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14. ABSTRACT

Traumatic brain injury (TBI) is a major public health problem in the U.S. and around the world. It plays a major role in approximately 30% of injury related civilian deaths in the U.S. and is often referred to as the "silent epidemic" because of associated complications that go undiagnosed and unnoticed, but might have a lasting effect. Furthermore, 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 and statistics becomes apparent with the military's increased focus on Prolonged Field Care (PFC) and prolonged damage control resuscitation (pDCR). PFC is defined by Keenan as the "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." Approximately 20% of individuals with combat-related severe TBI suffer acute neurological deterioration in the first 72 hours following injury, the potential time window of PFC. The austere, resource-constrained combat environment and lack of diagnostic capabilities could lead to delayed recognition of the severity of a TBI or in having rationale treatment end-points, resulting in exacerbated (secondary) brain damage and increased TBI-related disabilities. This is especially true when TBI-related injuries are combined with other injuries requiring pDCR.

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. The Joint Theater Trauma System (JTTS) Clinical Practice Guideline for TBI Management (CPG) has a major focus on early management of ICP for the management of severe TBI—in particular, the prevention of any secondary neurologic decline as a result of an expanding intracranial hematoma and the subsequent cerebral herniation and ischemia. However, monitoring of ICP during PFC is problematic and challenging since invasive monitoring and computed tomography (CT) imaging is unavailable or difficult to implement in these settings. Therefore, the current CPG relies on clinical neurological deterioration to trigger treatment of raised ICP, by which time irreversible brain injury may have already occurred. In addition, following ICP in a patient with an already altered mental status or who is intubated and sedated is problematic. 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 (CAR) 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). 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. CAR 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 CAR 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. Robust methods of noninvasive monitoring of CAR 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 CAR and ICP, utilizing the eye as a window to the brain.

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 ocular bioimpedance in two swine TBI models. Months 0-36**
    1. A swine model of blunt trauma. Months 3-36
    2. A swine TBI model with provocative maneuvers to manipulate cerebral blood flow (elevated blood pressure, systemic hemorrhage, elevations in ICP and changes in ventilation. Months 3-36

  - **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**

  - **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 0-36**

  - **Major Task 4: Development of an ultrasound video analytic system to evaluate ONSD. Months 6-36**

- **What was accomplished under these goals?**

1. **Major Task 1:** *Evaluation of ocular bioimpedance 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: 26
    c. USDA pain category for all animals used: D

All animals used to date for this study were subjected to Model 1: Provocative maneuvers to manipulate cerebral blood flow (CBF) systemic blood pressure (MAP) and ICP.
A combination of maneuvers and injuries were performed including hyperventilation, slow infusion of vasopressors (epinephrine) to increase MAP to ~ 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 received the same surgical Instrumentation for 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)

a. The left and right femoral artery are cannulated for removal of blood during controlled hemorrhage, measurement of arterial blood pressure and blood sampling.
b. One external jugular vein is cannulated for delivery of resuscitation fluids.
c. 2-3mm burr holes are drilled into the skull and used for placement of an LDF probe, pressure catheter for monitoring ICP and placement of an 8 French Foley catheter to simulate hematoma.
d. Non-invasive bipolar ECG electrodes will be placed and secured on the animal's upper eyelids to measure ocular bio-impedance. A Biopac EBI100C electro-bioimpedance amplifier will be connected to the eye electrodes and used to apply low current (0.1-1 mA) and continuously detect potential. In addition, an ultrasound probe is placed at the temporal window of the skull for transcranial doppler assessment of cerebral blood flow, measured as a time averaged mean flow (TAMEAN) of the middle cerebral artery.

Injury and maneuvers:

a. Hyperventilation: The respiratory rate (RR) is increased by increments of 10 breaths per minute until PetCO2 is reduced to ~20mmHg. After 10min, RR will be decreased by 10 breaths until back to baseline.
b. Vasopressor (norepinephrine) administration: Norepinephrine will be administered and titrated upward to increase MAP to ~ 150-160 mmHg. MAP will be maintained for 2-5 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.
c. Epidural Hematoma: Simulation of an epidural hematoma was created using a 3F 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 30-40mmHg. When the target ICP was reached, the pressure will be maintained for a period of 1-5 minutes. After the monitoring period, balloon will be deflated till ICP reaches baseline level.
d. 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.

e. Combination of A-D above will be performed to simulate intracranial pathology and various concomitant injuries (systemic hemorrhage) and treatments (hyperventilation, 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.

4) Significant Results:
    a. Data collection on Provocative maneuvers model

    b. 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. Our initial analysis pipeline involved the hand-measurement of peak-to-peak respiratory amplitude, however, we have made progress in two major areas. One, we have been able to fully automate the quantification of the respiratory amplitude in an effort to move to a continuous real-time analytic. Secondly, 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 order to automate the quantification of the amplitude of the respiratory component of the trans-ocular bioimpedance signal, we use a windowed root-mean-square (RMS) envelope. The advantage of using a time-domain method such as RMS, as compared to spectra in the frequency domain, is that the RMS envelope is significantly less sensitive to respiratory and heart rate as well as variability in those rates. The RMS envelope is also more resistant to impulse noise such as movement artifact, as it settles back down to baseline within 15 seconds. We term this metric *dz* in the figures below, as it is the peak-to-peak delta of impedance (often denoted as *Z*).

In addition to the respiratory component of the bioimpedance signal, there is also a cardiac frequency that (until the provocative maneuver model) had not been investigated. Using two 4th-order, zero-phase Butterworth bandpass filters, the respiratory and cardiac components are isolated (Figure 1). The amplitude of each component is then estimated via windowed RMS envelope, and the ratio of cardiac to respiratory amplitude is calculated and termed "*dz Ratio"* in the figures below. In the provocative maneuvers model, both *dz* and *dz Ratio* have been found to track of cerebrovascular autoregulatory parameters such as MAP, ICP, CPP, and CBF. *dz Ratio* offers several advantages - namely, being a ratio, it is somewhat normalized both between animals and with regard to impulse noise. While further analysis is required to fully investigate the differences between these two analytics, Figures 2 & 3 display the potential predictive power of these analytics (in both time-domain and regression models).

Lastly, we have attempted create a surrogate of the pressure reactivity index (PRx). PRx is calculated as the moving Pearson correlation between MAP and ICP, and positive PRx values may be indicative of impaired CAR function. Similarly, we sought to create a bioimpedance index (termed DZx) using *dz* and MAP in a similar calculation. An example is included in Figure 2. We are still investigating

the relationship between DZx, PRx, and CAR, however, it is notable that DZx and PRx often move opposite one another due to the inverse relationship between *dz* and ICP.

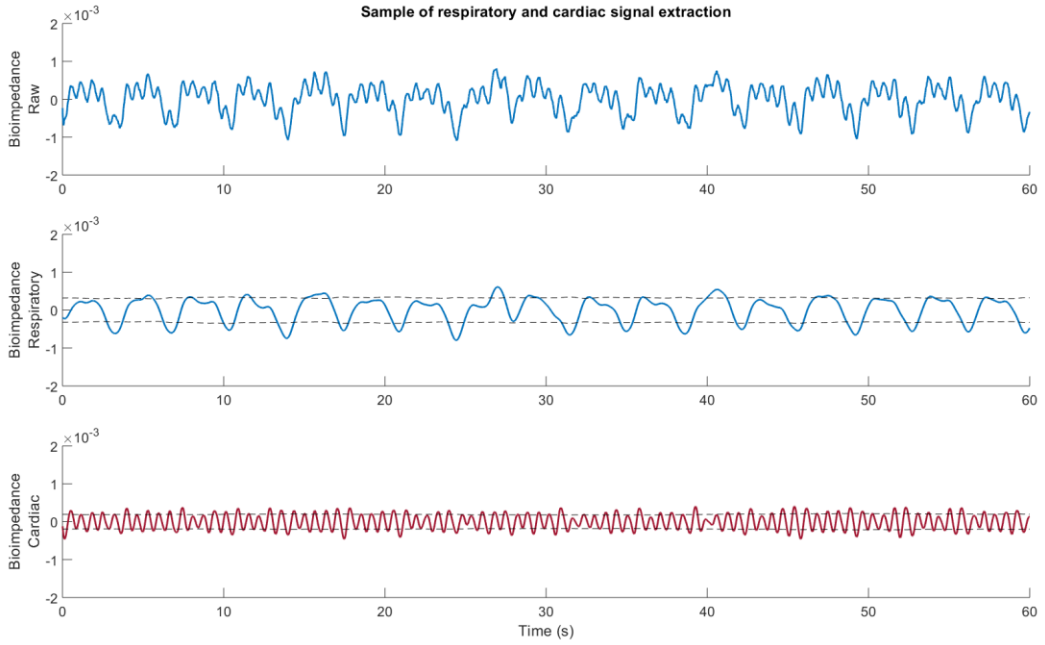


Figure 1: Isolation and quantification of respiratory and cardiac contributions. Two fourth-order zero-phase Butterworth filters are applied to the brain derived impedance waveform (topmost subplot) in order to isolate the respiratory and cardiac frequencies. The respiratory and cardiac amplitude are quantified via windowed root-mean-square (RMS) envelope (depicted as a black dotted line). The respiratory amplitude (*dz*) and the ratio of cardiac to respiratory amplitudes (*dz Ratio*) are compared to cerebrovascular autoregulatory parameters below.

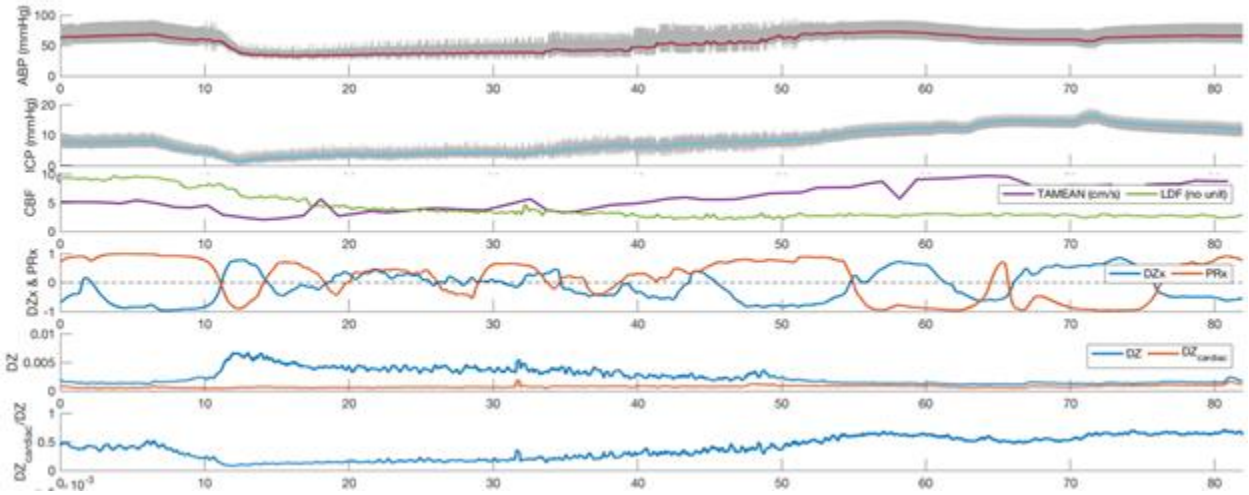


Figure 2. **Cerebrovascular hemodynamic metrics in a swine model of traumatic brain injury, hemorrhage, and resuscitation.** Animals were hemorrhaged at a rate of 50 mL/min to a mean arterial pressure (MAP) of 30 mmHg, then resuscitated using crystalloid fluids. MAP, intracranial pressure (ICP), cerebral perfusion pressure (CPP), and laser-doppler flow (LDF) were measured non-invasively. The time-average mean (TAMEAN) flow of the middle cerebral artery (MCA) was measured using transcranial doppler (TCD) ultrasonography. Bioimpedance was measured through electrodes placed over the eyelids, and respiratory variability (dz), cardiac variability contribution (dz Ratio) and DZx (an index of dz and MAP created in an analogous fashion to PRx) were calculated.

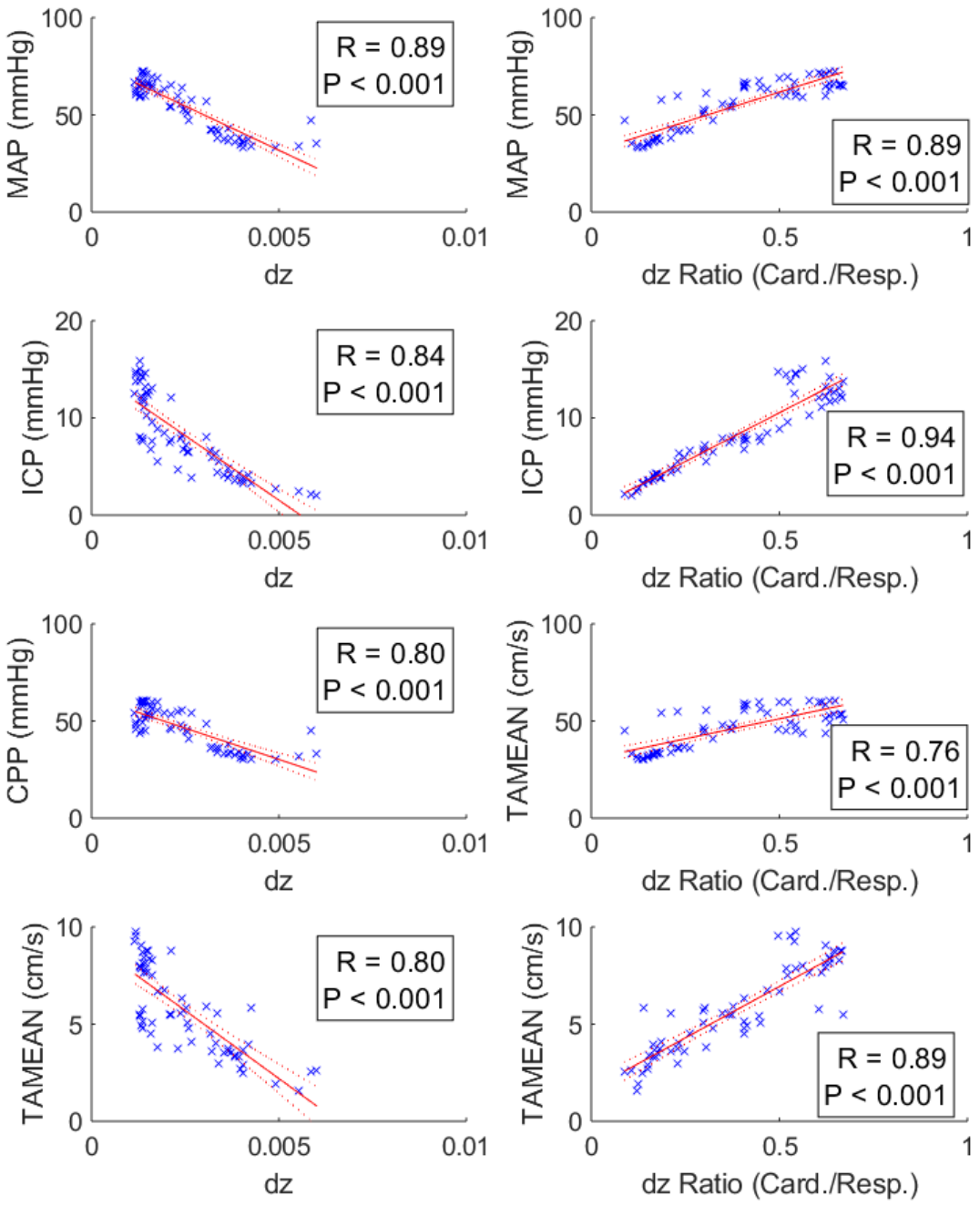


Figure 3: Regression models of several cerebrovascular hemodynamic metrics as they relate to *dz* and *dz Ratio*. The hemodynamic and bioimpedance data from the animal displayed in the previous figure are shown here.

