to obtain an ultrasound image first to be analyzed by the algorithm might seem to pose a limitation. However, we believe that with the widespread use of ultrasound, miniaturization of imaging units, and the availability of training programs, this might be envisioned to be a minor or a non-issue.²⁶ If this technology is adapted into practice and put to use by first responders, an accelerated training program can be initiated.

CONCLUSION

This fully automated technique is a reliable method to process ultrasound images and measure ONSD. It performs with high precision when compared to ONSD as measured by expert operators. This noninvasive assessment of ONSD may allow for a standardized prediction of ICP and improve management and informed decision-making during the early care of brain injury. More studies are warranted to allow for a validation of the technology at earlier stages of neurologic injury and wider ranges of ICP.

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CONFLICT OF INTEREST

A provisional patent application "Automated Optic Nerve Sheath Diameter Measurement" was filed on July 23, 2019, and assigned Serial No. 62/877,539. VR, RS, KN, JG, KRW, and MHT are authors on this patent application.

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Trans-ocular brain impedance index for assessment of cerebral autoregulation in a porcine model of cerebral hemodynamic perturbation

Mohamad H. Tiba^{1,6} · Brendan M. McCracken^{1,6} · Danielle C. Leander^{1,6} · Carmen I. Colmenero^{1,6} · Brandon C. Cummings^{1,6} · Nicholas L. Greer^{1,6} · Paul Picton⁵ · Craig A. Williamson^{3,4,6} · Kevin R. Ward^{1,2,6}

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Abstract

Cerebrovascular autoregulation (CA) is often impaired following traumatic brain injury. Established technologies and metrics used to assess CA are invasive and conducive for measurement, but not for continuous monitoring. We developed a trans-ocular brain impedance (TOBI) method that may provide non-invasive and continuous indices to assess CA. In this study, we monitored impedance metrics such as respiratory-induced impedance amplitude changes (dz) as well as a novel impedance index (DZx), which is a moving Pearson correlation between mean arterial pressure (MAP) and dz . Yorkshire swine were instrumented to continuously record ICP, MAP, and cerebral blood flow (CBF). TOBI was recorded by placement of standard ECG electrodes on closed eyelids and connected to a data acquisition system. MAP, ICP and CBF were manipulated utilizing an intravenous vasopressor challenge. TOBI indices (dz and DZx) were compared to the hemodynamic indicators as well as pressure reactivity index (PRx). During the vasopressor challenge, dz was highly correlated with ICP, CPP, and CBF ($r = -0.49$, $p < 0.0001$). ICP, CPP, and CBF had a mean percent increase (standard deviation) from baseline of 29(23.2)%, 70(25)%, and 37(72.6)% respectively while dz decreased by 31(15.6)%. Receiver operator curve test showed high predictive performance of DZx when compared to PRx with area under the curve above 0.86, with high sensitivity and specificity. Impedance indices appear to track changes in PRx and hemodynamics that affect cerebral autoregulation. TOBI may be a suitable less invasive surrogate to PRx and capable of tracking cerebral autoregulation.

Keywords Cerebral autoregulation · Bioimpedance · Pressure reactivity index · Traumatic brain injury

✉ Mohamad H. Tiba
tibam@med.umich.edu

Brendan M. McCracken
bmccrac@med.umich.edu

Danielle C. Leander
danlean@umich.edu

Carmen I. Colmenero
cico@med.umich.edu

Brandon C. Cummings
cummingb@med.umich.edu

Nicholas L. Greer
nlgreer@med.umich.edu

Paul Picton
ppicton@med.umich.edu

Craig A. Williamson
craigaw@med.umich.edu

Kevin R. Ward
keward@med.umich.edu

¹ Department of Emergency Medicine, University of Michigan, 2800 Plymouth Road, Ann Arbor, MI 26-323N48109, USA

² Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI, USA

³ Department of Neurological Surgery, University of Michigan, Ann Arbor, MI, USA

⁴ Department of Neurology, University of Michigan, Ann Arbor, MI, USA

⁵ Department of Anesthesiology, University of Michigan, Ann Arbor, MI, USA

⁶ Michigan Center for Integrative Research in Critical Care (MCIRCC), University of Michigan, Ann Arbor, MI, USA

1 Introduction

Cerebrovascular autoregulation (CA) is a complex process and is considered one of the most important central nervous system auto-protective mechanisms against secondary brain injury after traumatic brain injury (TBI) [1]. CA is described as the ability of vessels to modulate their tone in response to changes in cerebral perfusion pressure and in so doing, maintain constant levels of cerebral blood flow (CBF) to match metabolic demand [2, 3]. It is often impaired after injury [4–6] and has been shown to be a significant predictor of outcome in patients with various acute neurological diseases, including severe TBI-related and ischemic stroke [7–9]. In addition, continuous monitoring of autoregulation is envisioned to be potentially beneficial as a means to personalize optimization of CPP on a patient-by-patient basis [10, 11]. The Brain Trauma Foundation currently does not recommend CA monitoring but it does recommend CPP-monitoring during the management of severe TBI (level IIb) [12].

Direct and indirect assessment of CA has proven to be difficult. In addition to standard physical examination and clinical judgment, approaches and methods such as transcranial-Doppler [13], brain tissue oxygenation [14], near-infrared spectroscopy measured hemoglobin saturation [15], and Laser-Doppler flowmetry of CBF [16] have proposed to evaluate CA non-invasively and continuously however, with mixed results [11]. Such methods hold promise but have several challenges due to the intermittent or invasive nature of the measure, inability to fully measure and track meaningful changes, or the need for a high level of operator experience. There is currently a lack of technology available in far-forward echelons of care for CA monitoring [11].

A newer approach to assess and monitor CA is the computation of the pressure reactivity index (PRx), which simultaneously tracks dynamic changes in mean arterial blood pressure (MAP) and intracranial pressure (ICP) as an indicator of intact or impaired CA after cerebral injury [11]. PRx is calculated as the moving Pearson correlation coefficient between MAP and ICP with positive values indicating impaired autoregulation (pressure-passive behavior of the arterial walls) and negative values indicating intact autoregulation (vascular bed with active vasomotor responses) [17–19]. PRx measurements provide an independent predictor of outcomes after TBI [11, 17–19] and appear reliable for the evaluation of CA. PRx assessment of CA however, is currently limited in its use. The invasive nature of the measurements, the complexity of signal processing, and inherent signal noise have potentially constrained its application to mainly academic institutions that are capable of adequate signal acquisition

and have specialized processing software [17, 20]. For these reasons, its application at early stages of care is problematic.

Here we investigate a novel methodology to assess CA utilizing trans-ocular brain impedance (TOBI). Impedance (dz) is coupled with MAP to continuously calculate an index (DZx) capable of monitoring CA without the need for ICP measurement. TOBI uses alternating current delivered externally through closed eyelids that is capable of penetrating deep into the brain to measure changes in cerebral blood volume (CBV). We have shown previously that respiratory-induced brain bioimpedance changes (dz) track changes in cerebral blood volume (CBV) CBF, ICP, and CPP with high precision [21]. In this study, we use changes in dz to produce the novel DZx parameter and compare its performance with the more established PRx as a metric for the assessment of CA. The inherent relationship between ICP and CBV suggests DZx may be a potential technique to monitor and assess changes in CA similar to PRx. We hypothesized that DZx will track changes in PRx and assess CA with high precision.

2 Materials and methods

2.1 Anesthesia and surgical instrumentation

Twelve male Yorkshire mix swine with a mean (standard deviation) weight of 44(4.2) kg were initially sedated using ketamine/xylazine (20/2 mg kg⁻¹). Anesthesia was induced using 2.5% isoflurane in a fraction of inspired oxygen (FiO₂) of 100% and maintained at 1.5–2.5% isoflurane and an FiO₂ of 30–40%. Animals were intubated using a standard cuffed 7.5 mm endotracheal tube. Core temperature was maintained at 37–38 °C using a warming blanket (Blanketrol®, Cincinnati Sub-Zero, Cincinnati, OH) for the duration of all procedures. Mechanical ventilation was set using volume control with tidal volume at 7–8 mL kg⁻¹ (Draeger FabiusGS Premium, Draeger Inc. Telford, PA). Respiratory rate was adjusted to titrate end-tidal CO₂ (PetCO₂) to 35–45 mmHg (Biopac Data Acquisition System, Biopac Inc. Goleta, CA).

The right common femoral artery was cannulated for continuous arterial pressure measurements. The left and right external jugular veins were cannulated with 9Fr introducers (Arrow International Inc., Reading, PA) using an ultrasound guided Seldinger technique (Mindray M9, Mindray Corp. Mahwah, NJ). The right introducer was used for placement of a triple lumen central venous catheter (Arrow International Inc., Reading, PA) for central venous pressure measurements (CVP), drug delivery, and blood sampling, and the left for administration of fluids. At the conclusion of vessel cannulations, animals were turned to a prone position for the remainder of the experiment. Two, 2–3 mm burr holes were

drilled into the left skull through a small circular skin window. A laser Doppler flow probe TSD144 (Biopac Systems Inc. Goleta, CA) and a 2F solid state pressure catheter SPR-320 Micro-Tip (Millar, Houston, TX) were placed directly into the brain parenchyma (cerebral cortex) through the burr holes for CBF and ICP monitoring respectively.

2.2 Trans-ocular bioimpedance setup and processing

Two disposable silver-silver chloride electrocardiographic (ECG) electrodes, (Positrac RTL, ConMed Corp. Utica, NY) were placed on the closed eyelids and secured by an adhesive tape. The electrodes were connected to a bioimpedance amplifier EBI100C (Biopac Systems Inc.) using shielded leads. A low electrical alternating current (0.1–1 mA at 50 kHz) was introduced through the electrodes, and the potential between the two electrodes was measured. The TOBI signal was passed through a series of digital filters to remove baseline drift and high-frequency noise, then movement artifacts were detected via adaptive thresholding and removed. The respiratory and cardiac components were then isolated via filtering. The amplitude of these components is quantified using a root-mean-square envelope in a frequency-independent manner, meaning that the resulting metrics are largely independent of respiratory and heart rate (Fig. 1). PRx is calculated as the moving Pearson correlation coefficient between MAP and ICP over a five-minute window with a step size of one second, while the bioimpedance index DZx was calculated as the moving Pearson correlation coefficient between MAP and dz over a five-minute window with a step size of one second. However, it is notable that DZx and PRx often move opposite one another due to the inverse relationship between dz and ICP caused by changes in cerebral blood volume. Being calculated as a Pearson

correlation coefficient, both PRx and DZx may have values between -1 and 1 [17].

2.3 Hemodynamic perturbation (vasopressor challenge)

Following instrumentation and baseline sample collection, animals were subjected to maneuvers to manipulate CBF, MAP, ICP and disrupt CA. Norepinephrine solution ($4 \mu\text{g mL}^{-1}$) was prepared by mixing 2 mg norepinephrine in 500 mL of 5% dextrose in 0.9% NaCl saline solution and was administered through an Alaris IVAC 7130B infusion pump (BD company, Franklin Lakes, NJ). The infusion rate was slowly titrated upward to increase blood pressure and reach a MAP of 150 mmHg or greater as well as to produce an increase in ICP which frequently was also associated with a loss of CA. MAP was maintained for 15 to 30 min followed by the titrated reduction or cessation of the infusion and allowing the animal's MAP to return to near baseline. The vasopressor challenge was performed twice. Impedance data as well as all other hemodynamic data described above were recorded continuously using Biopac Data Acquisition System MP150 (Biopac Systems Inc.). MAP, CVP, ICP, CBF, and TOBI were all collected continuously throughout the duration of the experiment using a Biopac MP160 and Acknowledge data acquisition software (Biopac Inc. Goleta, CA).

2.4 Statistical analysis

Continuous data is presented either as mean and standard deviation or as mean and standard error (figures). Pearson correlation was used to test the strength and direction of the relationship between dz and hemodynamic metrics (ICP, CPP, and CBF). Percentage change from baseline for dz and hemodynamic metrics were calculated during the

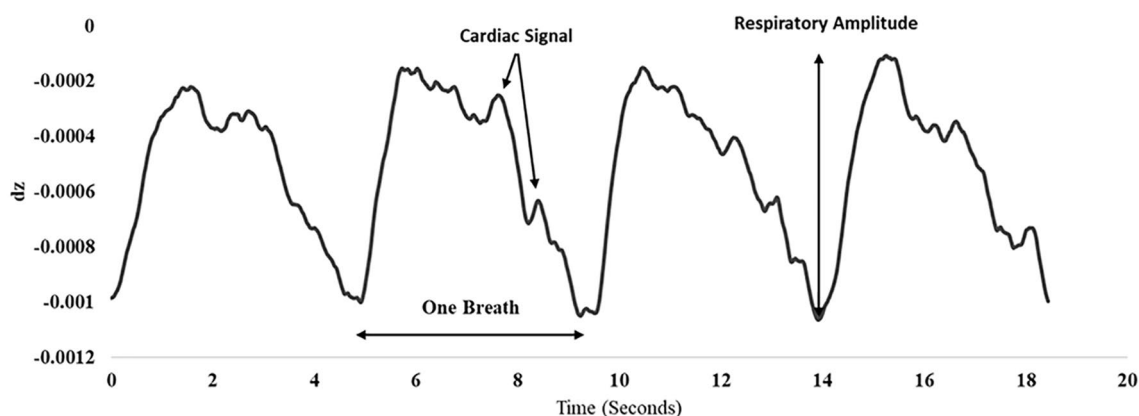


Fig. 1 Respiratory-induced changes in trans-ocular brain impedance. The figure shows four breaths. dz is calculated as respiratory amplitude in the impedance signal

vasopressor challenge. Receiver operator curve (ROC) and area under the curve (AUC) were used to assess the predictive performance of DZx at different thresholds of PRx (> 0 , > 0.10 , > 0.20 , and > 0.30). DeLong Methodology [22] was used for the calculation of the standard error of the AUCs. Binomial exact confidence intervals were calculated for the AUCs. Average value of sensitivity for all possible values of specificity, as well as the average value of specificity for all possible values of sensitivity were calculated. Optimal criterion values of DZx corresponding to the best fit of the coordinates of the ROC curves were calculated. Positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), as well as negative likelihood ratio (NLR) for DZx were calculated. Statistical significance was set at $\alpha = 0.05$, and statistical analyses were performed using MedCalc 19.1.3, GraphPad Prism 8, and MATLAB R2019a.

3 Results

During the vasopressor challenge, MAP, ICP, CPP, and CBF had a mean percent increase (SD) from baseline of 64(22.2)%, 29(23.2)%, 70(25)%, and 37(72.6)% respectively, all of which were statistically significant and considered clinically significant with changes above 15%. Of note is the considerable increase in MAP and CPP over ICP, which can be contributed to the direct systemic effect of norepinephrine on the vasculature whilst the moderate increase in ICP is more related to the increase in cerebral blood volume especially, when these animals lose autoregulation [23, 24]. There was a significant decrease in dz by 31(15.6)

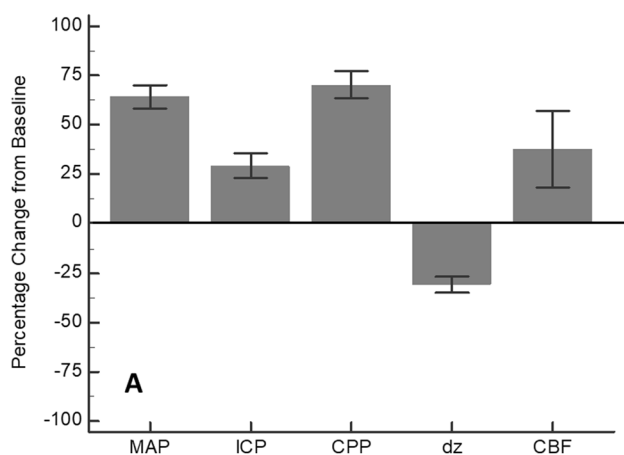


Fig. 2 Percent change from baseline of MAP, ICP, CPP, dz , and CBF during vasopressors challenge. *MAP* mean arterial pressure, *ICP* intracranial pressure, *CPP* cerebral perfusion pressure, *CBF* cerebral blood flow, *dz* impedance respiratory amplitude. Data is presented as means and standard errors

% (Fig. 2) and significant negative correlation between dz and ICP, CPP, and CBF, with across animals' average (SD) correlation coefficients of $-0.64(0.15)$, $-0.57(0.36)$, and $-0.49(0.21)$ ($p < 0.0001$) respectively indicating that impedance decreased with increases in CBV, which is consistent with the conductive properties of blood when compared to other bodily tissues. In addition, there was a significant correlation between CPP and CBF ($r = 0.74$, $p < 0.0001$). Table 1 lists descriptive statistics (minimum, maximum, range as well as 95% confidence intervals) of the mean percent change. Figure 3 provides an example of the longitudinal changes in MAP, ICP, CBF, and dz during the vasopressor challenge. The figure demonstrates increases in MAP, ICP and CBF simultaneous with a decrease in impedance amplitude (dz), as a reflection of increased CBV. Pooled DZx from all animals was highly and inversely correlated to PRx ($r = -0.47$, $p < 0.0001$).