5) Other achievements:
Established a state of the art large animal model of TBI to be utilized as testing bed for this and other technologies

- **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) Patient recruitment: 31 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 (15 patients) but also for brain tumors (4), hematoma (3), trauma (2), intracranial hemorrhage (2), hydrocephalus (1), compression of the brain stem (1), cortical hemorrhage (1), dermoid cyst (1), and intraventricular hemorrhage (1). 15 females and 17 males were enrolled with an average age of 48.2(16.6).

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 4 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 begun to investigate the cardiac component of the signal in conjunction with the respiratory oscillations to glean additional information from the signal. Figure 4 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 developed two different analytic techniques to quantify this change: a spectral analytic tool based on the Peripheral I.V. Analytic[1] and another using the root-mean-square (RMS) envelope described above.

Figure 5 depicts the power spectral density of the same portions of waveform depicted in Figure 4. Notice that both cardiac and respiratory peaks decrease as the ventriculostomy is clamped and ICP increases. Figure 6represents a sample of the time-domain analytic, using the root-mean-square envelope of the band-pass filtered signals as a substitute for the spectral power density estimate. Notably, this analytic is independent of both respiratory and heart rate as well as respiratory and heart rate variability.

We are currently engaged in more analysis of the human data and aim to provide more details in the next quarterly report.

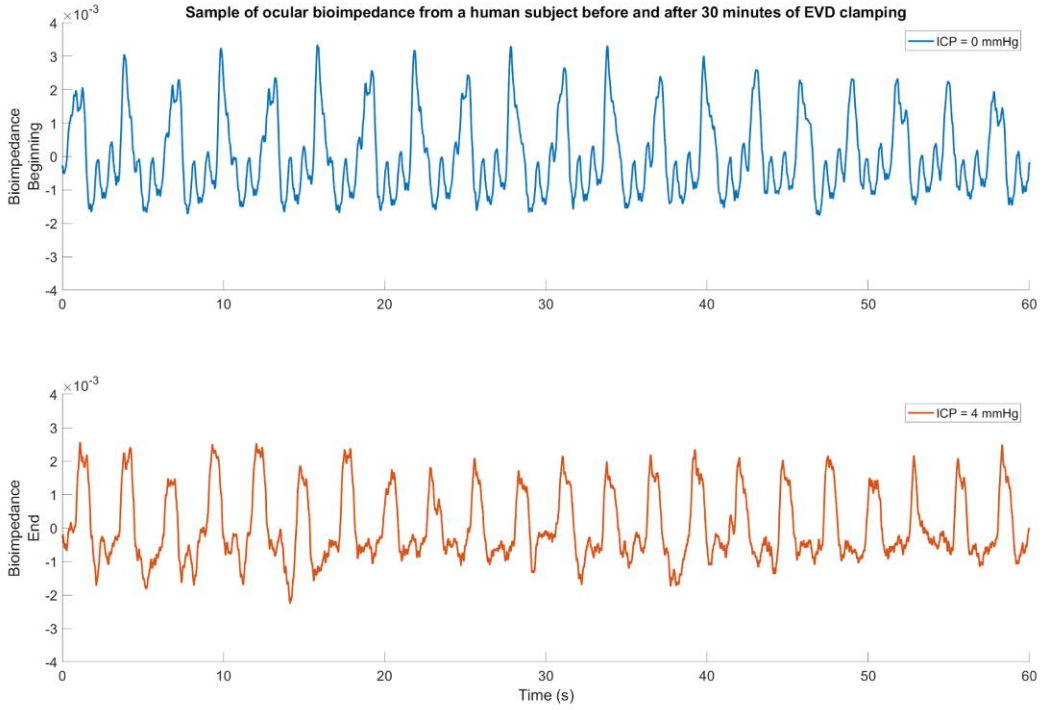


Figure 4: Sample of transocular bioimpedance waveform before (blue) and 30 minutes after EVD clamping (red). Note the differences in wave morphology - while the respiratory amplitude decreases slightly, the cardiac component is significantly lessened.

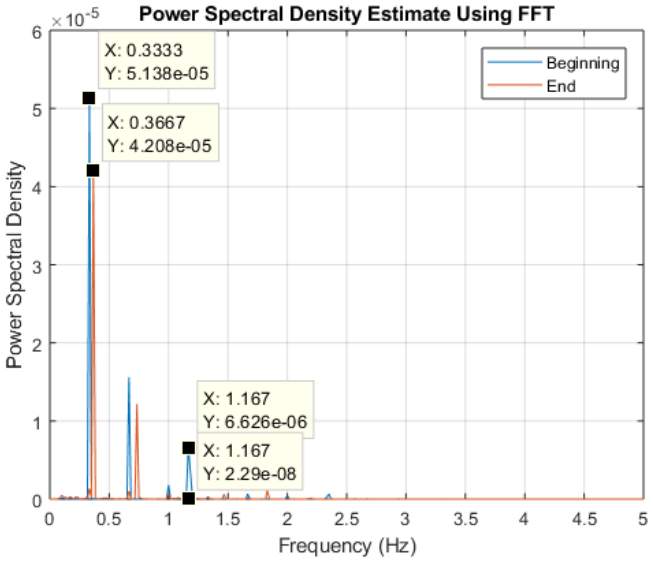


Figure 5: Power Spectral Density Estimate. Using the same two sections of signal identified above, the differences in respiratory and cardiac morphology can be quantified. Note that this method is highly dependent on both rate and rate variability in the two components.

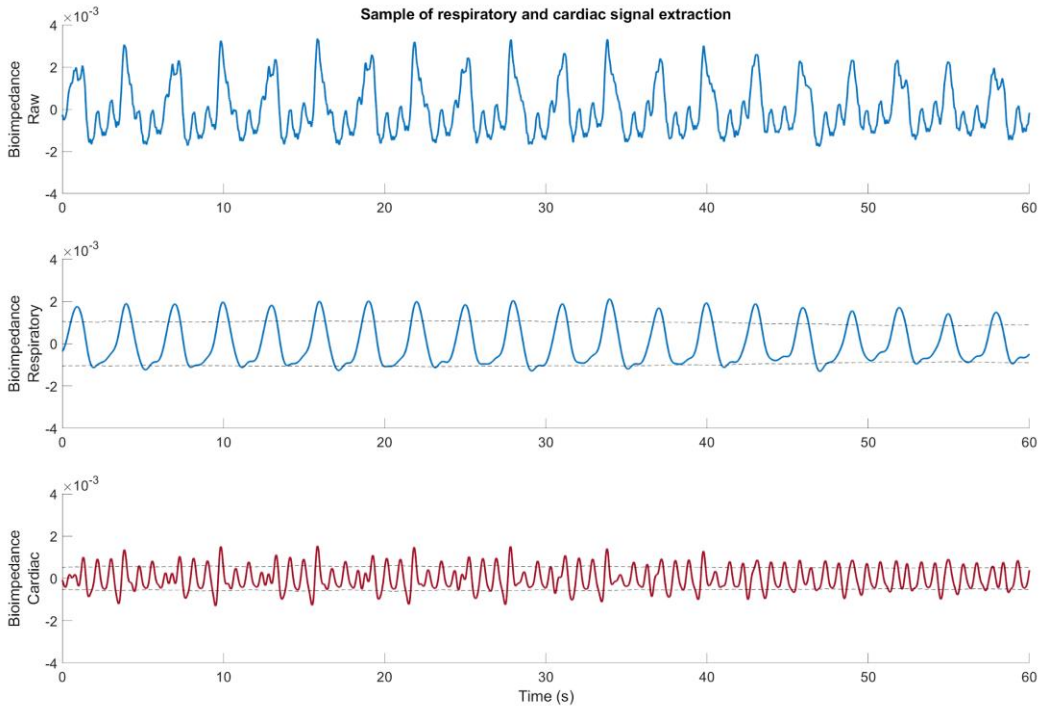


Figure 6: Sample of respiratory and cardiac signal extraction. This figure depicts the time-domain analytic using the root-mean-square (RMS) envelope of the bandpass-filtered signals. Two fourth-order Butterworth filters are constructed and applied to the impedance waveform to isolate respiratory and cardiac frequencies. The amplitude is then estimated using a root-mean-square envelope, depicted as a black dotted line. The advantage of this RMS method is that it performs independently of variations in respiratory or heart rate which may partially confound the spectral method described above. The respiratory and cardiac RMS envelope are being investigated independently and in ratio form as an indicator of cerebrovascular autoregulatory status. If successful, this method may allow us to track cerebrovascular autoregulation without concurrent arterial blood pressure.

References

1. Hocking KM, Sileshi B, Baudenbacher FJ, Boyer RB, Kohorst KL, Brophy CM, Eagle SS. "Peripheral Venous Waveform Analysis for Detecting Hemorrhage and Iatrogenic Volume Overload in a Porcine Model." Shock. 2016 Oct;46(4):447-52.

2. Other achievements

Development of novel electrodes in collaboration with In2Being, LLC. 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 7).

Figure 7. Goggles with new electrodes.

- **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 0-36*

1. Specific Objectives:
    a. IRB approval May 11, 2017
    b. HRPO approval September 22, 2017
    c. Patient recruitment: 26 patients

The optic nerve sheath (ONS) is a continuation of the brain's dura mater. Characteristics of the ONS, as well as blood flow to the eye, are known to be affected by ICP and CBF, potentially allowing the eye to serve as a window into the brain. Elevated ICP results in swelling of the optic disk (papilledema) due to the effect of high pressure within the subarachnoid space. Studies have shown that an increase in ICP results in distension of the retrobulbar ONS within seconds. Measurement of the Optic Nerve Sheath Diameter (ONSD) at a standardized 3mm distance behind the globe could be performed to identify distension using point-of-care ultrasound devices with specific transducers with ocular imaging presets (Figure 8).

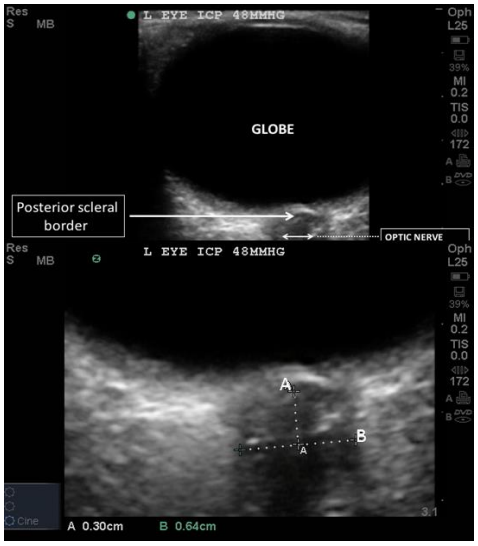


Figure 8: Magnified image. Caliper A demarcates a point 3mm behind the posterior scleral border and Caliper B measures the ONSD.

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.

ONUS was performed with the patient's eye closed, using a linear array transducer placed on the upper margin of the orbit to obtain a sonographic image of the eye. Imaging was performed on both eyes for each patient.

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

In order to find out if there is any correlation between ICP and ONSD we performed several calculations. In each one we computed the correlation between ICP and different ONSD measures such as maximum of left and right ONSD, average of left ONSD (L) and right ONSD (R), shown in the following table.

	Max(L, R)	**Mean(L, R)**	**Abs(L, R)**
Pearson (Rho/P-value)	0.1/0.64	0.06/0.75	0.12/0.55
Kendal (Rho/P-value)	0/1	-0.04/0.79	0.13/0.39
Spearman (Rho/P-value)	-0.02/0.9	-0.05/0.8	0.19/0.34

This table shows that the most correlation is between the ICP and the absolute difference of right and left ONSD. However, this correlation is not statistically significant. We are working on recruiting more patients and optimizing our approach.

- **Major Task 4:** *Development of an ultrasound video analytic system to evaluate ONSD. Months 6-36*

1. Specific objectives:
    a. Development of ultrasound analytic system
    b. Compare reading of automated ONSD with manual reading by clinicians

We develop an automated algorithm using image processing techniques to analyze ultrasound(US) images and calculate the optic nerve sheath diameter(ONSD) in 3 mm posterior to the orbit/globe as shown in Figure 8. The schematic diagram of the proposed method is shown in Figure 2. 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 region. We also denoise images using a technique called image guided filtering [3] which is an edge-preserving method. Suppose that the filtering input image and guidance image are P and I respectively. The images are divided to overlapped windows with radius of r and following coefficients are computed in each window:

$$a_k = \frac{cov_k(I,P)}{var_k(I)+\varepsilon} \qquad b_k = \bar{p}_k - a_k\bar{I}_k \tag{1}$$

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

$$v(i) = \sum_{j=1}^{M} I_d(j,i) \tag{2}$$

This signal has two main peaks, Max_1 and Max_2, corresponding to the vertical borders of the ROI and a local minimum between these peaks corresponding to the dark region inside the sheaths. Suppose that the minimum of this signal is gth element of the signal which corresponds to the column where we can find the globe.

After finding the globe point and the ROI, we use a superpixel segmentation technique called simple linear iterative clustering (SLIC) to segment each image to superpixels. 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. We analyze the peaks and also derivatives of this row to calculate the ONSD. We repeat this process for all the images in the Ultrasound video and then we calculate the median of all the values (Voting).