ROC tests demonstrated the predictive performance of DZx when compared to PRx at different PRx thresholds between 0 and 0.3 yielding a high predictive power of DZx with high AUC, sensitivity and specificity. Table 2 lists DZx's AUC, sensitivity, specificity, PPV, NPV, PLR, as well as NLR at their associated PRx thresholds. Figure 4a shows a representative ROC plot at a PRx threshold of 0.10. In addition, the ROC test yielded the highest DZx performance at a criterion between -0.016 and -0.08 (Table 2). Figure 4b shows the best DZx criterion and its associated sensitivity and specificity at the same PRx threshold of 0.10.

4 Discussion

Our study has shown that utilizing a transocular pathway to measure changes in brain impedance might constitute an effective alternative to PRx to assess CA and CPP that does

Table 1 Percent change during vasopressor challenge

Percent change from baseline	MAP	ICP	CPP	dz	CBF
Number of values	14	14	14	14	14
Minimum	36.5	0	43.6	-61	-30.3
Maximum	120.5	68.8	134.4	-10.9	259.6
Range	84	68.8	90.8	50.1	289.9
Mean	64.0	29.1	70.4	-31.0	37.8
Std. deviation	22.22	23.15	24.98	15.57	72.62
Std. error of mean	5.939	6.187	6.676	4.161	19.41
Lower 95% CI of mean	51.2	15.8	56.0	-30.0	-4.1
Upper 95% CI of mean	76.8	42.5	84.9	-22.0	79.7

Descriptive statistics of percent change

MAP mean arterial pressure, *ICP* intracranial pressure, *CPP* cerebral perfusion pressure, *CBF* cerebral blood flow, *dz* respiratory change in impedance amplitude during the vasopressor challenge

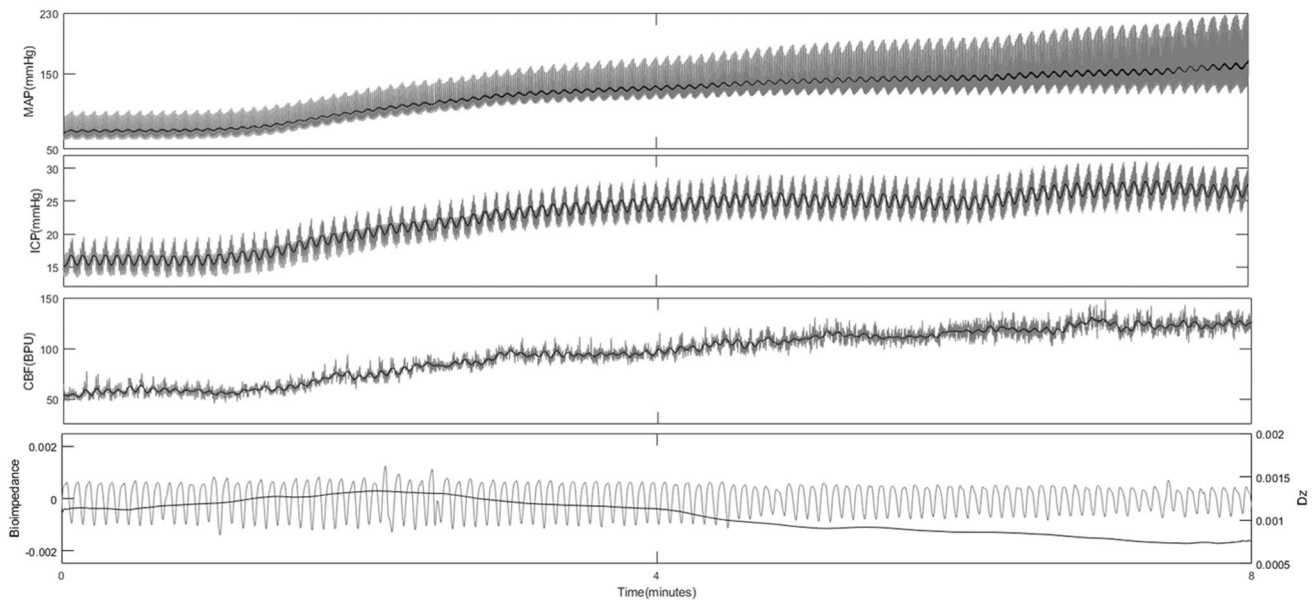


Fig. 3 A sample longitudinal view of hemodynamics, and brain impedance during the vasopressor challenge. *MAP* mean arterial pressure, *ICP* intracranial pressure, *CBF* cerebral blood flow. The

solid lines in the upper three tracing represent the mean change, while the line in the lower tracing represents changes in impedance respiratory amplitude

Table 2 Receiver operator curve and area under the curve of *DZx*

<i>DZx</i>	<i>PRx</i> threshold > 0.3	<i>PRx</i> threshold > 0.2	<i>PRx</i> threshold > 0.1	<i>PRx</i> threshold > 0
Sample size	177	177	177	177
Positive group	103 (58.19%)	107 (60.45%)	112 (63.28%)	114 (64.41%)
Negative group	74 (41.81%)	70 (39.55%)	65 (36.72%)	63 (35.59%)
Area under the ROC curve (AUC)	0.88	0.89	0.87	0.89
Standard error	0.0251	0.0246	0.0276	0.0247
95% confidence interval of AUC	0.835 to 0.933	0.845 to 0.942	0.817 to 0.925	0.842 to 0.939
Significance level <i>P</i> (area=0.5)	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Associated criterion for <i>DZx</i>	≤ -0.16	≤ -0.08	≤ -0.08	≤ -0.08
Sensitivity	0.82	0.81	0.78	0.79
Specificity	0.81	0.82	0.83	0.82
Positive predictive value	0.69	0.68	0.65	0.62
Negative predictive value	0.90	0.90	0.90	0.91
Positive likelihood ratio	4.3	4.4	4.5	4.4
Negative likelihood ratio	0.23	0.23	0.22	0.22

Area under the curve for *DZx* and its associated test performance metrics and criterion at different thresholds of *PRx*

DZx impedance index, *PRx* pressure reactivity index

not require invasive ICP monitoring. Our novel impedance metrics of d_z by itself, or as an index (*DZx*), were shown to be capable of tracking changes in *PRx*, *CPP*, and *CBF* with high fidelity and as a result provide assessment of *CA*.

In the vast majority of clinical settings, early changes in cerebral hemodynamics are difficult to assess, due to limited ability to visualize or detect changes in intracranial pressure or blood flow. Thus, detection and assessment of *TBI* severity and associated secondary injuries remains a challenge

[25]. Monitoring modalities that enable assessment of *ICP* and *CA* might be a valuable tool to target optimized *CPP* and therefore maintain optimal *CBF*, as means to prevent and mitigate secondary brain injury [26]. *PRx* has been shown to be a promising methodology to assess *CA*, and predict severity and outcome post *TBI* [27]. However, because *PRx* requires *ICP* and intra-arterial blood pressure monitoring it seems only suitable in structured and controlled environments existing at higher echelons of care [28]. *TOBI* may

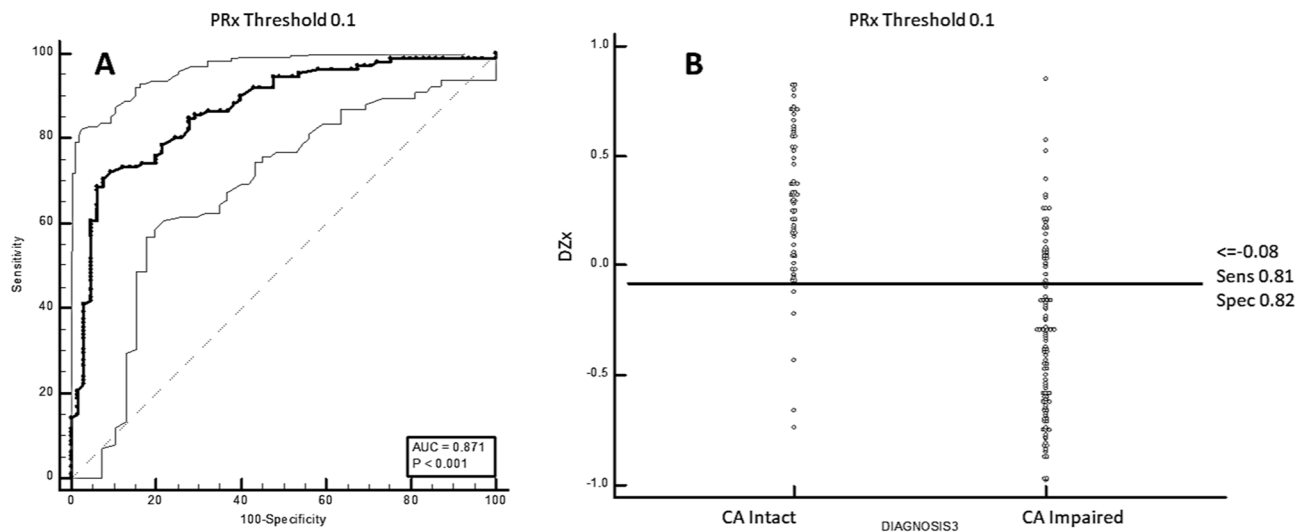


Fig. 4 **a** ROC for DZx at PRx threshold of 10. **b** Associated criterion, sensitivity and specificity of DZx at a PRx Threshold of 0.10

allow early assessment of changes in CBV and cerebral autoregulation without the need for invasive ICP monitoring (but still with the need for invasive MAP monitoring). We are currently exploring the potential of using continuous noninvasive MAP monitoring to make the system completely noninvasive.

Bioimpedance has been used recently for monitoring and measurements related to cardiovascular and respiratory systems such as cardiac output, lung water content, and respiratory effort [29]. It is a measure of biological tissue's passive electricity and resistance to an induced current or voltage [30, 31]. Blood is a good conductor of electrical current and blood volume has a distinct effect on impedance, which allows impedance measurements to detect changes in blood volume in an area of interest. In addition, bioimpedance is indirectly affected by respiration due to the change in blood volume produced during inspiration and expiration (Fig. 1). In this study, we measured brain bioimpedance through an ocular window by placing two electrodes on the animal's closed eyelids using a bipolar arrangement as outlined by previous work [21]. As the low electrical current is applied through the ocular pathway, the impedance respiratory-induced differences primarily reflect the blood volume inside the skull. We have previously demonstrated that this ocular pathway and technique selectively targets the brain and overcomes issues with transcranial (scalp) impedance [21].

In this study, we investigated the loss of CA by the use of a vasopressor challenge as a means to rapidly elevate CPP to a level above the compensatory range. We chose this model to create a reproducible and unequivocal state of loss of CA indicated by a rise in ICP during elevation of MAP and based on the knowledge that sudden elevation of CPP

is known to be associated with aggravation of the secondary injury post TBI [32]. We also chose vasopressor as a reversible challenge to modulate changes in MAP, ICP, and CBF which are the metrics used for the calculation of PRx. Such modulation creates a wide range of these metrics that enables the determination of a DZx threshold where we can define autoregulation as intact or impaired and compare it to the more established PRx parameter. The establishment of such threshold will begin to enable further study of the use of such index during neurological patient management where perturbations are less extreme. In this study as with our previous study, dz once again correlated highly with ICP, CPP, and CBF changes. This correlation was expected as dz changes are sensitive to changes in blood volume during the vasopressor challenge, decreasing while blood volume increases and vice versa.

The receiver operator test revealed that DZx, as a non-invasive impedance metric, has a high predictive power with area under the curve in the upper 80s when compared to PRx. Although PPV might seem modest in this study, the combination of the high values of the sensitivity, specificity, and NPV are an indication of the robustness of the impedance metric. Furthermore, the combination of high PLR as well as low NLR indicate that DZx is capable of assessing the presence or absence of CA with high probability. TOBI and the presented indices of impedance represent a less invasive technique that may be performed in the early care of neurologic injury to assess CA and ICP. This technique may prove to have potential to enable early detection of severe TBI, guide triage and manage treatment, as well as improve outcomes by alleviating secondary brain injury associated with the loss of CA. It is envisioned to be applied as a rapid

point of care diagnostic indicator of severity of TBI and other cerebral injuries allowing for earlier intervention in more far forward echelons of care.

4.1 Limitation

This study has several limitations. We have used male animals only in this investigation. Future studies will include both males and females to investigate the role of gender and its effect on impedance and autoregulation. This study tested the performance of bioimpedance and its indices in a large animal model of hemodynamic perturbations without TBI and while animals were under general anesthesia. More testing is needed in animals with TBI that also have perturbed physiology such as hypertension and hypotension to assess the ability of TOBI to track CA. We also measured CBF using LDF which provides only a relative measure of CBF in arbitrary units and is subject to noise. Furthermore, we used PRx as a gold standard metric for comparison. However, PRx is still not without controversy and with insufficient high-quality data to support a recommendation for use in clinical practice [33–35]. Further studies in animals and humans are currently underway to further validate this promising technology.

5 Conclusion

TOBI produces the indices dz and DZx which track changes in parameters that affect CA such as ICP, CPP, and CBF, and indicate the state of CA such as PRx. Further development of such indices might prove to be a more easily accessible alternative and suitable surrogate for the more invasive, time consuming, and expensive standard methods. The information that can be extracted from the impedance signal may prove to be useful as part of a portable, easily-applied high fidelity diagnostics device.

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Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Mohamad Tiba, Brendan McCracken, Danielle Leander, Carmen Colmenero, Brandon Cummings, and Nicholas Greer. The first draft of the manuscript was written by Mohamad Tiba, Brendan McCracken and Kevin Ward. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability All data and materials support our published claims and comply with field standards.

Code availability Not applicable.

Compliance with ethical standards

Conflict of interest Dr. Tiba and Dr. Ward have intellectual property on the technology and methodology described through the University of Michigan. The technology has been licensed by New Vital Signs, Inc. in which Dr. Ward is a founder.

Consent to participate Not applicable.

Consent for publication Not applicable.

Ethical approval All procedures outlined in this study adhere to the principles stated in the eighth edition of the Guide for the Care and Use of Laboratory Animals and were approved by the University of Michigan's Institutional Animal Care and Use Committee.

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Trans-ocular brain impedance indices predict pressure reactivity index changes in a porcine model of hypotension and cerebral autoregulation perturbation

Mohamad H. Tiba, MD, MS^{1,6}, Brendan M. McCracken, BS^{1,6}, Danielle C. Leander, BS^{1,6},
Carmen I. Colmenero, BS^{1,6}, Nicholas L. Greer, BS^{1,6}, Paul Picton, MD^{5,6}, Craig A. Williamson,
MD, MS^{3,4,6}, Kevin R. Ward, MD^{1,2,6}

¹Department of Emergency Medicine, University of Michigan, Ann Arbor, Michigan

²Department of Biomedical Engineering, University of Michigan, Ann Arbor, Michigan

³Department of Neurological Surgery, University of Michigan, Ann Arbor, Michigan

⁴Department of Neurology, University of Michigan, Ann Arbor, Michigan

⁵Department of Anesthesiology, University of Michigan, Ann Arbor, Michigan

⁶Michigan Center for Integrative Research in Critical Care (MCIRCC), University of Michigan,

Ann Arbor, Michigan

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Corresponding Author:

Mohamad Hakam Tiba, MD, MS

Research Assistant Professor

2800 Plymouth Road, 26-323N

Ann Arbor, MI 48109

Phone: 734-764-6702

Fax: 734-763-9389

tibam@med.umich.edu

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12

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15
16
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18 McCracken, Danielle Leander, Carmen Colmenero, Brandon Cummings, and Nicholas Greer.
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20 The first draft of the manuscript was written by Mohamad Tiba, Brendan McCracken and Kevin
21 Ward. All authors commented on previous versions of the manuscript. All authors read and
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23
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27

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29

30 Dr. Tiba and Dr. Ward report grants from Department of Defense, during the conduct of the
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32
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34

35 Dr. Williamson reports grants from Department of Defense, during the conduct of the study.
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37 Dr. Picton, Mr. McCracken, Ms. Leander, Ms. Colmenero, and Mr. Greer have nothing to
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43 **Ethics approval:** All procedures outlined in this study adhere to the principles stated in the
44 eighth edition of the *Guide for the Care and Use of Laboratory Animals* and were approved by
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Abstract

Introduction: Cerebrovascular autoregulation (CA) is a protective mechanism that enables the cerebral vasculature to auto-modulate tone in response to changes in cerebral perfusion pressure to ensure constant levels of cerebral blood flow and oxygen delivery. CA can be impaired after neurological injury and contributes to secondary brain injury. In this study, we report novel impedance indices utilizing trans-ocular brain impedance (TOBI) during controlled systemic hemorrhage and hypotension to assess CA in comparison to pressure reactivity index (PRx).

Methods: Yorkshire swine were instrumented to record intracranial pressure (ICP), mean arterial pressure (MAP), and cerebral blood flow (CBF). TOBI was recorded using ECG electrodes placed on the closed eyelids and measuring impedance (dz) in response to injecting 0.4 mA of current. MAP, ICP, and CBF were also measured. Animals were subjected to a controlled hemorrhage removing a mean (SD) blood volume of 34 (5.3)% over a duration of 26 (10) minutes. Hemorrhage was titrated to maintain a MAP above 30 mmHg and end-tidal carbon dioxide above 28 mmHg. PRx was calculated as moving Pearson correlation between MAP and ICP. TOBI indices were calculated as the amplitude of the respiratory-induced changes in dz . DZx was calculated as a moving Pearson correlation between dz and MAP. TOBI indices (dz and DZx) were compared to hemodynamic indicators and PRx.