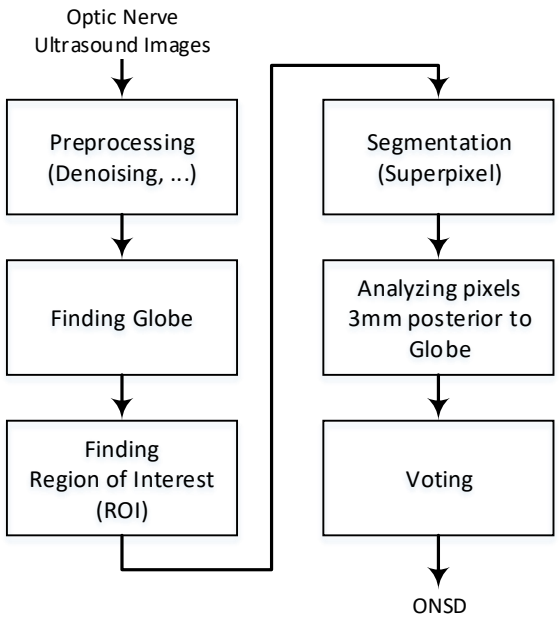


Figure 8: Schematic diagram of the proposed method

$$g = \underset{Max_1 \le i \le Max_2}{argmin} \; v(i) \qquad (3)$$

2. Significant results

We applied the proposed method on 52 videos of 26 patients (for each patient we have US images of both eyes) and calculated the average of the error between the proposed method and the ground truth (i.e. point of care manual measurements). The automated algorithm was able to process images, determine and measure ONSD with high precision when compared to clinicians' manual measurement with percentage of error difference between the two methods at 6.5% safely within the clinically accepted error. We will continue data collection and refinement of the algorithm to reduce the percentage error even further.

References:

1) Williams, P., 2017. Optic Nerve Sheath Diameter as a Bedside Assessment for Elevated Intracranial Pressure. *Case reports in critical care*, *2017*.
2) Kimberly HH, Shah S, Marill K, Noble V. Correlation of optic nerve sheath diameter with direct measurement of intracranial pressure. Academic Emergency Medicine. 2008 Feb 1;15(2):201-4.
3) He K, Sun J, Tang X. Guided image filtering. IEEE transactions on pattern analysis and machine intelligence. 2013 Jun;35(6):1397-409.
4) Achanta R, Shaji A, Smith K, Lucchi A, Fua P, Süsstrunk S. SLIC superpixels compared to state-of-the-art superpixel methods. IEEE transactions on pattern analysis and machine intelligence. 2012 Nov;34(11):2274-82.

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

Opportunity was provided for Mr. Brandon Cummings, a graduate student in the Bioinformatics Master Degree Program to present data at the 2018 MHSRS Symposium. Mr. Cummings works with the PI and Co-I on signal processing and data analysis. Mr. Cummings presented an abstract in a form of a poster presentation: (Abstract and poster are provided in the appendices)

- Brandon Cummings, BS, Brendan McCracken, BS, Chandler Rygalski, BS, Ashwin Belle, PhD, Kevin Ward, MD, M. Hakam Tiba, MD, MS.: A Signal Processing Approach for the Calculation of a Bioimpedance Index in the Assessment of Cerebrovascular Autoregulatory Status., Military Health System Research Symposium (MHSRS), Kissimmee, Florida, 2018.

B. How were the results disseminated to communities of interest?

Data was presented to the community of scientific peers at the Military Health System Research Symposium (MHSRS), Kissimmee, Florida, 2018 in the form of 2 poster presentation. (Abstracts and posters will be provided in the append

1. M. Hakam Tiba, MD, MS, Krishna Rajajee, MD, Craig Williamson, MD, Ashwin Belle, PhD, Sardar Ansari, PhD, Brandon Cummings, BS, Brendan McCracken, BS, Amanda Pennington, MS, Kevin Ward, MD.: Monitoring Traumatic Brain Injury Patients using Transocular Brain Impedance (TBI)., Military Health System Research Symposium (MHSRS), Kissimmee, Florida, 2018.
2. Brandon Cummings, BS, Brendan McCracken, BS, Chandler Rygalski, BS, Ashwin Belle, PhD, Kevin Ward, MD, M. Hakam Tiba, MD, MS.: A Signal Processing Approach for the Calculation of a Bioimpedance Index in the Assessment of Cerebrovascular Autoregulatory Status., Military Health System Research Symposium (MHSRS), Kissimmee, Florida, 2018.

C. 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 model and begin the model of blunt trauma TBI at a pace targeting 5 animals (either model)/ quarter. Human subjects' recruitment and testing will be continued with a target of 15 patients/ quarter. 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 next reporting period (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. Manuscript writing

D. 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?

i. Provisional patent application (62/506,971) Ocular Impedance-Based System for Brain Health Monitoring. Submitted May 16, 2017.
ii. Invention disclosure (D2018-0119) Automated Method to Calculate the Optic Nerve Sheath Diameter. Filed with the University of Michigan Office of Technology Transfer.
iii. Prototype developed by In2Being, LLC.
iv. Technology now exclusively licensed to New Vital Signs, Inc.

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 CAR 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.

E. CHANGES/PROBLEMS:

a. Changes in approach and reasons for change
Nothing to report

b. Actual or anticipated problems or delays and actions or plans to resolve them

i. We have encountered a lower than anticipated enrollment at the beginning of the reporting period due to the low number of Codman ICP monitors placed at Michigan Medicine. In order to continue to enroll patients we are including patients who have a ventriculostomy which has been clamped as part of their clinical care as well as a subdural screw or epidural sensor. The addition of ventriculostomy has enhanced our recruitment to meet our goal.
ii. The Michigan health system has experienced several computer connectivity issues that prevented us from collecting patients' waveforms from part of June and July. The health system IT department resolved the issue and restored connectivity.

c. Changes that had a significant impact on expenditures
Nothing to report

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

i. **Significant changes in use or care of human subjects:** None to report
ii. **Significant changes in use or care of vertebrate animals:** None to report
iii. **Significant changes in use of biohazards and/or select agents:** None to report

F. PRODUCTS:

a. Publications, conference papers, and presentations

i. **Journal publications.** Nothing to report
ii. **Books or other non-periodical, one-time publications.** Nothing to report

iii. **Other publications, conference papers, and presentations.**

Two abstracts have been submitted to the 2018 Military Health System Research Symposium (MHSRS) and have been accepted for poster presentations.

1. MHSRS-18-0614: Hakam Tiba, MD, MS, Krishna Rajajee, MD, Craig Williamson, MD, Ashwin Belle, PhD, Sardar Ansari, PhD, Brandon Cummings, BS, Brendan McCracken, BS, Amanda Pennington, MS, Kevin Ward, MD. Monitoring Traumatic Brain Injury Patients using Transocular Brain Impedance (TBI).
2. MHSRS-18-0734: Brandon Cummings, BS, Brendan McCracken, BS, Chandler Rygalski, BS, Ashwin Belle, PhD, Kevin Ward, MD, M. Hakam Tiba, MD, MS. A Signal Processing Approach for the Calculation of a Bioimpedance Index in the Assessment of Cerebrovascular Autoregulatory Status

b. **Website(s) or other Internet site(s)**
Nothing to report

c. **Technologies or techniques**
Nothing to report

d. **Inventions, patent applications, and/or licenses**

i. Provisional patent application (62/506,971) Submitted May 16, 2017. (Patent application included as part of the appendices.
ii. Invention disclosure (D2018-0119) Filed June 11, 2018 with the University of Michigan Office of Technology Transfer.

e. **Other Products**
Created a one-page description of the methodology for patients and their families. Material is provided in the appendices.

f. 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

G. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

a. **What individuals have worked on the project?**

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*

Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award).*

b.

Name:	*Mohamad Hakam Tiba, MD, MS*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	3
Contribution to Project:	*Oversight of data collection and analysis*
Funding Support:	

Name:	*Kevin Ward, MD*
Project Role:	*Co-I*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*Oversight of data collection and analysis*
Funding Support:	

Name:	*Venkatakrishna Rajajee, MD*
Project Role:	*Co-I*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*Perform ultrasounds, medical consultation*
Funding Support:	

Name:	*Craig Williamson, MD*
Project Role:	*Co-I*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*Perform ultrasounds, medical consultation*
Funding Support:	

Name:	*Hasan Alam, MD PhD*
Project Role:	*Co-I*

Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*Oversight of data collection and analysis*
Funding Support:	

Name:	*Kayvan Najarian, PhD*
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
Funding Support:	

Name:	*Reza Soroushmehr, PhD*
Project Role:	*Research Staff*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*5*
Contribution to Project:	Development of a computer image analysis algorithm
Funding Support:	

Name:	*Amanda Pennington, MS*
Project Role:	Clinical Project Manager
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*5*
Contribution to Project:	*Subject screening and enrollment, regulatory and compliance management, data collection*
Funding Support:	

Name:	*Brendan McCracken, BS*
Project Role:	*Laboratory Assistant Director*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*4*
Contribution to Project:	*Oversight and lab management, data collection, data analysis*
Funding Support:	

Name:	*Brandon Cummings, BS*
Project Role:	*Research Staff*
Researcher Identifier (e.g. ORCID ID):	

Nearest person month worked:	1
Contribution to Project:	Data collection, signal processing and data analysis
Funding Support:	

Name:	*Carmen Colmenero, BS*
Project Role:	*Research Staff*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	4
Contribution to Project:	*Animal lab duties, data collection, data analysis*
Funding Support:	

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

Name:	*Chandler Rygalski, BS*
Project Role:	*Research Staff*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	*Animal lab duties, data collection, data analysis*
Funding Support:	

Name:	*Daniel Taylor, MA*
Project Role:	*Data Engineer*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*3*
Contribution to Project:	Signal processing, data storage and analysis
Funding Support:	

Name:	*Mark Salamango, PhD*
Project Role:	*Data Engineer*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Signal processing, data storage and analysis
Funding Support:	

Name:	*Justin Massey, BS*
Project Role:	*Research Staff*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*3*
Contribution to Project:	*Screening and consenting patients, data collection*
Funding Support:	

Name:	*Erin Bisco, BS*
Project Role:	*Research Staff*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*Screening and consenting patients, data collection*
Funding Support:	

c. **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

d. **What other organizations were involved as partners?**
None

e. **Other.**
Nothing to report

H. SPECIAL REPORTING REQUIREMENTS

a. COLLABORATIVE AWARDS:
None

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

I. APPENDICES:

I. Abstract MHSRS-18-0614 and Poster
II. Abstract MHSRS-18-0734 and Poster
III. Educational Material for
- One-page Protocol Description for Patients and Patients' families
- Healthcare staff.

IV. Invention Disclosure
V. Patent Application
VI. PI Curriculum Vitae

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

DM160225 Prolonged Field Care Research Award

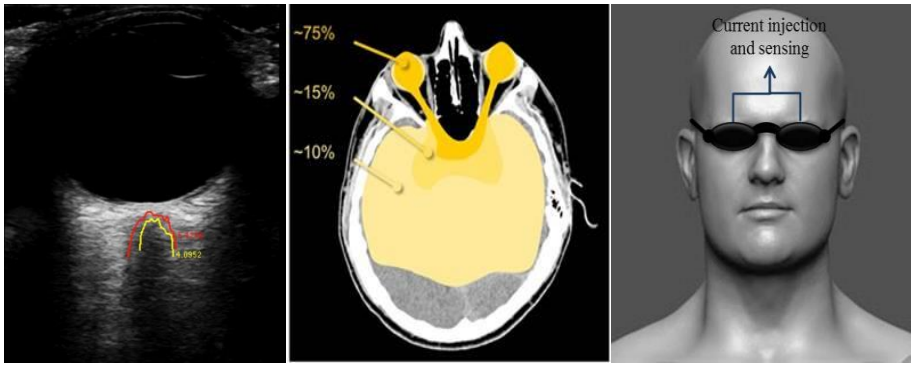
Co-PIs: Mohamad Hakam Tiba and Kevin R. Ward **Org:** University of Michigan **Award Amount:** $1,480,171

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**	

Updated: (04.12.2018)

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: None

- **Budget Expenditure to Date: $495,856**

II. Abstract MHSRS-18-0614

Monitoring Traumatic Brain Injury Patients using Transocular Brain Impedance (TBI).

M. Hakam Tiba, MD, MS[1,2], Krishna Rajajee, MD[2,3], Craig Williamson, MD[2,3], Ashwin Belle, PhD[1,2], Sardar Ansari, PhD[1,2], Brandon Cummings, BS[1,2], Brendan McCracken, BS[1,2], Amanda Pennington, MS[1,2], Kevin Ward, MD[1,2,4]

[1] Department of Emergency Medicine, University of Michigan, Ann Arbor, MI.
[2] Michigan Center of Integrative Research in Critical Care (MCIRCC), University of Michigan, Ann Arbor, MI.
[3] Department of Neurosurgery, University of Michigan, Ann Arbor, MI.
[4] Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI.

Introduction: Cerebrovascular autoregulation (CAR) is an auto-protective mechanism where intracranial vessels modulate their tone in order to maintain consistent levels of cerebral blood flow (CBF) in the face of changing intracranial or systemic pressure. CAR is often impaired after traumatic brain injury (TBI) which may result in secondary brain injury. CAR has been found to be a significant predictor of outcome after TBI as well as a beneficial means of optimizing cerebral perfusion pressure (CPP). Monitoring and assessment of CAR is envisioned to be useful and valuable during the management of TBI patients. However, direct assessment of CAR is difficult and has proven to be elusive. Current modalities assessing CAR are often invasive and hard to obtain in a meaningful and timely manner. The pressure-reactivity index (PRx), which describes how intracranial pressure (ICP) and mean arterial pressure (MAP) vary in relation to each other has been found to be an acceptable method of CAR assessment. However, the feasibility of PRx measurement is limited as it requires the use of ICP monitoring and heavy filtering to remove signal noise. In this investigation, we propose a novel measure to assess CAR non-invasively and in real time using brain bioimpedance measured through a transocular pathway. Bioimpedance measures the passive electrical properties of tissue and is affected directly by the volume of blood in the interrogated area, and indirectly by respiration. By harnessing such effects on bioimpedance, we hypothesize that this methodology will provide a real time and non-invasive assessment of CAR. **Methods:** This investigation utilizes a large animal model of TBI as well as monitoring of TBI patients in the ICU. In the animal model, male Yorkshire swine with a mean(SD) weight of 39.8(1.5) kg were anesthetized, mechanically ventilated, and instrumented to continuously monitor and record brain bioimpedance, ICP, MAP, and CBF. Cerebral blood volume and CPP were manipulated with maneuvers such as intravenous norepinephrine challenge, epidural hematoma or systemic hemorrhage. Brain bioimpedance was also continuously monitored in human TBI patients without any provocative maneuvers, provided that their ICP and MAP were already being monitored as part of their clinical management. In both the animal model and human monitoring, brain bioimpedance was obtained by placing ECG electrodes on the eyelids. PRx was calculated as the moving Pearson correlation between mean ICP and MAP over a two-minute window. The novel bioimpedance index (DZx) was calculated as a moving correlation between the respiratory changes in bioimpedance (dz) and MAP. **Results:** The diagnostic performance of DZx to predict CAR impairment was evaluated using the Receiver-Operator Characteristic (ROC) curves and Area Under the Curve (AUC). DZx was compared to PRx which was used as a reference point and gold standard at a threshold value of zero, with positive values indicating CAR impairment and negative values indicating active vasogenic vessels and intact CAR. The mean(SD) area under the ROC curve (AUC) for DZx was 0.82(0.12)% and 0.78 for animals and patients respectively, indicating a significant predictive ability. **Conclusion:** In this study, DZx appears to track changes in PRx with high precision. This indicates that DZx may prove useful as a portable, easily-applied, and significantly less-invasive alternative to PRx as a diagnostic index for the early assessment and detection of CAR impairment. Further studies in animals and humans are currently underway to further validate this promising technology.

Monitoring Traumatic Brain Injury Patients using Transocular Brain Impedance (TOBI)

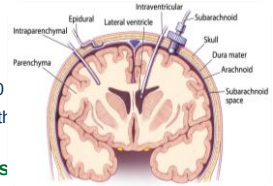
M. Hakam Tiba, MD, MS[1,2], Brendan M. McCracken , BS[1,2], Brandon Cummings, BS[1,2], Krishna Rajajee, MD[2,3], Craig Williamson, MD[2,3], Ashwin Belle, PhD[1,2], Sardar Ansari, PhD[1,2], Amanda Pennington, MS[1,2], Kevin Ward, MD[1,2,4]

[1] Department of Emergency Medicine, [2] Michigan Center of Integrative Research in Critical Care (MCIRCC), [3] Department of Neurosurgery, [4] Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI.

INTRODUCTION

Traumatic Brain Injury (TBI)

- "Silent epidemic" because of associated complications
- 2.5 million people sustained a TBI in 2010
- Accounts for 30% of all injury related death

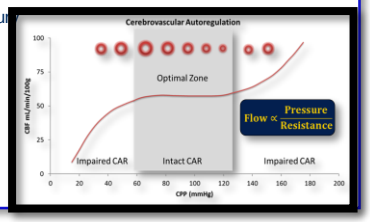


Management & Monitoring Strategies

- Monitoring of intracranial pressure (ICP)
  - *Invasive, increased risk of infection and further damage to the brain*
- Optimization of cerebral perfusion pressure (CPP) to a target level
- Preventing secondary brain damage (ischemia, edema)

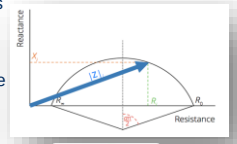
Cerebrovascular Autoregulation

- Vessels modulate their tone in response to pressure changes
- Prevention of secondary brain injur
- Auto-protective mechanism
- Maintains constant levels of cerebral blood flow (CBF)
- Impaired in severe head injury or acute ischemic stroke
- Predictor of poor outcomes in acute neurological disease



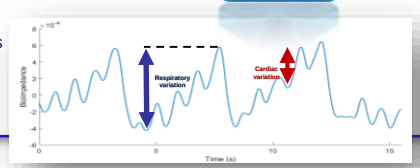
BIOIMPEDANCE

- Opposition to an electrical current flow through tissues
  - Passive bioelectricity. Tissues' response to external electrical excitation.
  - Cumulative effect of individual impedances
- **Blood** has a distinct effect on bioimpedance:
  - Good conductor of electricity
  - More blood present → lower bioimpedance
- **RESPIRATION** affects bioimpedance indirectly
- Thoracic pressure gradient
- Changes in venous return



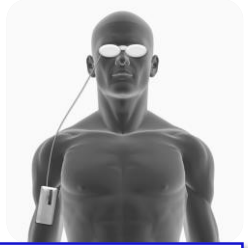
Transocular Brain Impedance (TOBI)

- Bipolar impedance measured from noninvasive electrodes placed over the eyelids
- Brain encounters a significant portion of the electrical current
- Impedance respiratory variation reflects changes in brain blood volume



AIM & Methods

- Utilize Transocular Brain Impedance to assess cerebrovascular autoregulation by comparing respiratory changes in bioimpedance to MAP, ICP, CPP, and cerebral blood flow.
- Use TOBI to create new and novel indices predictive of changes in cerebrovascular autoregulation.



Large Animal Model

- Anesthetized animals weighing an average(SD) of 39(0) kg were instrumented to monitor MAP, ICP, and CBF (using LDF and TCD)
- Bioimpedance was monitored through ECG-electrodes placed over eyelids
- Challenges such as vasopressors (norepinephrine) infusion, creation of epidural hematoma, and systemic hemorrhage were used to manipulate level of MAP, ICP and CBF out of optimal zone and temporarily impairing CAR
- **PRx:** was calculated as moving Pearson correlation of MAP and mean ICP
- **DZx (New index):** was computed as the moving Pearson correlation of MAP and DZ (Respiratory variability in the bioimpedance signal)

Clinical testing:

Moderate to severe TBI patients were recruited and bioimpedance was monitored alongside blood pressure and ICP for a period of 45 – 90min

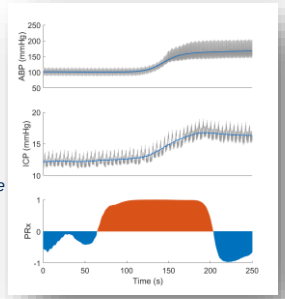
CEREBROVASCULAR AUTOREGULATION

- Continuous monitoring is beneficial to optimize CPP
- Precision or personalized approach in managing the components of CPP

Measuring autoregulation remains a challenge

Current monitoring modalities include:

- *Hemoglobin saturation by near-infrared spectroscopy (NIRS)*
- *Laser Doppler flowmetry of CBF*
- *Transcranial Doppler (TCD)*
  - *Invasive*
  - *Intermittent spot-checks*
  - *Require high levels of expertise*
  - *Unavailable at earlier echelons of care*
  - *Produce mixed results*



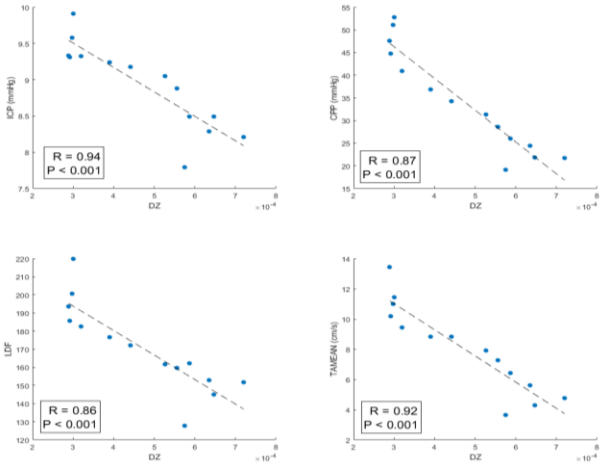
Pressure reactivity index (PRx)

Moving Pearson correlation between MAP and ICP

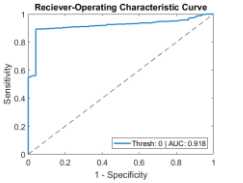
- Requires invasive ICP measurement
- Calculation is complex with noisy signal
- Often unavailable outside of research-minded academic settings

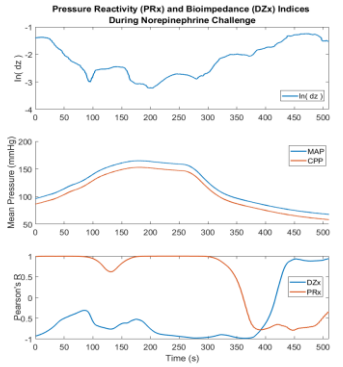
RESULTS

- The diagnostic ability of DZ and DZx to predict autoregulation impairment was assessed using:
  - Linear Regression
  - Receiver-Operator Characteristic (ROC) curves and Area Under the Curve
  - PRx was used as the gold standard at a threshold value of zero



- Mean(SD) AUC: **88.5(4.0)%**
- DZx and PRx are typically inverted about the zero point
- Negative PRx values indicate intact autoregulation
- Positive DZx values indicate intac





CONCLUSION

- TOBI may be used to track cerebrovascular autoregulation status with high precision
- Noninvasive techniques to assess CAR may prove to have tremendous potential in guiding patient triage and management, as well as improving outcomes

III. Abstract MHSRS-18-0734:

A Signal Processing Approach for the Calculation of a Bioimpedance Index in the Assessment of Cerebrovascular Autoregulatory Status

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Background: Cerebrovascular autoregulation (CAR) is an auto-protective mechanism in which the brain maintains consistent levels of cerebral blood flow (CBF) in the face of changing systemic and intracranial pressures by modulating vascular tone. Traumatic brain injuries (TBI) often impair CAR function, which can result in secondary injuries including ischemia, inflammation, and edema. Although CAR is believed to predict outcome and aid in optimization of cerebral perfusion pressure (CPP), direct assessment of CAR has proven elusive. The pressure reactivity index (PRx), which describes the relationship between intracranial pressure (ICP) and mean arterial pressure (MAP), is becoming an acceptable method of CAR measurement. Its values range from negative one to positive one, with negative values indicating intact CAR with active vasogenic vessels and positive values indicating impaired autoregulatory function. However, the feasibility of this measure is limited as it requires the use of continuous and invasive ICP monitoring. We previously described the ability of respiratory-driven changes in trans-ocular impedance (dz) to be a potential indicator of cerebrovascular parameters such as ICP and CBF, and further preliminary work shows that the combination of this metric with continuous MAP recording may provide an alternative to PRx measurement which does not require invasive ICP measurement. However, there exists a previously unmet need for continuous, real-time, algorithmic analysis of this bioimpedance index (DZx). Here, we introduce an algorithm which robustly quantifies respiratory variation and couples this data with continuous MAP to produce an index analogous to PRx. **Methods:** Data collection: Four anesthetized Yorkshire swine were surgically instrumented to measure ICP, MAP, and CBF. ICP and MAP were manipulated using challenges such as norepinephrine, simulated hematoma, and controlled hemorrhage. Additionally, two human patients with indwelling ICP and arterial blood pressure monitors were recruited from the neurosurgical ICU and passively monitored. In both cases, trans-ocular brain impedance was monitored at 200 Hz from two standard Ag/AgCl ECG electrodes placed over the eyelids for up to one hour. This yielded a combination of over XX hours of data from which to build the algorithm. Algorithm: The trans-ocular bioimpedance was first pre-processed to remove fluctuations in baseline and high-frequency noise. This was accomplished using a fourth-order, zero-phase Butterworth IIR bandpass filter with cutoff frequencies of 0.1 and 2 Hz. The result was a composite signal containing clear respiratory and cardiac component frequencies. The magnitude of the respiratory component (dz) was quantified using a root-mean-square (RMS) envelope with a window size of 30 seconds. This technique was chosen over a more direct peak-to-peak measure as it was found to be more robust when considering the high breath-to-breath variability in respiratory rate and tidal volume observed during spontaneous ventilation. MAP was estimated from a continuous arterial pressure waveform using a windowed moving average with a window size of 30 seconds. The bioimpedance index (DZx) was computed in a fashion analogous to PRx calculation, using a moving Pearson correlation with a window size of five minutes and a step size of one second. **Results:** The algorithm described above yields a continuous DZx signal with values ranging from negative one to positive one, inclusive. We observed that DZx tracks PRx in an opposite manner, which is consistent with previous observations that respiratory variations in bioimpedance (dz) are negatively correlated with ICP and CBF. Thus, it appears that negative values of DZx are indicate impaired CAR and positive values indicate intact CAR with active vasogenic vessels. Receiver-Operator Characteristic (ROC) curves were used to assess the predictive capability of DZx during several of the maneuvers in animals, with a threshold of PRx = 0. Mean(SD) area under the curve was found to be 0.82(0.12), indicating significant predictive ability. **Conclusion**: Respiratory variations in bioimpedance (dz) have been previously described as a novel alternative to traditional highly-invasive methods of cerebrovascular autoregulatory (CAR) status. Furthermore, coupling this metric with continuous MAP data results in a bioimpedance index (DZx) which may prove to be a viable alternative to the pressure-reactivity index (PRx) in the assessment of autoregulatory status.

A Signal Processing Approach for the Calculation of a Bioimpedance Index in the Assessment of Cerebrovascular Autoregulation

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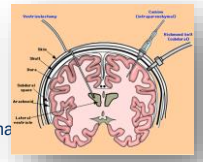
INTRODUCTION

Traumatic Brain Injury (TBI)



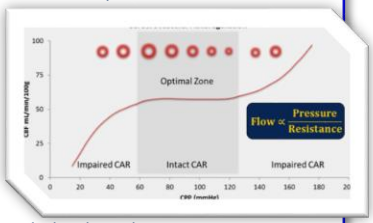
- 2.5 million people sustained a TBI in 2010
- TBI accounts for 30% of all injury related deaths

Current Management & Monitoring Strategies

- Preventing secondary brain damage (ischemia, edema
- Monitoring of intracranial pressure (ICP)
  - *Invasive, increased risk of infection and further damage to the brain*
- Optimization of cerebral perfusion pressure (CPP) to a target level

Cerebrovascular Autoregulation (CAR)

- The ability of vessels to modulate their tone in response to pressure changes
- Auto-protective mechanism which maintains constant levels of cerebral blood flow (CBF) to match metabolic demand
- Critical in the prevention of secondary brain injury
- Predictor of poor outcomes in acute neurological disease
- Impaired in severe head injury or acute ischemic stroke



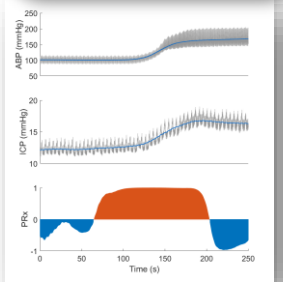
CURRENT MONITORING STRATEGIES

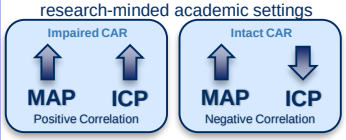
Measuring autoregulation remains a challenge

- Current monitoring modalities include:
  - *Transcranial Doppler (TCD)*
  - *Near-Infrared Spectroscopy (NIRS)*
  - *Laser Doppler Flowmetry (LDF)*
- Many of these methods are:
  - *Invasive*
  - *Intermittent spot-checks*
  - *Require high levels of expertise*
  - *Unavailable at earlier echelons of care*
  - *Produce mixed results*

Pressure reactivity index (PRx)

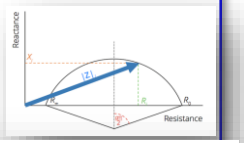
- Moving Pearson correlation between MAP and ICP
- Requires invasive ICP measurement
- Calculation produces noisy signal that may be difficult to interpret
- Often unavailable outside of research-minded academic settings





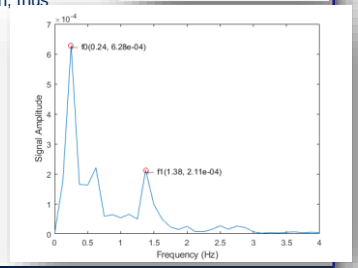
BIOIMPEDANCE

- Bioimpedance: the opposition of a tissue to an externally applied electric current
- Cumulative effect of individual impedances of each tissue component (muscle, adipose tissue, extracellular fluid, blood, etc.)
- Blood has a distinct effect on bioimpedance:
  - Good conductor of electricity
  - Changes with cardiac/respiratory cycles
- Respiratory variation causes thoracic pressure gradient which changes venous return, thus affecting local blood volume



Transocular Brain Impedance (TOBI)

- Bipolar impedance measured from noninvasive electrodes placed over the eyelids
- Brain encounters a significant portion of the electrical current sent through the globes
- Signal contains respiratory and cardiac components



AIM

To develop a noninvasive index of cerebrovascular autoregulation using characteristics from the trans-ocular brain impedance waveform.