Results: dz was shown to be highly correlated with MAP, ICP, CPP, and CBF ($r = -0.823$, -0.723 , -0.813 , and -0.726) respectively ($p < 0.0001$). During hemorrhage, CPP, and CBF had a mean percent decrease (Standard Deviation) from baseline of -54.2 (12.5)% and -28.3 (14.7)% respectively while dz increased by 277 (268)%. Receiver operator characteristics (ROC) and precision-recall curves (PRC) demonstrated high predictive performance of DZx when compared to PRx with area under the curve above 0.82 and 0.89 for both ROC and PRC respectively, with

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4 high sensitivity and positive predictive power. **Conclusions:** TOBI indices appear to track
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6 changes in PRx and hemodynamics that affect CA during hemorrhage induced hypotension.
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9 TOBI may offer a suitable less invasive surrogate to PRx for monitoring and assessing
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11 cerebrovascular autoregulation.
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Introduction

Cerebral autoregulation (CA) is an important auto-protective mechanisms against ischemic brain injury especially after traumatic brain injury¹ where it is often found to be impaired²⁻⁴.

Furthermore, CA has been shown to be a significant predictor of outcome in patients with various acute neurological diseases, including severe TBI-related injuries and ischemic stroke⁵⁻⁷.

To date, assessment and quantification of CA has proven to be difficult and elusive. In addition to standard physical examination and clinical judgment, several methods have been proposed to evaluate CA such as transcranial-Doppler⁸, brain tissue oxygenation⁹, near-infrared spectroscopy measured hemoglobin saturation¹⁰. However, all have performed with mixed results¹¹.

Newer approaches to assess and monitor CA such as the computation of the pressure reactivity index (PRx) has also been proposed and investigated for the past 2 decades¹². PRx tracks dynamic changes in mean arterial blood pressure (MAP) and intracranial pressure (ICP) simultaneously as an indicator of an intact or impaired CA after cerebral injury¹¹ and appears to provide an independent predictor of outcomes after TBI^{11,13-15}. PRx is the mathematical result of a moving Pearson correlation coefficient between MAP and ICP with values indicating either pressure-passive behavior of the arterial walls (impaired autoregulation) or active vasomotor responses (intact autoregulation)¹³⁻¹⁵. However, PRx calculations require the invasive measurements of both MAP and ICP which limits PRx use. In addition, the invasive nature of the measurements, the complexity of signal processing, and inherent signal noise have potentially constrained its application to mainly academic institutions that are capable of adequate signal acquisition and have specialized processing software^{13,16}. Such perceived limitations rendered the utility of PRx at early stages of care as problematic.

Here we present a new methodology to assess CA utilizing trans-ocular brain impedance (TOBI) in response to hemorrhage induced hypotension. TOBI uses low dose alternating current delivered externally through electrodes placed on the closed eyelids. This current is capable of penetrating deep into the brain to measure changes in cerebral blood volume (CBV)¹⁷. The TOBI metric dz is coupled with MAP to continuously calculate an index (DZx) capable of monitoring CA without the need for ICP measurement. The inherent relationship between TOBI and CBV suggests DZx may be a potential technique to monitor and assess changes in CA similar to PRx. We have shown in previous investigations that the impedance indices (dz and DZx) are capable of tracking changes in parameters that affect CA such as ICP, CPP, and CBF, as well as predict PRx with high precision in a large animal model of systemic hypertension and increased CPP¹⁸. In this study, we similarly utilized dz in conjunction with MAP to compare DZx's performance to PRx in a large animal model of hypotension due to systemic hemorrhage and further evaluate the indices' utility for assessment of CA. We hypothesized that DZx will predict changes in PRx and assess CA with high precision.

Materials and Methods

All procedures outlined in this study adhere to the principles stated in the eighth edition of the *Guide for the Care and Use of Laboratory Animals*¹⁹ and were approved by the University of Michigan's Institutional Animal Care and Use Committee.

Anesthesia and Surgical Instrumentation: Eleven male Yorkshire mix swine with a mean (standard deviation) weight of 44(3.71) kg were initially sedated using ketamine/xylazine (20/2 mg/kg). Anesthesia was induced using 2.5% isoflurane in a fraction of inspired oxygen (FiO₂) of 100% and maintained at 1.5-2.5% isoflurane and an FiO₂ of 30-40%. Animals were intubated

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4 using a standard cuffed 7.5 mm endotracheal tube. Core temperature was maintained at 37-38°C
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6 using a warming blanket (Blanketrol®, Cincinnati Sub-Zero, Cincinnati, OH) for the duration of
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9 all procedures. Mechanical ventilation was set using volume control with tidal volume at 7-8
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11 mL/kg (Draeger FabiusGS Premium. Draeger Inc. Telford, PA). Respiratory rate was adjusted to
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13 titrate end-tidal CO₂ (PetCO₂) to 35-45 mmHg (Biopac Data Acquisition System. Biopac Inc.
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15 Goleta, CA). The right and left common femoral arteries were cannulated for continuous arterial
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17 pressure monitoring and for controlled hemorrhage. The left and right external jugular veins
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19 were cannulated for drug delivery, blood sampling, and for administration of fluids. At the
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21 conclusion of vessel cannulations, animals were turned to a prone position for the remainder of
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23 the experiment. Two, 2–3mm burr holes were drilled into the left skull through a small circular
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25 skin window. A laser Doppler flow probe TSD144 (Biopac Systems Inc. Goleta, CA) and a 2F
26
27 solid state pressure catheter SPR-320 Micro-Tip (Millar, Houston, TX) were placed directly into
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29 the brain parenchyma (cerebral cortex) through the burr holes for CBF and ICP monitoring
30
31 respectively (Figure 1).
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41 Trans-Ocular Bioimpedance setup and processing: Two disposable silver-silver chloride
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43 electrocardiographic (ECG) electrodes, (Positrac RTL, ConMed Corp. Utica, NY) were placed
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45 on the closed eyelids and secured by adhesive tape. The electrodes were connected to a
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47 bioimpedance amplifier EBI100C (Biopac Systems Inc.) using shielded leads. Alternating
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49 current (0.1-1mA at 50 kHz) was introduced through the electrodes, and the potential between
50
51 the two electrodes was received back by the same electrodes and displayed as the TOBI
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53 waveform. TOBI signal was passed through a series of digital filters to remove baseline drift and
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55 high-frequency noise. Movement artifacts were detected via adaptive thresholding and then
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4 removed. The amplitude of the respiratory component (dz) was isolated and quantified using a
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6 root-mean-square envelope in a frequency-independent manner, meaning that the resulting
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8 metrics are largely independent of respiratory and heart rate (Figure 2). PRx was calculated as
9
10 the moving Pearson correlation coefficient between MAP and ICP over a five-minute window
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12 with a step size of one second, while the TOBI index DZx was calculated using the same method
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14 between MAP and dz . Of note is that DZx and PRx often move opposite one another due to the
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16 inverse relationship between dz and ICP which is caused by changes in cerebral blood volume.
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18 As a Pearson correlation coefficient, both PRx and DZx may only have values limited between -
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20 1 and 1¹³ with PRx values below zero indicating intact CA, and impaired CA is indicated by PRx
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22 values above zero, and vice versa for DZx.
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31 Systemic Hemorrhage: Following instrumentation and baseline sample collection, animals were
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33 subjected to systemic hemorrhage to manipulate CBF, MAP, ICP and ultimately disrupt CA.
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35 Controlled hemorrhage occurred from the left common femoral artery using a Cole-Palmer
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37 Master Flex L/S (Vernon Hills, Illinois) at a rate of 50mL/min to remove 34 (5.3)% blood over a
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39 duration of 26 (10) minutes. Hemorrhage was titrated as needed to maintain a MAP above 30
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41 mmHg and etCO₂ above 28 mmHg. TOBI and hemodynamics were recorded continuously using
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43 Biopac Data Acquisition System MP150 (Biopac Systems Inc.). Following all data collection,
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45 animals were euthanized using 1-2 meq/dL of potassium chloride under general anesthesia.
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53 Statistical analysis: Continuous data are presented either as mean and standard deviation or as
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55 mean and standard error. Pearson correlation was used to test the strength and direction of the
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57 relationship between dz and hemodynamic metrics (CPP, and CBF). Percentage change from
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baseline for *dz* and hemodynamic metrics were calculated during hemorrhage. The Area under the Receiver Operator Curve (AUROC) was used to assess the predictive performance of DZx at different thresholds of PRx (>0, >0.10, >0.20, and >0.30) consistent with previous studies^{12,20}. DeLong Methodology²¹ was used for the calculation of the standard error of the AUCs. Binomial exact confidence intervals were calculated for the AUCs. Area under the precision-recall curves (AUPRC) were calculated for DZx at same thresholds of PRx and 95% bootstrap confidence interval were calculated as described by Efron et al²². AUPRC is a plot of the precision (positive predictive value, y-axis) against the recall (sensitivity, x-axis) and is an alternative for the ROC curve^{23,24}.