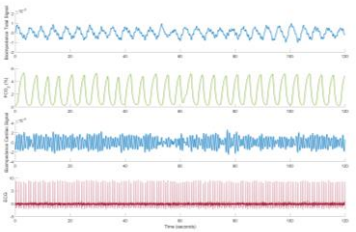
METHODS

Large Animal Model

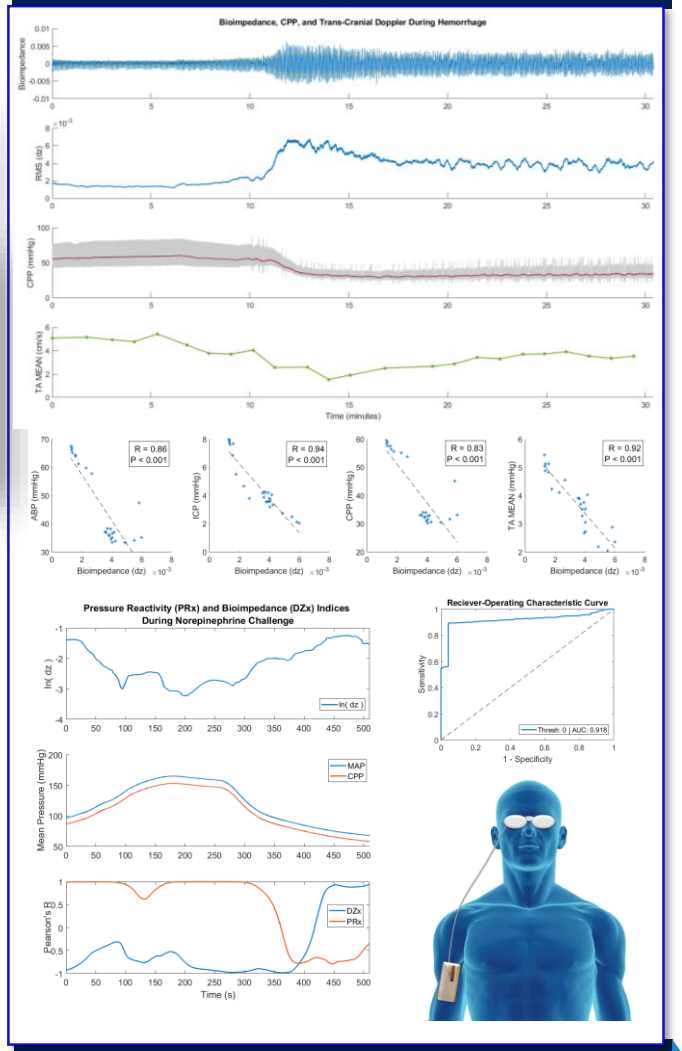
- Anesthetized swine weighing 40-45 kg were instrumented to monitor ICP, MAP, CBF, & TCD
- Bioimpedance was monitored noninvasively through ECG electrodes placed over eyelids
- Maneuvers such as norepinephrine challenges, simulated hematomas, and controlled arterial hemorrhage were used to manipulate CPP outside of optimal zone

Bioimpedance Signal Analysis

- Impedance waveform was pre-processed to remove baseline fluctuations and high-frequency noise
- Pre-processing results in composite signal containing cardia and respiratory frequencies
- *dz* calculated based on respirator signal amplitude
- A novel bioimpedance index (DZx) was calculated using MAP and *dz* in a fashion analogous to PRx.



RESULTS



CONCLUSION

- TOBI impedance may be used to track cerebrovascular autoregulation status with high precision and help optimize CPP
- Noninvasive techniques to assess CAR may prove to have tremendous potential in guiding patient triage and management, as well as improving outcomes

ASSESSMENT OF CEREBROVASCULAR AUTOREGULATION AND ICP USING BIOIMPEDANCE AND OCULAR ULTRASOUND

Background: Traumatic brain injury (TBI) is a major public health problem in the U.S. and around the world. The Defense and Veterans Brain Injury Center (DVBIC) has reported over 34,000 moderate to severe combat-related TBI events since 2000, and the CDC states that approximately 30% of injury related civilian deaths in the U.S. One of the significant management strategies in the management of TBI is aimed at preventing secondary brain damage, which mainly manifests itself as a brain ischemia and inflammation. Monitoring of intracranial pressure (ICP) and cerebrovascular autoregulation (CAR) to optimize cerebral perfusion pressure (CPP) to target and maintain cerebral blood flow (CBF) are the primary methods to prevent secondary injury and are the mainstays of current practice. Nonetheless, assessment of these parameters can be difficult, invasive, and are not typically available outside of research-minded neurosurgical ICUs. We propose two novel noninvasive methods to measure ICP and assess CAR using the eye as a window to the brain.

Specific Aim 1: Use non-invasive ocular electrical bioimpedance methodologies to track dynamic changes is cerebral blood flow (CBF) and associated changes in cerebrovascular autoregulation (CAR). Bioimpedance, a passive electrical property of tissues, has previously been shown in animals to track dynamic changes in cerebral blood flow associated with changes in ICP, MAP, CPP, and the pressure-reactivity index (a surrogate measure of CAR). Ultimately, we would like to develop new techniques and technologies that enhance the ability to rapidly and non-invasively assess ICP and CAR in the early stages of care for victims of TBI.

For the purposes of this study, ocular bioimpedance is measured using two noninvasive adhesive ECG electrodes placed over the eyelids for ~ 90 minutes. Our inclusion criteria require that subjects by 18 years old or older, admitted to a Michigan Medicine ICU with acute brain injury (TBI, cerebrovascular accident, subarachnoid hemorrhage, etc.) and have invasive intracranial pressure and arterial blood pressure monitoring in place. Patients who are younger than 18 years old, have a known pregnancy, have pre-existing eye disease (excluding vision issues such as near/far-sightedness, astigmatism, etc.) or traumatic globe injury, or are prisoners will be excluded from the study. Research staff will identify patients who fit these criteria and obtain informed consent. Testing may take up to several hours and may be repeated at a later date up to three times.

Specific Aim 2: Develop a computer image analysis algorithm and software program capable of automating the analysis of images of the optic nerve sheath diameter (ONSD) obtained by ultrasound to evaluate ICP. The optic nerve sheath (ONS) is a continuation of the brain's dura mater. Characteristics of the ONS, as well as blood flow to the eye, are known to be affected by ICP and CBF, potentially allowing the eye to serve as a window to the brain. Swelling of the optic disk (papilledema) due to the effect of high pressure in the subarachnoid space can take hours or days, making it unsuitable as a guide for the management of acute TBI. However, studies have shown that an increase in ICP results in the distension of the retrobulbular ONS within seconds. Measurement of the ONS diameter (ONSD) at a standardized 3mm distance behind the globe could be performed to identify distension using point-of-care ultrasound devices with specific transducers and imaging presets, however, manual measurement requires a highly trained operator and is subject to inter-operator variability. Preliminary data from our work on automated image analysis has been used to develop a speckle-tracking algorithm to image and quantify changes in ONSD. Once this algorithm has been successfully validated, a software program and user interface will be developed to automate the analysis of ONSD images to evaluate ICP.

For the purpose of this study, a linear array ultrasound transducer will be placed on the upper margin of the orbit (with the eyes closed). B-mode images will be collected and subjected to manual and algorithm measurement. Both of these measures will be evaluated as predictors of ICP. The ultrasound imaging will be performed on both eyes for each patient by Drs. Rajajee or Williamson. The inclusion and exclusion criteria are identical to those listed in Specific Aim 1.

For questions, comments, or concerns, please see the contact information listed below. This study has been approved by IRB-MED as protocol HUM00098976. This study is funded by the Department of Defense (Grant #DM160225) from 01/01/2018 through 12/31/2020.

Contact Information

PI: Dr. Hakam Tiba (734-764-6702)
Co-Is: Drs. Krishna Rajajee, Craig Williamson, Kevin Ward
Recruitment Contacts: Amanda Pennington (primary, 734-936-5947), Justin Massey, Erin Bisco
Research Staff: Brandon Cummings, Chandler Rygalski

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Assessment of Cerebrovascular Autoregulation and ICP using Bioimpedance and Ocular Ultrasound

26 January 2018

Aims and Hypothesis

Hypothesis: We hypothesize that ocular bioimpedance will non-invasively and continuously track changes in cerebral blood volume and predict CAR impairment, and that ultrasound assessment of ONSD using automated image analysis will enable a non-invasive estimation of ICP.

Specific Aims:

1. Use non-invasive ocular bioimpedance methodologies to track dynamic changes in CBF and autoregulation
2. Develop an algorithm to automate optic nerve sheath diameter measurement obtained by ultrasound to evaluate ICP

Bioimpedance

- Noninvasive, adhesive ECG electrodes placed over eyelids for up to 90 minutes
- Measures passive electrical properties of the brain through the optic nerve (bioimpedance)
- Respiratory-driven changes in bioimpedance are thought to correspond to changes in ICP and other neurological parameters[1]
- If successful, would result in a continuous, noninvasive, and dynamic measure of cerebrovascular autoregulation

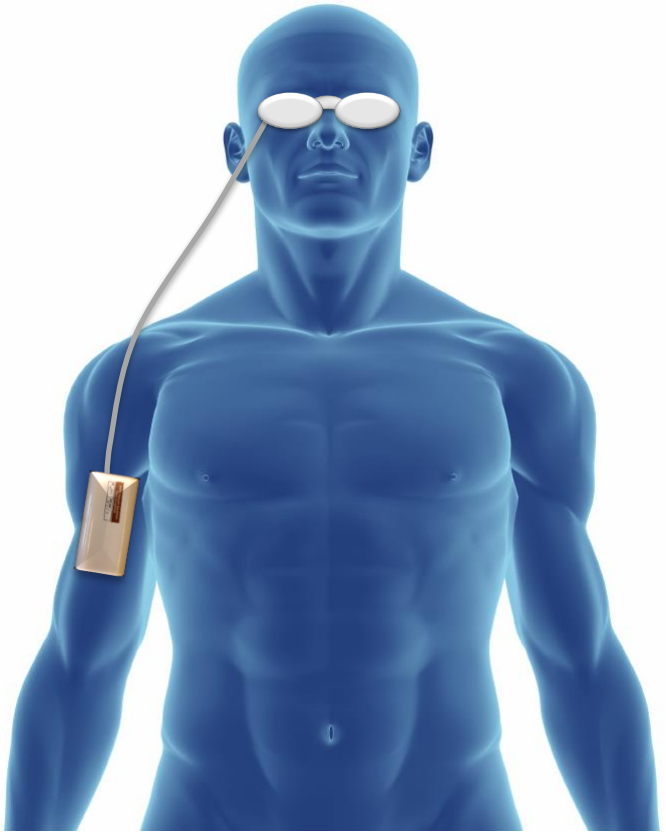

Figure 1. Illustration of future device prototype

1. Mohamad H. Tiba, Brendan M. McCracken, Sardar Ansari, Ashwin Belle, Brandon Cummings, Venkatakrishna Rajajee, Hasan Alam, Kevin R. Ward. “Novel Noninvasive Method of Cerebrovascular Blood Volume Assessment Using Brain Bioimpedance.” Journal of Neurotrauma, 2017, 34(22):3089-3096.

Optic Nerve Ultrasound

- Linear array transducer placed on upper margin of orbit (eyes closed)
- B-mode images will be subjected to novel algorithm to measure optic nerve sheath diameter
- Optic nerve sheath diameter is thought to be a noninvasive method of ICP assessment[2]
- Imaging will be performed on both eyes for each patient by Drs. Rajajee or Williamson

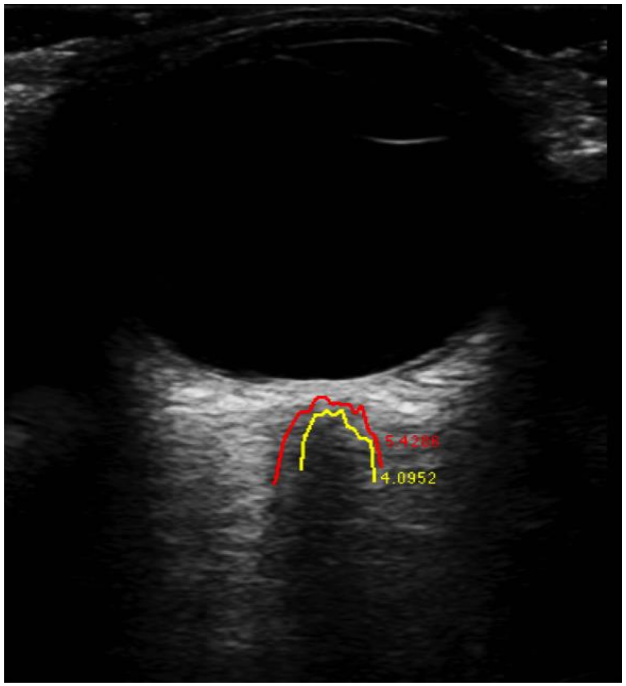

Figure 2. Optic nerve ultrasound image with inner and outer diameter of optic nerve sheath determined by multiple threshold segmentation algorithm.

2. Rajajee V, Fletcher JJ, Rochlen LR, Jacobs TL. “Comparison of accuracy of optic nerve ultrasound for the detection of intracranial hypertension in the setting of acutely fluctuating vs stable intracranial pressure: post-hoc analysis of data from a prospective, blinded single center study.” Crit Care. 2012 May 11;16(3):R79. doi: 10.1186/cc11336.

Enrollment Criteria

Inclusion

- Age ≥ 18 years
- Admitted to ICU at UMHS with brain injury
- Have invasive ICP and arterial blood pressure monitoring
  - Invasive ICP can be gathered from either an ICP monitor or an EVD which is clamped for ≥ 15mins

Exclusion

- Age < 18 years
- Known pregnancy
- Prisoners
- Pre-existing eye disease
  - Other than nearsightedness, farsightedness, age-related vision loss, or astigmatism
- Traumatic globe or facial injury

Recruitment:

- Research staff will identify patients who fit these criteria and obtain informed consent.
- Testing may take up to several hours and may be repeated at a later date up to three times

Personnel

- **PI:** Hakam Tiba (734-764-6702)
- **Co-I:** Krishna Rajajee, Craig Williamson, Kevin Ward
- **Recruitment contacts:**
  - Amanda Pennington (primary): (734 936-5947)
  - Justin Massey
  - Erin Bisco
- **Research Staff:** Brandon Cummings, Chandler Rygalski

Additional Information

- IRB Protocol #: HUM00098976
- Funded by Department of Defense
  - Grant #DM160225
  - Length of Study: 01/01/2018 to 12/31/2020

Automated method to calculate the optic nerve sheath diameter

The optic nerve is part of the central nervous system surrounded by cerebrospinal fluid (CSF) and encased in a sheath [1]. The sheath is continuous with the dura mater and diameter of this sheath changes rapidly with changing CSF pressure [1]. It has been shown that ventriculostomy measurements of intracranial pressure (ICP) are correlated with Ultrasound (US) optic nerve sheath diameter (ONSD) measurements [2]. Therefore, ONSD can be used as a non-invasive test for elevated ICP [2]. 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.