Average values of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) that correspond to DZx AUCs were also calculated. Statistical significance was set at $\alpha = 0.05$, and statistical analyses were performed using MedCalc 19.6, GraphPad Prism 8, and MATLAB R2019a.

Results

At the end of hemorrhage, MAP, ICP, CPP, and CBF had a mean percent decrease (SD) from baseline of -50.3 (11.9)%, -35.5 (29.7)%, -54.2 (12.5)%, and -28.3 (14.7)% respectively, all of which were statistically significant ($p < 0.0010$) and clinically notable with changes above 20% (Figure 3). Concurrently, measurements of *dz* significantly increased from baseline by 277.8 (268)% ($p < 0.0010$) (Figure 3). Figure 4 provides an example of the longitudinal changes in CPP, CBF, and *dz* as well as PRx and DZx during the hemorrhage period. The figure demonstrates significant decrease in average CPP and CBF simultaneous with a considerable increase in *dz* amplitude. These observed changes are consistent with the conductive properties

of blood which lead to an increased impedance to current when blood volume is decreased. The divergence of the respiratory signal and dz (solid line) are due to signal drift but do not affect the measure of changes in dz . Table 1 presents correlations between dz and MAP, ICP, CPP, and CBF. On average there was a significant negative correlation between dz and all metrics ($p<0.0001$). In addition, there was a significant positive correlation between CPP and CBF across all animals ($p<0.0001$) (Table 1).

During the hemorrhage period, DZx and PRx changed inversely between -1 and 1 (Figure 4) indicating fluctuations in CA between being intact and impaired. Comparison of DZx at different thresholds of PRx between 0 and 0.3^{12,20} yielded a high AUROC indicating high predictive performance of DZx . Furthermore, the AUPRC for DZx at the same thresholds of PRx demonstrated excellent performance. Table 2 lists DZx 's AUCROC, AUPRC, as well as sensitivity, specificity, PPV, NPV at each corresponding PRx threshold.

Discussion

Electrical bioimpedance is a passive electrical property of tissue. Specifically it is the tissue's resistance to an externally induced electrical current or voltage^{25,26}. Blood is a good conductor of electrical current. As such, it has a distinct effect on impedance when the amount of volume of blood is changed allowing impedance monitoring to detect changes in blood volume in an area of interest. Such properties enabled the use of impedance in applications related to cardiovascular and respiratory systems such as cardiac output measurement, lung water content, and respiratory effort²⁷. In addition, bioimpedance is indirectly affected by respiration due to the change in blood volume produced during inspiration and expiration (Figure 2). In this study, we measured brain impedance through an ocular pathway by placing two electrodes on the animal's closed eyelids

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4 using a bipolar arrangement^{17,18}. The respiratory-induced impedance differences primarily reflect
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6 the blood volume changes inside the skull. The use of the ocular pathway results in the ability to
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8 deliver 40% greater current to the brain compared to transcranial delivery through the scalp¹⁷.
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11 In this study, we investigated the loss of CA during hypovolemia and hypotension
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13 resulting from systemic hemorrhage. Controlled hemorrhage was chosen to induce a
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15 reproducible and unambiguous state of loss of CA. CA impairment was indicated by the
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17 considerable drop observed in CPP and CBF across all animals. Reducing CPP below critical
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19 threshold is known to be associated with impairment of CA. Furthermore, hemorrhage and
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21 hypotension are known to produce secondary injury after TBI²⁸. Systemic hemorrhage is also a
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23 strong modulator of both MAP and ICP, which are the metrics used for the calculation of PRx.
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25 Hypovolemia and hypotension resulted in a profound reduction in cerebral blood volume which
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27 directly affected changes in dz . Such modulation leads to changes in hemodynamics (MAP, ICP,
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29 CBF) over wide range which enables the determination of an appropriate DZx threshold where
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31 CA can be defined as intact or impaired. The establishment of such thresholds will be beneficial
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33 for future studies to enable the use of TOBI indices during neurological patient management
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35 where perturbations are less extreme. Our previous reported data^{17,18} have shown that DZx is
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37 capable of assessing CA during hemodynamic perturbations resulting in elevated CPP. This
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39 study however expands on this by suggesting that DZx is again capable of detecting CA
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41 impairment during the reduction of CPP below the autoregulatory threshold.
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51 Our indices of dz and DZx were again shown to be capable of tracking changes in PRx,
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53 CPP, ICP and CBF with high fidelity and as a result provide assessment of CA during
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55 hypotension. dz demonstrated a high level of correlation with CPP, ICP, and CBF indicating dz 's
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57 sensitivity to changes in blood volume during the hypovolemia state, resulting in considerable
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measurable increase while blood volume decreased. The receiver operator test revealed that DZx is capable of predicting changes in PRx with high confidence as demonstrated by the high AUROCC (> 0.80) regardless of what threshold of PRx is selected. In addition to AUROC, we calculated the area under the precision-recall curve (AUPRC) which is usually used as an alternative²⁴ when there is a moderate to large class imbalance between the disease state (impaired CA) and no disease (intact CA) as was the case in our data. The AUPRC describes the average PPV across the range of sensitivities. As with the case of AUROC, the AUPRC demonstrated high predictive performance of DZx with $AUC > 0.90$ at all thresholds of PRx. These AUCs, in addition to the high sensitivity and PPV, indicate that DZx is capable of assessing the presence or absence of CA impairment with high precision during hypotension. We have previously demonstrated similar performance when loss of CA occurs due to hypertension¹⁸.

PRx has been investigated during the past two decades as a methodology to assess CA with promising results as a predictor of the severity and outcome of TBI²⁹. However, PRx requires invasive measurement of both ICP and MAP making the measurement only available in structured and controlled environments existing at higher echelons of care³⁰. TOBI may allow early assessment of changes in CA without the need for invasive ICP monitoring, however invasive MAP monitoring is still needed to calculate DZx. TOBI indices are envisioned to represent a less invasive technique that might be incorporated into the management and care of neurologic injury by early assessment of CA especially those which do not use traditional ICP monitoring like stroke, post-cardiac arrest care, sepsis, and complex operative management of patients where loss of CA is known to occur^{29,31-36}.

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4 This study has several limitations. In this study, we used PRx as a gold standard metric to
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6 compare our index to. However, PRx still lacks an unambiguous interpretation which limits its
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8 use in clinical practice. In this study we tested the performance of TOBI and its indices in a large
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10 animal model of hemodynamic perturbations without TBI while animals were under general
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12 anesthesia. More investigations are needed utilizing TBI or other cerebral insults as a primary
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14 injury accompanied with hemodynamic perturbation as hypertension and hypotension to assess
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16 TOBI ability to predict CA impairment. Lastly, we have used male animals only in this
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18 investigation. Future studies are planned to investigate the role of gender and its effect on
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20 impedance and autoregulation.
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28 **Conclusion**

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30 TOBI indices, dz and DZx correlated significantly with hemodynamics that contributed to CA
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32 perturbation during hypotension, such as MAP, ICP, CPP, and CBF, and also predict PRx with
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34 high precision. TOBI may prove to be a less invasive modality to assess CA or as an adjunct to
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36 the more invasive, time consuming, and expensive standard methods which include ICP
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38 monitoring.
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46
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Figure Legends:

Figure 1. Modeling of the equipment used to measure the changes in a porcine model of cerebral autoregulation perturbation. TOBI, intracranial pressure, and laser Doppler flow are recorded using the data acquisition system which is stored on the computer.

Figure 2. Smooth TOBI waveform A) prior to starting hemorrhage and B) post hemorrhage. Both exhibit cardiac peaks, respiratory signal, and length of inspiration. Of note is that the respiratory signal amplitude post hemorrhage is approximately doubled from pre hemorrhage. This reflects increased impedance from decreased cerebral blood volume.

Figure 3: Percent changes during hemorrhage of MAP, ICP, CPP, CBF, and dz . MAP is mean arterial pressure. ICP (intracranial pressure), CPP (cerebral perfusion pressure), CBF (cerebral perfusion flow), dz (amplitude change in TOBI respiratory signal).

Figure 4: Longitudinal changes in CPP, CBF, dz , PRx and DZx. "Smooth Impedance" panel show both respiratory signal as well as the dz (amplitude change) in solid line. CPP is cerebral perfusion pressure (mmHg). CBF is cerebral blood flow (measured in xx units). dz is amplitude change (units) in TOBI respiratory signal. PRx is pressure reactivity index. DZx is TOBI index.