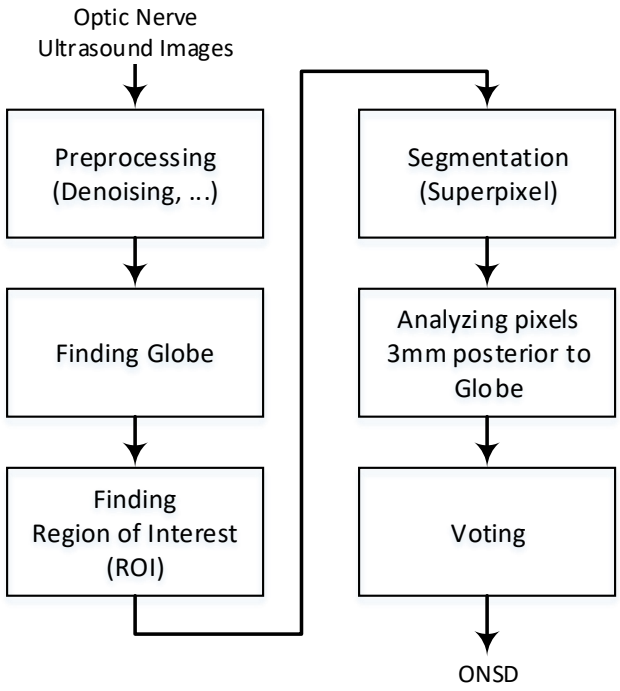

Figure 1: Schematic diagram of the proposed method

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. The schematic diagram of the proposed method is shown in figure 1. In the first stage of the proposed method, we perform preprocessing in which we denoise images and also normalize pixel intensities. After that and by analyzing the image integral we find the globe point. In order to find the region of interest we also analyze the image integral (summation of pixel values in each column). After that we use a superpixel segmentation technique called simple linear iterative clustering (SLIC) [3] to segment images to superpixels. Then, we analyze the row which is 3mm below the globe to calculate the ONSD. We repeat this process for all the images in the Ultrasound video and then we calculate the median of all the values (Voting).

References:

1) Williams, P., 2017. Optic Nerve Sheath Diameter as a Bedside Assessment for Elevated Intracranial Pressure. *Case reports in critical care*, *2017*.
2) Kimberly HH, Shah S, Marill K, Noble V. Correlation of optic nerve sheath diameter with direct measurement of intracranial pressure. Academic Emergency Medicine. 2008 Feb 1;15(2):201-4.
3) Achanta R, Shaji A, Smith K, Lucchi A, Fua P, Süsstrunk S. SLIC superpixels compared to state-of-the-art superpixel methods. IEEE transactions on pattern analysis and machine intelligence. 2012 Nov;34(11):2274-82.

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(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,

(54) Title: OCULAR IMPEDANCE-BASED SYSTEM FOR BRAIN HEALTH MONITORING

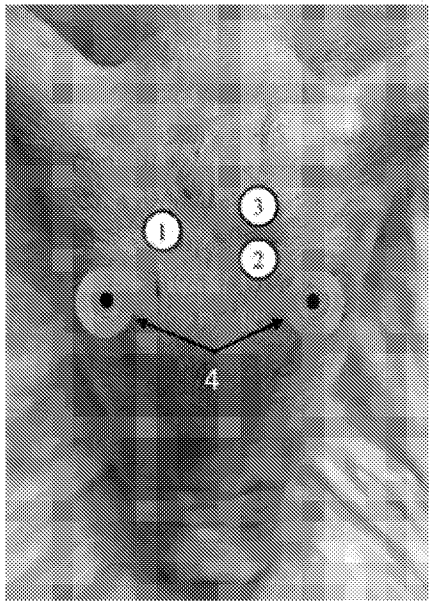

FIG. 1

(57) Abstract: Methods and systems monitor and assess brain bioimpedance through the use of an ocular window that assesses dynamic changes in cerebral blood volume (CBV). That ocular window is implemented through an ocular bioimpedance device that, in a non-invasive manner, measures numerous different brain health indicators using the bioimpedance measurements collected through the regions around the eyes. The ocular bioimpedance device may be goggles with localized measurement electrodes that include cathodes and anodes.

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[Continued on next page]

TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

OCULAR IMPEDANCE-BASED SYSTEM FOR BRAIN HEALTH MONITORING

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 62/506,971, filed May 16, 2017, entitled "Ocular Impedance Based System for Brain Health Monitoring," which is hereby incorporated by reference in its entirety.

FIELD OF THE DISCLOSURE

[0002] The present disclosure relates generally to techniques for monitoring and assessing brain health and, more particularly, to techniques for using an ocular impedance measurement to monitor and assess brain health.

BACKGROUND

[0003] The background description provided herein is for the purpose of generally presenting the context of the disclosure. Work of the presently named inventors, to the extent it is described in this background section, as well as aspects of the description that may not otherwise qualify as prior art at the time of filing, are neither expressly nor impliedly admitted as prior art against the present disclosure.

[0004] Traumatic brain injury (TBI) plays a major role in approximately 30% of injury related deaths in the United States and is often referred to as the "silent epidemic" due to associated complications that go undiagnosed and unnoticed, but that may have a lasting effect on health. Management strategies in the treatment of severe-TBI are usually aimed at preventing secondary brain injury, which mainly manifests itself as inflammation and brain ischemia. Monitoring of intracranial pressure (ICP) and optimization of cerebral perfusion pressure (CPP) to a target level have been proposed in the past as primary methods to prevent secondary injury and are the backbones of current practice. However, recent trials did not demonstrate clear benefits of ICP monitoring or targeted CPP to guide management.

[0005] Recent management approaches have attempted to utilize a more dynamic, and individualized precision optimization of CPP based on cerebrovascular autoregulation (CAR) using methods such as pressure reactivity index (PRx). Autoregulation is the ability of vessels to modulate their tone in response to changes in CPP and in so doing, maintain constant levels of cerebral blood flow (CBF) to match cerebral metabolic demand. CAR can be considered one of the most important

central nervous system auto-protective mechanisms against secondary brain injury. It is often impaired after severe-TBI and has been shown to be a predictor of outcome in patients with severe-TBI as well as various acute neurological diseases and ischemic injuries such as stroke, subarachnoid hemorrhage, brain tumors, cardiac arrest, hypertensive crises, and others.

[0006] However, current assessment methods of CAR lack the ability to directly monitor and track relative changes in cerebral blood volume. In addition, they cannot be utilized in settings outside the hospital. For example, current techniques using PRx require invasive monitoring.

[0007] There is a need for a technique that can be used to monitor dynamic changes in cerebral blood volume (CBV) as a reflection of CAR. There is a need for a portable, non-invasive sensor for measuring CBV changes in casualties with traumatic head injury and other cerebrovascular emergencies, suitable for use in varied environments (e.g., in civilian and military prehospital settings, emergency department trauma centers, intensive care units, etc.). This will allow early precision monitoring and treatment to prevent secondary brain damage.

SUMMARY OF THE INVENTION

[0008] The present techniques include methods and systems that monitor and assess brain bioimpedance through an ocular window as a method of assessing dynamic changes in cerebral blood volume (CBV). The techniques may be achieved in a non-invasive and continuous manner. The techniques monitor brain impedance to track changes in CBF, ICP and CPP that are associated with changes in cerebral blood volume. In this way, the techniques may be additionally used to evaluate CAR impairment

[0009] The present techniques provide a non-invasive way to measure numerous different brain health indicators using impedance measurements collected through the eye(s) of a subject. An ocular bioimpedance device is used to particularly localize measurement electrodes which may include combinations of cathodes and anodes.

[0010] In an example, an apparatus for evaluating brain health of a subject comprises: one or more electrodes; one or more processors; a computer-readable memory storing non-transient instructions that when executed by the one or more processors cause the apparatus to: provide, using the one or more electrodes, electrical current to an ocular region of the subject; sense, using the one or more electrodes, an electrical signal obtained from the ocular region of the subject, and determine a bioimpedance value of the subject from the electrical signal, wherein the

bioimpedance value represents a bioimpedance for a conduction path that includes at least a portion of the ocular and brain regions of the subject; and determine a brain health indicator from the bioimpedance information.

[0011] In another example, a method of evaluating brain health of a subject, the method comprising: in response to the provision of an electrical signal to an ocular region of a subject and detection of the electrical signal over a conduction path that includes at the ocular region and at least a portion of a brain region, determining an ocular-brain region bioimpedance value of the subject; determining, from the ocular-brain region bioimpedance value, changes in intracranial pressure over a sample time period, those changes corresponding to changes in cerebral blood volume (CBV); determining the effects of arterial pressure of the subject on CBV over the sample time period; determining the effects of mean intracranial pressure over the sample time period and mean arterial pressure over the sample time period on CBV; and determining a pressure reactivity index value from a correlation of the mean intracranial pressure and the mean arterial pressure, the pressure reactivity index on CBV indicating the brain health of the subject.

[0012] In another example, a method of evaluating brain health of a subject, the method comprising: receiving mean intracranial pressure data of the subject over a sample time period; receiving mean arterial pressure data for the subject over the sample time period; receiving a pressure reactivity index value determined from a correlation of the mean intracranial pressure and the mean arterial pressure, the pressure reactivity index indicating a brain health of the subject; in response to the provision of an electrical signal to an ocular region of the subject and detection of the electrical signal over a conduction path that includes at the ocular region and at least a portion of a brain region, determining an ocular-brain region bioimpedance of the subject over the sample time period; and combining the bioimpedance with the pressure reactivity index and producing a brain health indicator, the indicator having a positive value indicating a healthy brain state of the subject and a negative value indicating an unhealthy brain state of the subject.

[0013] In another example, a method of treating a brain condition of a subject, the method comprising: applying, to an ocular region of the subject, a brain-condition affecting treatment to the subject, the brain-condition affecting treatment being a transcranial direct current stimulation (tDCS), a transcranial alternating current stimulation (tACS), a biophotonic stimulation, and/or an acoustic stimulation.

[0014] In another example, an apparatus for treating a brain condition of a subject, the apparatus comprising: a housing configured to engage an ocular region of the subject, the housing having one or more electrodes configured to deliver electrical signals to the ocular region of the subject; one or more processors; a computer-readable memory storing non-transient instructions that when executed by the one or more processors cause the apparatus to: supply, using the one or more electrodes, an electrical signal in the form of a transcranial direct current stimulation (tDCS) and/or a transcranial alternating current stimulation (tACS) to the ocular region of the subject to treat the brain condition.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] The figures described below depict various aspects of the system and methods disclosed herein. It should be understood that each figure depicts an example of aspects of the present systems and methods.

[0016] FIG. 1 illustrates the placement on a test subject of a Foley catheter balloon (1), an ICP probe (2), a LDF probe (3) and ocular impedance electrodes (which may include combinations of cathodes and anodes) (4).

[0017] FIG. 2 is a plot of impedance waveform showing respiratory as well as cardiac cycle changes as measured using ocular impedance electrodes, in an example.

[0018] FIG. 3 illustrates scatter plots and correlation coefficients for A: During hyperventilation, Plot Al) dz vs. MAP, Plot A2) dz vs. ICP, Plot A3) dz vs. CPP, Plot A4) dz vs. CBF Change and Plot A5) dz vs. PetC02. B: During vasopressors infusion, Plot Bl) dz vs. MAP, Plot B2) dz vs. ICP, Plot B3) dz vs. CPP and Plot B4) dz vs. CBF Change. C: During epidural hematoma, Plot Cl) dz vs. ICP, Plot C2) dz vs. CPP, Plot C3) dz vs. CBF change. and D: During systemic hemorrhage, Plot Dl) dz vs. MAP, Plot D2) dz vs. ICP, Plot D3) dz vs. CPP and Plot D4) dz vs. CBF Change, where dz is the measured brain bioimpedance, MAP is the mean arterial pressure, ICP is the intracranial pressure, CPP is the cerebral perfusion pressure, and CBF is the cerebral blood flow.

[0019] FIG. 4 illustrates plots of an impedance waveform obtained with ocular impedance electrodes (cathode and anode) placed on various locations, namely plot Al) eyelids and plot A2) on scalp as well as the power spectral density for plot Bl) ocular impedance and plot B2) scalp impedance, respectively. The plots use the same scale.

[0020] FIG. 5 illustrates plots of brain-ocular impedance measurements obtained from ocular impedance electrodes. FIG. 5A) illustrates an example, measured impedance response during normal breathing. FIG. 5B) illustrates an example, measured impedance response during deep Breathing. FIG. 5C) illustrates an example, measured impedance response during a Valsalva maneuver. FIG. D) illustrates an example, measured impedance response while holding ones breath. Images scales vary change to allow visual inspection of the changes.

[0021] FIG. 6 illustrates changes in ICP, CBF, MAP and impedance during induction of epidural hematoma (in) then during removal of hematoma (out).

[0022] FIG. 7 illustrates an ocular bioimpedance measurement device, in accordance with an example.

[0023] FIG. 8 illustrates an ocular bioimpedance measurement device, in accordance with another example.

[0024] FIG. 9 illustrates an ocular bioimpedance measurement device, in accordance with another example.

[0025] FIG. 10 illustrates an example ocular bioimpedance assessment system, in accordance with an example herein.

[0026] FIG. 11 illustrates an ocular bioimpedance measurement device, in accordance with another example.

[0027] FIG. 12 illustrates an ocular bioimpedance measurement device, in accordance with another example.

DETAILED DESCRIPTION

[0028] Although the following text sets forth a detailed description of numerous different embodiments, it should be understood that the legal scope of the invention is defined by the words of the claims set forth at the end of this patent. The detailed description is to be construed as exemplary only and does not describe every possible embodiment, as describing every possible embodiment would be impractical, if not impossible. One could implement numerous alternate embodiments, using either current technology or technology developed after the filing date of this patent, which would still fall within the scope of the claims.

[0029] Bioimpedance is a measure of tissue resistance to an induced current or voltage. When the current is applied to the body, either as a whole or a portion thereof, bioimpedance will represent a cumulative effect of the impedances of each of the components through which the current flows. These components might include muscle tissue, bone, fat, intracellular and extracellular fluid, and blood. Blood, being a good conductor, has a distinct effect on impedance. Hence, physiologic or other induced events which modulate blood volume in an area of interest can be detected with impedance. An example of this is the effect of ventilation and even the cardiac cycle (FIG. 5). Therefore, the electrical impedance across a segment of tissue increases with decreased blood volume and decreases with increased blood volume. For example, the Valsalva maneuver is expected to increase cerebral volume (and hence reduce impedance) by increasing venous pressure and limiting venous return from the brain. Deep breathing is expected to demonstrate large swings in impedance as deep inhalation increases venous return from the brain, whereas breath holding is expected to minimize respiratory induced changes. The plots of FIGS. 5A - 5D provide examples. FIG. 6 illustrates trends and changes over time for MAP, ICP, CBF and impedance during the creation then removal of an epidural hematoma, a type of traumatic brain injury. As the plots of FIG. 6 demonstrate, impedance (dz) increases with decreased blood volume (i.e., decreased CBF) and vice versa.

[0030] The present techniques provide methods and systems to measure brain bioimpedance through the eyes, or other portions of the ocular region, using a bipolar arrangement. Example ocular bioimpedance devices are illustrated in FIGS. 7-9, 11, and 12. Because of the fluid interface and close proximity of the ocular bioimpedance devices to the brain along with a decrease in intervening tissues (hair, scalp, muscle, bone) and the direct connection of the ocular nerve to the brain, the present devices are able to ensure that the brain will encounter a significant portion of the electrical current sent through the devices. As small current may be applied through the eyes and the resulting the measured conductivity differences reflect the blood volume between the electrodes, which will include a large portion of the brain.

[0031] As discussed further herein, we've confirmed the assessment of bioimpedance through ocular measurements using various experimental maneuvers, such as through increasing ICP using inflation of the epidural balloon to demonstrate that changes in scalp or facial soft tissue blood flow are not responsible for the noted changes in impedance measured by the present techniques. In this way, we demonstrate an entirely new bioimpedance pathway measurement, uncorrelated to conventional scalp-based measurement techniques and heretofore unrecognized and un-isolated

for measurement and assessment. Further, the present techniques provide unexpected improvement in measuring bioimpedance and correlating that measurement to indicators of brain health, such as CBF, ICP and CPP.

[0032] Various experimental maneuvers (hyperventilation, vasopressors infusion, epidural hematoma and systemic hemorrhage) were used to vary the level of cerebral blood volume through changes in ICP, CPP and CBF for testing the efficacy of the present techniques. In each case, the ocular impedance measurement technique was able to detect changes in cerebral blood volume associated with the events. These tests demonstrated the ability of the present techniques to provide an effective mechanism for evaluating CAR and other intracranial events by monitoring changes in cerebral blood volume through impedance. As such, the techniques herein can be used to provide early evaluation of a patient with TBI or other cerebral insult, as a mechanism to evaluate CAR or the effect of other therapies on changes in cerebral blood volume prior to performing an invasive monitoring procedure on the patient or in conjunction with such invasive monitoring.

[0033] Furthermore, the present techniques may be combined with other monitoring techniques. For example, approaches such as calculation of the pressure reactivity index (PRx) (a moving Pearson correlation between mean arterial pressure MAP and ICP) have been shown to provide an independent predictor of brain health. The ocular measurement, bioimpedance techniques herein may be used in conjunction with PRx, where using an additional simultaneous measure such as cerebral impedance may allow improved use of PRx, which is an otherwise high noise measurement. Although overall tissue impedance changes over time, varies among individuals, and might be affected by the type and placement of electrodes (cathodes and anodes), the present techniques may reduce these effects by normalizing the impedance wave to its basal value negating the need to index to a baseline or normal value. Furthermore a PRx type measure utilizing MAP and cerebral impedance (using a moving Pearson correlation or other computational techniques) may be used as a precision measure of CAR.

[0034] The techniques herein can be used with PRx, and CAR more broadly in a number of ways. In some examples, the bioimpedance measurement techniques herein are used to determine ICP from which a more accurate PRx value can be determined, and a more accurate assessment of CAR results. In other examples, PRx may be determined independently, for example through known

techniques, and the PRx value may be correlated with bioimpedance for a more accurate assessment of CAR.

[0035] As an example embodiment, PRx is determined independently and then correlated with bioimpedance measured using the techniques described herein. For example, the bioimpedance can be combined with the pressure reactivity index to produce a brain health indicator, where, like the PRx value itself, that indicator having a negative value indicates a healthy brain state of the subject (i.e., an intact autoregulation) and the indicator having a positive value indicates an unhealthy brain state of the subject (i.e., an impaired autoregulation). The combination is a mathematical combination. For example, where the two values can be correlated over a sample time period using a moving Pearson correlation. Additionally, a moving Pearson correlation could be produced using MAP and dz measured by bioimpedance allowing both PRx and the additional MAP and dz correlation to be compared and tracked together.

[0036] We describe example testing procedures below. In a first example, we measured brain bioimpedance using an ocular-brain interface in a novel manner to assess real time changes in cerebral blood volume in response to a number of physiologic challenges. As blood is a good conductor of electricity, we hypothesized that changes in brain bioimpedance (dz) would track changes in cerebral blood volume. Six anesthetized swine were instrumented for invasive monitoring of ICP, mean arterial blood pressure (MAP), cerebral perfusion pressure (CPP) and cerebral blood flow (CBF). Bioimpedance was monitored continuously through ECG electrodes placed over the eyelids. Low current (0.1-1 mA, at 50 kHz) was applied and the electrical potential sensed through the same electrodes. Interventions such as hyperventilation, vasopressor administration, creation of an epidural hematoma, and systemic hemorrhage were used to manipulate levels of ICP, CPP, and CBF.

[0037] The results of the testing showed that bioimpedance (dz) is highly correlated to changes in ICP, CPP, and CBF ($r = -0.72$ to -0.88, $p < 0.0001$). The Receiver Operator Curve (ROC) for dz was plotted at different thresholds of CPP and percent change in CBF. The Area Under the Curve (AUC), sensitivity and specificity were calculated for each threshold. dz was shown to have a high predictive power with areas under the curve between (0.80 - 1.00, $p < 0.003$) with sensitivity and specificity varying between (83% - 100%) and (70% - 100%) respectively demonstrating the ability of dz to track changes in cerebral blood volume in real time.

[0038] Thus these experiments confirmed brain bioimpedance measured through the ocular brain interface can be used to track changes in CPP and CBF with high precision and are valuable assessing changes in cerebral blood volume and CAR.

[0039] Hyperventilation: The mechanical ventilator was initially set at baseline between 15-18 BPM to achieve an end tidal C02 (PetC02) at 35-40mm Hg. After baseline line readings, the respiratory rate (RR) was then increased fourfold in increments of 10 breaths until PetC02 reached ~20mm Hg. PetC02 was maintained at ~20mm Hg for 5-10min. RR was then decreased to baseline levels.

[0040] Vasopressor (norepinephrine) administration: Norepinephrine ^g/ml) was mixed with 500m L of 5% dextrose, administered by continuous infusion and titrated to reach an MAP of 160 mm Hg or greater. MAP was maintained at 160 mm Hg or greater for 5 minutes followed by stopping the infusion and allowing the animal's MAP to return to near baseline level. The norepinephrine infusion was repeated three times.

[0041] Epidural Hematoma: Simulation of an epidural hematoma was created using an 8 F Foley catheter as described by Metzger and colleagues. The balloon was filled with 6-8m L of normal saline at a rate of 0.5m L/min. ICP was monitored as the balloon was inflated to reach an ICP of 35-45mm Hg. The pressure was maintained for up to 5min followed by deflating the balloon at the same rate to bring ICP back to baseline level.

[0042] Systemic Hemorrhage: Lastly, animals were hemorrhaged through the femoral artery at a rate of 50-100mL/min. Hemorrhage continued uninterrupted for 16-20 minutes for a total volume of 800-1000m L representing 30-40% of the animals' estimated total blood volume.

[0043] In another experiment, three human subjects were consented and had electrodes placed on their closed eyelids for impedance monitoring using the same current and impedance monitoring parameters described in the animal experiments. Volunteers were placed in a supine position and then asked to perform the following maneuvers: normal breathing, deep breathing, breath holding, and Valsalva maneuvers.

[0044] We examined and evaluated changes in ocular-brain impedance as well as cerebral and systemic hemodynamics (CBF, ICP, CPP, MAP, PetC02) throughout baseline and during the various maneuvers. The raw impedance signal was initially smoothed and filtered using an iterative simple

moving average (three passes through a 20 point moving average). Impedance changes (dz) were calculated as $dz = (z_{max} - z_{min})/z_{max}$ then transformed using the natural logarithm.

[0045] For the two experiments, descriptive statistics used to assess effectiveness and to present means and standard deviations (SD), or median and interquartile ranges (IQR). A number of statistical analyses were utilized to compare the performance of dz with the invasive measures of MAP, ICP, CBF, CPP and PetC02 as follows. Pearson correlation was used to allow for visual inspection across a range of values. Receiver-Operator Characteristic (ROC) analysis and Area Under the Curve (AUC) were constructed to assess the predictive value of dz across a certain range of CBF and CPP values. The ROC graph depicts the relationship between true positive and false positive results; the greater the AUC, the better the predictive value. Significance level was considered at $a = 0.05$.

[0046] The results were as follows. For the first experiment, six animals with an average (SD) weight of 39.3(0.75) kg were tested. FIG. 2 demonstrates a baseline ocular-brain bioimpedance recording during mechanical ventilation noting both changes induced by respiration as well as superimposed cardiac cycle changes. Table 1 shows mean and (SD) values for weight MAP, ICP and CPP at baseline as well as range (minimum and maximum) and direction of changes during the various maneuvers. Pearson correlation showed high correlation between MAP, ICP, CPP, PetC02, CBF change and dz ($r = 0.6$ to 0.96, $p<0.0001$) *(see,* Table 1 and FIG. 3).

[0047] The ROC for dz during maneuvers was plotted at different thresholds of CPP and CBF changes. As shown in Table 2, AUCs, sensitivity and specificity were calculated for dz at each maneuver, dz demonstrated a high prediction capability with areas under the curve between (0.81 - 1.00, $p < 0.004$). The sensitivity and specificity of the impedance method associated with the above thresholds varied between (0.75 - 1.00) and (0.80 - 1.00) respectively. Table 2 lists various CPP and percent CBF change thresholds, and corresponding AUCs sensitivities and specificities for dz during maneuvers.

[0048] In order to better understand and quantitate the ability of the ocular pathway technique to incorporate or capture signal from the brain compared to scalp, we performed a separate experiment in one additional animal. The effectiveness of ocular current injection was compared to injection of the same amount of current through the scalp by placing one pair of electrodes on the eyelids and another pair close to the animal's ears with the same distance as the first pair. First, the resistance between the ocular and scalp electrodes was measured. Injecting current through the

ocular path resulted in a resistance of 0.5 MΩ compared to 3 MΩ, when current is injected into through the scalp indicating significantly better conductance through ocular injection of current. Next, the power spectral density was used to compare the amplitude of the respiratory component of dz *(see,* FIG. 4). The tidal respiration was controlled by the ventilator at rate of 16 breaths per minute. The power of the respiratory component was 6.5 times larger when the current was injected through the ocular path compared to the scalp path. The ratio was increased to 46 times when the animal was hyperventilated (RR=56).

[0049] The voltage gradient was then measured inside the brain by creating two burr holes in the skull, equally distanced between the ocular and scalp electrodes. The voltage gradients exerted by the current were measured by periodically interrupting the current injection. This was repeated 20 times and averaged using each pair of the electrodes. The results showed that the voltage gradient inside the brain was 40% higher when the current was injected through the ocular path compared to the scalp pathway, indicating that a larger portion of the current passes through the brain if current is injected through the ocular pathway. Finally, the animal was euthanized and the resistance between the two eyelids was measured absent of the electrical variations caused by brain activity and changes in the blood flow. This was repeated after a craniotomy was performed and the brain was removed followed by return of the removed cranium and scalp which was sutured back in place. The resistance values were R_T = lOkQ before and R_S = 30kΩ after the brain was removed. Assuming a parallel model for the resistance of the brain and the remaining tissue, skin and bone between the eyelids, the resistance of the brain was computed as R_B = RTRS/(RS-RT) = 300/20 kΩ = 15kQ. As a result, the ratio of current that passes through the brain to total current can be computed as I_B/I_T = RT/RB = 10/15. Hence, approximately two thirds of the current that is injected through the ocular pathway passes through the brain. While the current values for the electrical signal will vary for different subjects, with the improved techniques herein, bioimpedance can be measured from current values below about 10 mA, including below 5 mA, such as 4 mA and below or 2 mA and below. The lower bound of the current values will vary but may be 1 mA in some examples and even lower in other examples.

[0050] For the second experiment, the impedance data collected from the volunteer subjects demonstrated similar impedance waveforms noted from the animal experiments. Clear respiratory and cardiac cycle induced changes in the impedance waveform were observed. Deep inspiration and the Valsalva maneuver produced changes in impedance that would be expected from changes in cerebral blood volume produced by these respiratory maneuvers *(see,* FIG. 5).

[0051] FIGS. 7 -9 (as well as FIGS. 11 and 12) illustrate different example ocular bioimpedance devices and configurations.

[0052] FIG. 7 illustrates an example ocular bioimpedance device 100 in the form of goggles having a first lens 102 formed of a cap that may transparent, partially transparent or opaque. In the illustrated example, the first lens 102 further includes one or more electrodes 104, shown in FIG. 8, on an interior ocular region engagement portion of the lens 102. The engagement portion is configured such that when the lens 102 is put in place on a subject, the one or more electrodes 104 are in conductive contact with surface skin of the subject. The one or more electrodes 104 provides a conduction path to the skin for injecting current to the subject at a point of contact within and thus through the skin of the ocular region of the subject. That conductive contact may be a direct contact with the skin (such as the close eyelids), such that the point of contact with the electrodes 104 is direct, or that point of contact may be through another electrical conductor positioned between the electrodes 104 and the skin, for example, through a conductive film positioned on or around the ocular region for dispersing the electrical current more uniformly to the patient. The device 100 includes a second lens 106 that may be similar or identical to the first lens 102 except that the electrodes in the second lens 106 may be configured for sensing the injected current from the first lens and thereby being used as a bioimpedance sensor. Electrodes 108 of the second lens 106 may be in direct contact with the skin or in indirect contact, like that of the electrodes 104. Furthermore, while the electrical current path is described as starting with lens 102 and terminating with lens 106, such orientation may be imposed by the control circuitry coupled thereto (see, e.g., FIG. 10). The control circuitry could reverse the current flow direction and the operation would be the same. In some examples, the electrodes 104 and 108 are not identical, but may differ in electrode pattern and/or positioning. In such examples, the particular direction of current injection and sensing may be established, at least in part, based on the differences in those electrodes. The lens 102 and 106 are physically connected by a bridge 110 formed for a non-conducting material to further provide proper electrical isolation of the electrodes 104 and 108.