Figure 1

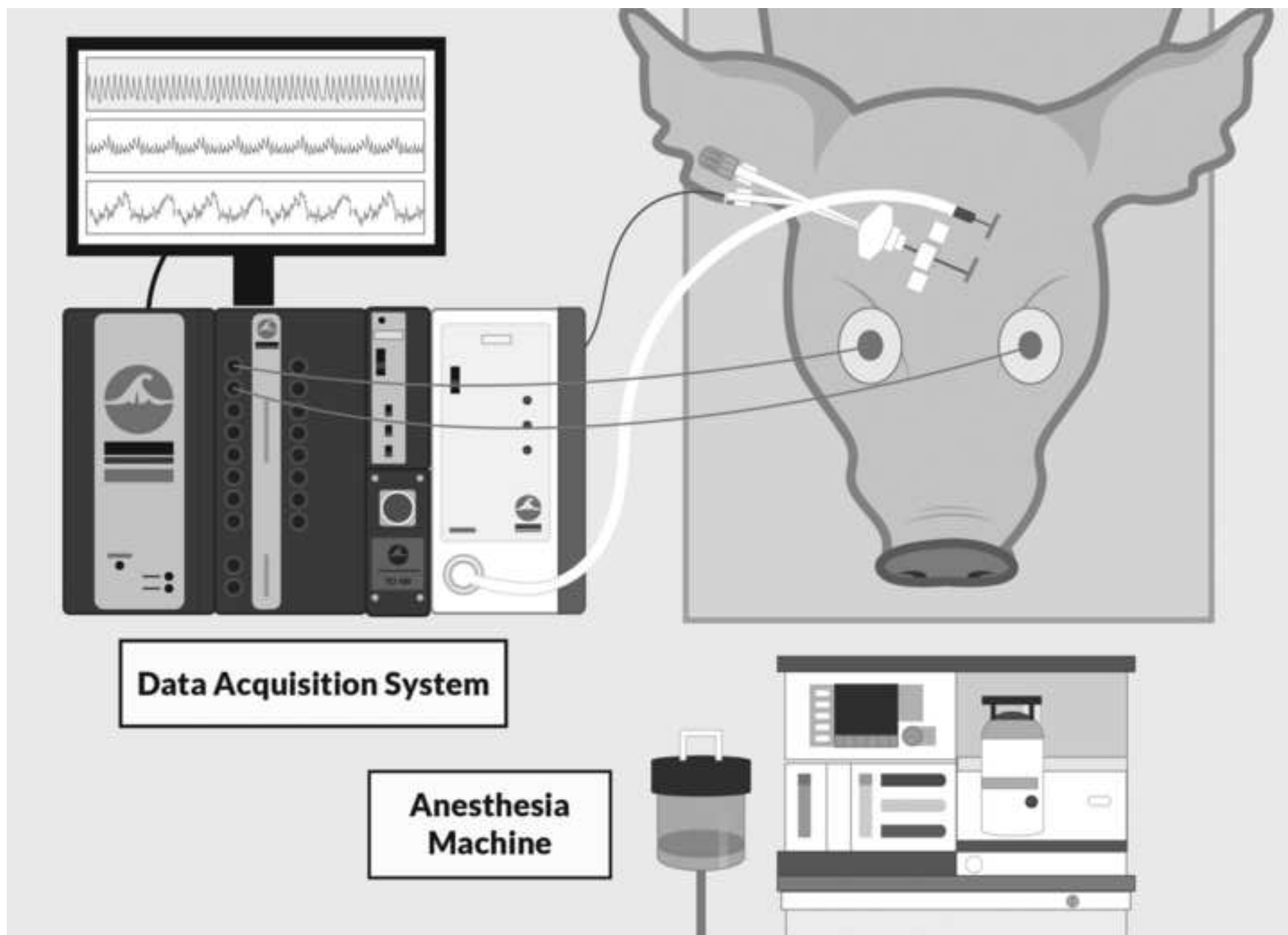


Figure 2

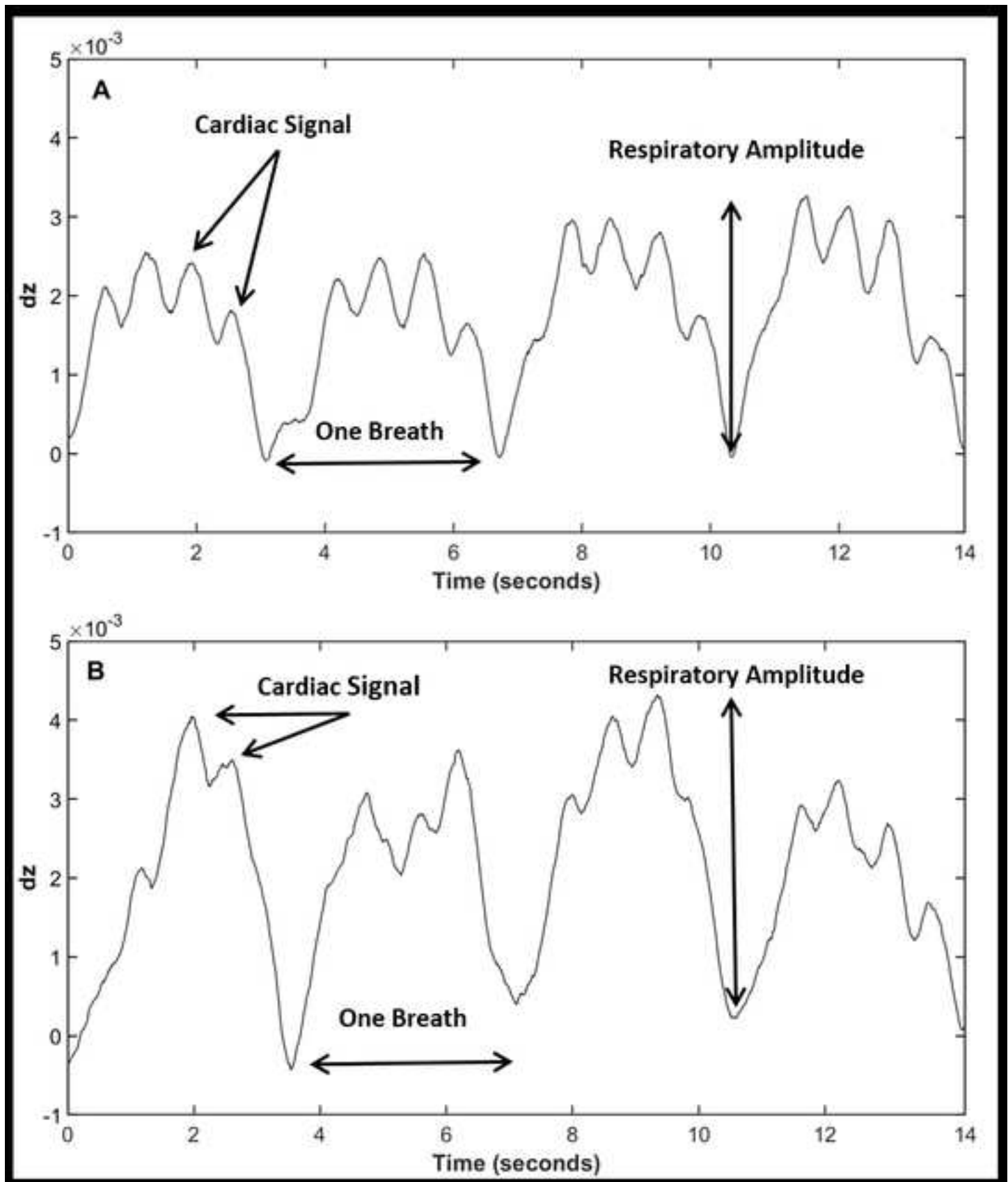


Figure 3

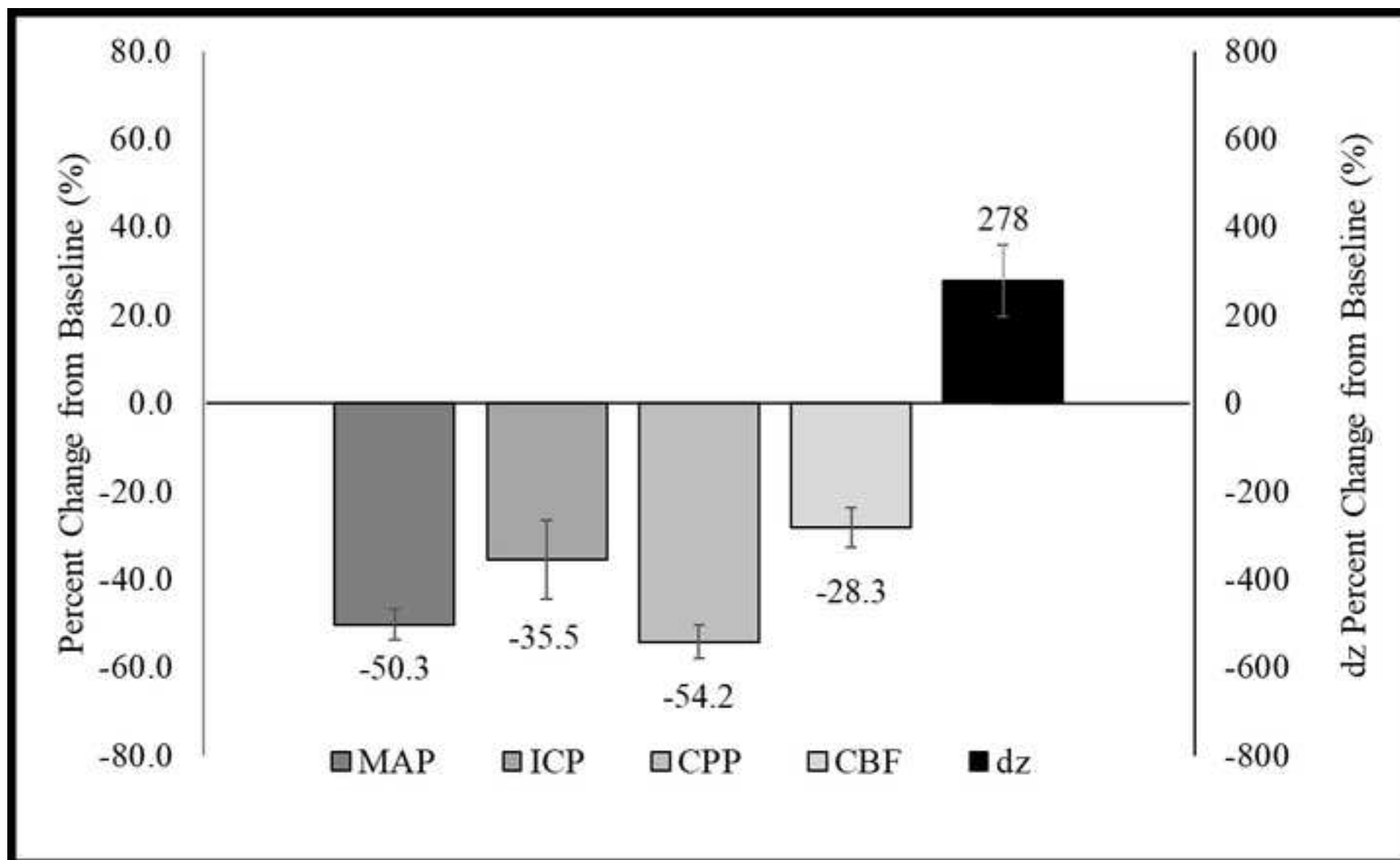


Figure 4

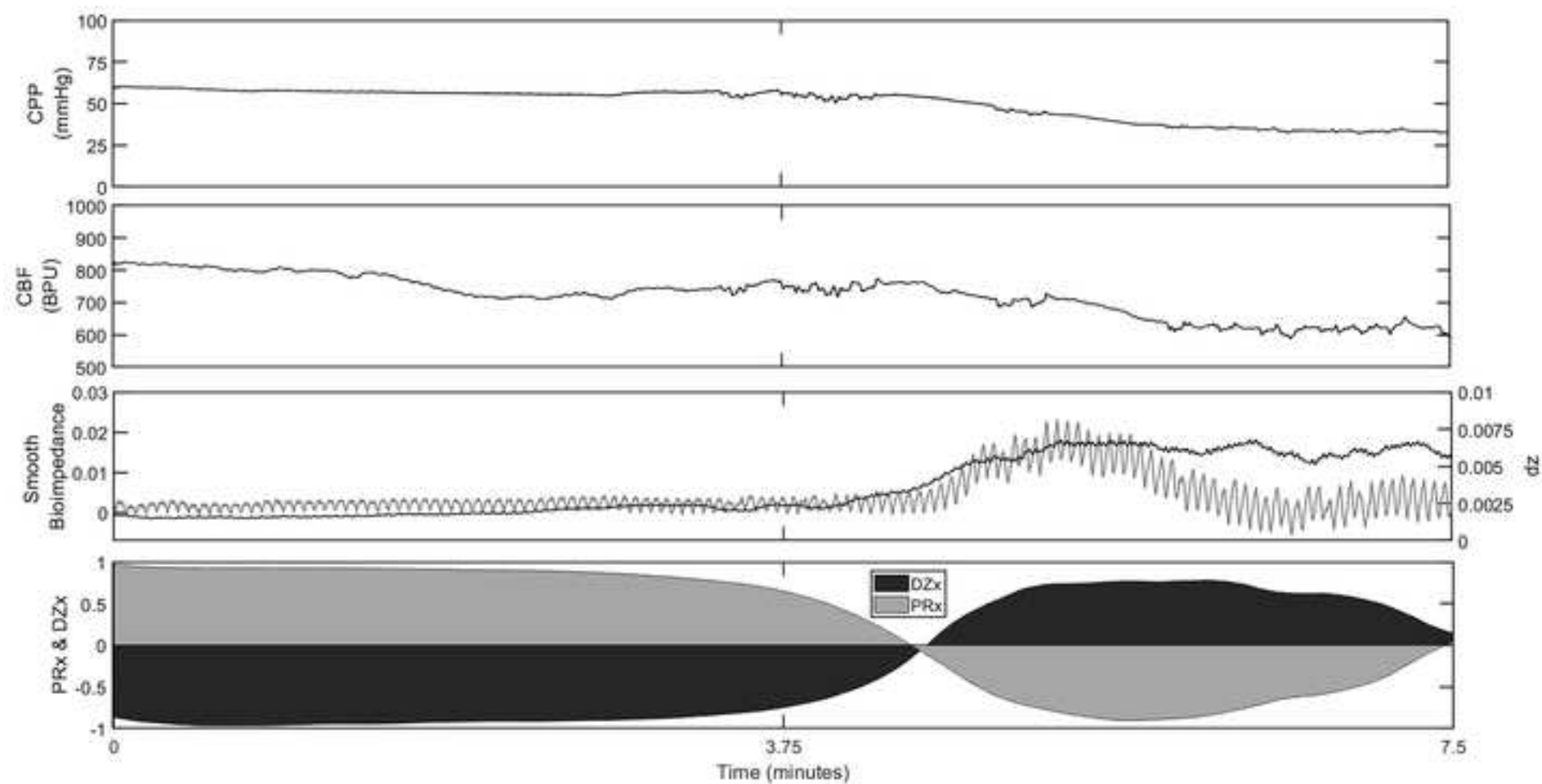


Table 1: Pearson correlations

	<i>dz</i> vs. MAP	<i>dz</i> vs. ICP	<i>dz</i> vs. CPP	<i>dz</i> vs. CBF	CPP vs. CBF
Mean	-0.823	-0.723	-0.813	-0.726	0.867
Std. Deviation	0.1097	0.1911	0.1170	0.1432	0.1292
Std. Error of Mean	0.03306	0.05763	0.03528	0.04317	0.03897
Lower 95% CI of mean	-0.8962	-0.8509	-0.8912	-0.8219	0.7805
Upper 95% CI of mean	-0.7489	-0.594	-0.734	-0.6295	0.9542

Table 1: Average Pearson correlations between *dz* and MAP, ICP, CPP, and CBF as well as between CPP and CBF. MAP is mean arterial pressure. ICP is intracranial pressure. CPP is cerebral perfusion pressure. CBF is cerebral perfusion flow. *dz* is amplitude change in TOBI respiratory signal.

Table 2. Receiver Operator Characteristics and Precision-Recall Curves. Average of 11 animals

	DZx at PRx	DZx at PRx	DZx at PRx	DZx at PRx
	Threshold (0)	Threshold (0.1)	Threshold (0.2)	Threshold (0.3)
Number of values	10	11	11	11
ROC (AUC) Mean	0.852*	0.848*	0.829*	0.821*
Std. Deviation	0.1428	0.1375	0.1568	0.1500
Std. Error of Mean	0.04515	0.04145	0.04728	0.04523
Lower 95% CI of mean	0.750	0.756	0.724	0.720
Upper 95% CI of mean	0.955	0.941	0.935	0.921
Precision-Recall (AUC) Mean	0.928*	0.927*	0.895*	0.889*
Std. Deviation	0.0974	0.0962	0.1312	0.1389
Std. Error of Mean	0.03079	0.02901	0.03957	0.04189
Lower 95% CI of mean	0.858	0.862	0.807	0.796
Upper 95% CI of mean	0.997	0.991	0.983	0.982
Sensitivity	0.815	0.848	0.871	0.898
Specificity	0.673	0.571	0.559	0.510

PPV	0.856	0.831	0.795	0.783
NPV	0.553	0.611	0.637	0.693

Table 2: Average AUC for DZx at different thresholds of PRx. PRx is pressure reactivity index. DZx is TOBI index. ROC is Receiver Operator Characteristics. AUC is area under the curve. CI is confidence intervals. *Denotes and statistically significant value (p<0.0001). $\alpha=0.05$.