[0053] FIG. 9 illustrates another example configuration of an ocular bioimpedance device 200 similarly formed of a first lens 202 and a second lens 204. For the device 200 each lens includes both injection electrodes 206 and sensing electrodes 208. The patterning of the electrodes 206 and 208 can vary in pattern and position, as well. In the illustrated example, the injection electrodes 206 are disposed closer to a centroid of each lens 202 and 204, while the sensing electrodes 208

are positioned distally further from the centroid. The converse orientation may be used instead. In some examples, the electrodes 206 and 208 may be positioned in an alternating manner around the engagement surface of the lens. As is the case for the device 100, in some examples, only one of each electrode type is used on each lens.

[0054] While examples are shown of a device in contact with the skin, in yet other examples, contact is achieved between the corneal tissue and the device in a contact lens type manner.

[0055] The ocular bioimpedance techniques herein may be implemented in devices offering a combination of features. For example, lens-based devices for measuring bioimpedance may be combined with lens based devices and also include light transmitters in the lens cap, transmitters that are able to provide light therapy to a patient, such as goggles that provide white light therapy through light emitting diodes (LEDs), high color temperature light therapy (500 lux, 1000 lux, 1500 lux, or higher), blue light therapy devices (e.g., emitting at wavelengths at or between 450 nm and 500 nm), various near infrared and infrared wavelengths (730-770 nm, 850-890 nm, 880-920 nm, 950-970 nm) for cerebral blood oxygenation monitoring, mitochondrial repair, and others. Some such devices are used to treat Seasonal Affective Disorder (SAD), as well as migraines and other brain related conditions. In yet other examples, the ocular bioimpedance techniques herein may be used with an acoustic energy application device, such as that described in U.S. Patent No. 8,172,769, entitled "Method and apparatus for monitoring intra ocular and intra cranial pressure," the entire specification of which is hereby incorporated by reference.

[0056] Example devices are illustrated in FIGS. 11 and 12. FIG. 11 illustrates an ocular treatment device 400 having a lens 402 and a lens 406, each embedded with a photonic treatment LED array 410 and 412, respectively. The LED arrays 410 and 412 may be positioned over centralized portion of the cap forming the lens 402 and 406. These caps, as with the other example lens herein, may be opaque blocking external light from impinging upon the subject. Instead, for these examples, only photons from the arrays 410 and 412 would imping upon the subject. Of course, in other examples, the lens described herein may be transparent or semi-transparent (i.e., translucent). The arrays 410 and 412 generate photonic stimulation thereby providing therapy to the subject and/or diagnostic information to the subject, via this integrated goggle configuration. The device 400 may be controlled by a controller, an example of which is described in FIG. 10, that controls both photonic stimulation and electrical signals. The photonic stimulation may be provided during supply of an electrical signal applied and sensed through electrodes (not shown) that may be

positioned at the lens rim for ocular region contact, as shown in the examples of Figs. 8 and 9. The electrodes (not shown) would provide electrical signals for sensing bioimpedance and/or for treating the subject. In some examples, the photonic stimulation signals do not overlap with the supply of the electrical signal.

[0057] FIG. 12 illustrates a device 500 having lens 502 and 504 and integrated with an acoustic stimulation stage formed by two speakers 506 that are configured to provide acoustic stimulation for therapeutic or diagnostic purposes to the subject. While not limited to these examples, the speakers may be ear-plug styled headphones, over the ear headphones, miniature speakers attached to side of the subject or near the ocular region, including near or at a subject's temple, etc. That is, the speakers 506 may be configured to provide the acoustic stimulation at the ocular region and/or at a region on the subject other than the ocular region. Electrodes (not shown) would provide electrical signals for sensing bioimpedance and/or for treating the subject. A controller, like that of Fig. 10 would be used to control both electrical signals and acoustic stimulation signals.

[0058] FIG. 10 is an example block diagram 300 illustrating the various components used in implementing an example embodiment of the ocular bioimpedance measuring techniques herein. An analysis apparatus 302 is coupled to a patient 320 (e.g., a human or animal) via an ocular bioimpedance device 316 in accordance with executing the functions of the disclosed embodiments, and more specifically by current injecting electrodes 350 electrically coupled to the ocular region of the patient 320 and sensing electrodes 352 also electrically coupled to the ocular region of the patient 320. The analysis apparatus 302 may have a controller 304 operatively connected to the database 314 via a link 322 connected to an input/output (I/O) circuit 312. It should be noted that, while not shown, additional databases may be linked to the controller 304 in a known manner. The controller 304 includes a program memory 306, the processor 308 (may be called a microcontroller or a microprocessor), a random-access memory (RAM) 310, and the input/output (I/O) circuit 312, all of which are interconnected via an address/data bus 320. It should be appreciated that although only one microprocessor 308 is shown, the controller 304 may include multiple microprocessors 308. Similarly, the memory of the controller 304 may include multiple RAMs 310 and multiple program memories 306. Although the I/O circuit 312 is shown as a single block, it should be appreciated that the I/O circuit 312 may include a number of different types of I/O circuits. The RAM(s) 310 and the program memories 306 may be implemented as semiconductor memories, magnetically readable memories, and/or optically readable memories, for example. A link 324 may operatively connect the controller 304 to the ocular bioimpedance

device 316 through the I/O circuit 312. The ocular bioimpedance device 316 is operatively connected to the patient 320 via electrodes 350 and 352.

[0059] The program memory 306 and/or the RAM 310 may store various applications (i.e., machine readable instructions) for execution by the microprocessor 308. For example, an operating system 330 may generally control the operation of the testing apparatus 302 and provide a user interface to the testing apparatus 302 to implement the processes described herein. The program memory 306 and/or the RAM 310 may also store a variety of subroutines 332 for accessing specific functions of the testing apparatus 302. By way of example, and without limitation, the subroutines 332 may include, among other things: a subroutine for providing electrical current to the ocular region, a subroutine for taking bioimpedance measurements with the ocular bioimpedance device 316, a subroutine for determining a brain health indicator such as MAP, ICP, CBF, CPP, and ocular-brain impedance, and other subroutines, for example, implementing software keyboard functionality, interfacing with other hardware in the analysis apparatus 302, etc. For example, the processes described hereinabove may be stored on the program memory 306 for execution by the processor 308. The program memory 306 and/or the RAM 310 may further store data related to the configuration and/or operation of the analysis apparatus 302, and/or related to the operation of one or more subroutines 252. For example, the data may be data gathered by the ocular bioimpedance device 316, data determined and/or calculated by the processor 308, etc. In addition to the controller 304, the analysis apparatus 302 may include other hardware resources. The analysis apparatus 302 may also include various types of input/output hardware such as a visual display 326 and input device(s) 328 (e.g., keypad, keyboard, etc.). In an embodiment, the display 326 is touch-sensitive, and may cooperate with a software keyboard routine as one of the software routines 332 to accept user input. It may be advantageous for the analysis apparatus to communicate with a broader medical treatment network (not shown) through any of a number of known networking devices and techniques (e.g., through a commuter network such as a hospital or clinic intranet, the Internet, etc.). For example, the analysis apparatus may be connected to a medical records database, hospital management processing system, health care professional terminals (e.g., doctor stations, nurse stations), patient monitoring systems, automated drug delivery systems such as smart pumps, smart infusion systems, automated drug delivery systems, etc. Accordingly, the disclosed embodiments may be used as part of an automated closed loop system or as part of a decision assist system. By way of

example, a network interface 334 is coupled to the I/O interface 312 for connecting the analysis apparatus 302 to a network 336, through a wired or wireless connection.

[0060] In this way, the system 300 may be configured to determine the bioimpedance of the patient and then further assess brain health, by determining, for example, whether the bioimpedance changes over time, changes in response to treatment, or changes based on some other conditions. The system 300 is configured to determine brain health indicators such as MAP, ICP, CBF, CPP, and/or ocular-brain impedance and measure the same over time. As discussed further, changes in brain impedance can be used to titrate specific therapies such as MAP, ventilation parameters, ICP (through removal of cerebral spinal fluid), blood and fluid transfusions in order to optimize CPP and preserve CAR to improve cerebral outcomes. For example decreases in brain impedance in response to a rising MAP (indicating abnormal CAR) may prompt health care providers to reduce MAP. Another example may include an increase in impedance with no change in MAP or current care may indicate a rise in ICP thus prompting therapies to reduce ICP.

[0061] Thus, in further example embodiments, the bioimpedance determination techniques herein are combined with treatment techniques to improve the efficacy of such treatments.

[0062] For example, transcranial direct current stimulation (tDCS) has been proposed as a neuromodulation technique in the treatment of psychiatric illnesses, such as depression or schizophrenia, as well as in providing cognitive enhancement, such as memory enhancement, executive function enhancement, attention enhancement, and fluency enhancement. The techniques can include applying direct current stimulation to the brain through the use of electrodes externally placed on the skin at various locations on the scalp. However, the amount of current that actually penetrates the scalp and flows into the brain is believed to be very small. By including, through the techniques herein, electrodes in the ocular region it is now possible to deliver higher levels of current to the brain as outlined in the previously described experiments where ocular versus scalp pathways were compared in their ability to penetrate into the brain. This ocular pathway for delivery of direct current may be coupled with the simultaneous or intermittent measuring of brain bioimpedance in accordance with the present techniques as a means to help monitor therapy, as desired. This bioimpedance-based feedback can then be used to further guide the treatment, either manually or through completely- or partially-automated computer processing of the treatment signal. For example, in the context of determining an enhanced PRx using the present techniques, the transcranial direct current stimulation controller that controls the electrical

stimulation signals sent to the brain can be configured to automatically re-adjust the electrical signals (i.e., current value, frequency, waveform, voltage, etc.) in response to changes in the enhanced PRx, e.g., from the PRx changing from a negative value to a positive value.

[0063] In some example embodiments, traditional tDCS using the scalp as the site of current injection may be directed by using the ocular-brain bioimpedance signal to optimize the location of the tDCS electrodes. For example, tDCS electrodes may be positioned on a subject and a treatment is commenced. The bioimpedance is measured; and the electrodes are placed at another location, from which the bioimpedance is re-measured. By assessing the bioimpedance at each location, or a brain health indicator determined from the bioimpedance at each location, a treatment professional can determine which tDCS electrode location is better for treating the subject, for example, which location results in the better brain health indicator value.

[0064] These ocular-brain region bioimpedance enhanced treatment techniques are not limited to tDCS. The techniques can be used in a similar manner with transcranial alternating current stimulation (tACS) to control stimulation signal characteristics, the location of the tACS stimulation electrodes, etc. tACS is used similar to tDCS for numerous neuro- and neuro-psychiatric conditions ranging from stroke to depression. Thus the ocular-brain pathway techniques herein may be used to both deliver tACS and/or tDCS as well as monitor brain bioimpedance in addition to the ocular-brain pathway of bioimpedance being used to optimize scalp electrode placement for tDCS and tACS.

[0065] In yet other examples, these ocular-brain bioimpedance enhanced treatments may include biophotonic-based treatments and acoustic-based treatments. Biophotonic treatments include proton photonic stimulation to a subject and monitoring the effects thereof. These biophotonic treatments include what is commonly referred to as red light therapy, blue light therapy, infrared therapy, where stimulation photons are provided through the vision system of a subject. The bioimpedance techniques described herein may be used to monitor the effectiveness of biophotonic therapy by measuring, for example, a brain health indicator during treatment and assessing the effectiveness of that treatment in response.

[0066] Acoustic-based treatments may be analyzed in a similar manner. In some examples, acoustic energy is applied to the head of a subject to detect increases in intracranial pressure. Acoustic eye patches, for example, are applied to a patient's eye or eyelid, and an ultrasonic sweep generator applies an acoustic signal across the patient's skull, the signal being swept across a

predetermined range. The eye patches have piezoelectric film sensors for measuring the acoustic signal. In one embodiment the predetermined range is in the ultrasonic band and an analyzer determines from the output of the sensors a resonant frequency and a damping of acoustic amplitude at said resonant frequency, there being a correlation between said damping and intra cranial pressure. In another embodiment the predetermined range includes a range less than 20 kHz and the analyzer determines retinal artery pulsations, with pressure being applied to the eye until the pulsations disappear, such pressure being a measure of intra cranial pressure. These acoustic eye patches are configured with bioimpedance electrodes that measure the ocular-brain region bioimpedance of the subject during application of the acoustic signal. The effectiveness of the acoustic signals may then be assessed based on the changes in the bioimpedance values or brain health indicator(s) derived therefrom. And, as is the case with the other treatment examples herein (tDCS, tACS, biophotonics, etc.), the treatment signals may be adjusted to improve brain health based on the measured bioimpedance response.

[0067] Throughout this specification, plural instances may implement components, operations, or structures described as a single instance. Although individual operations of one or more methods are illustrated and described as separate operations, one or more of the individual operations may be performed concurrently, and nothing requires that the operations be performed in the order illustrated. Structures and functionality presented as separate components in example configurations may be implemented as a combined structure or component. Similarly, structures and functionality presented as a single component may be implemented as separate components. These and other variations, modifications, additions, and improvements fall within the scope of the subject matter herein.

[0068] Additionally, certain embodiments are described herein as including logic or a number of routines, subroutines, applications, or instructions. These may constitute either software (e.g., code embodied on a machine-readable medium or in a transmission signal) or hardware. In hardware, the routines, etc., are tangible units capable of performing certain operations and may be configured or arranged in a certain manner. In example embodiments, one or more computer systems (e.g., a standalone, client or server computer system) or one or more hardware modules of a computer system (e.g., a processor or a group of processors) may be configured by software (e.g., an application or application portion) as a hardware module that operates to perform certain operations as described herein.

[0069] In various embodiments, a hardware module may be implemented mechanically or electronically. For example, a hardware module may comprise dedicated circuitry or logic that is permanently configured (e.g., as a special-purpose processor, such as a field programmable gate array (FPGA) or an application-specific integrated circuit (ASIC)) to perform certain operations. A hardware module may also comprise programmable logic or circuitry (e.g., as encompassed within a general-purpose processor or other programmable processor) that is temporarily configured by software to perform certain operations. It will be appreciated that the decision to implement a hardware module mechanically, in dedicated and permanently configured circuitry, or in temporarily configured circuitry (e.g., configured by software) may be driven by cost and time considerations.

[0070] Accordingly, the term "hardware module" should be understood to encompass a tangible entity, be that an entity that is physically constructed, permanently configured (e.g., hardwired), or temporarily configured (e.g., programmed) to operate in a certain manner or to perform certain operations described herein. Considering embodiments in which hardware modules are temporarily configured (e.g., programmed), each of the hardware modules need not be configured or instantiated at any one instance in time. For example, where the hardware modules comprise a general-purpose processor configured using software, the general-purpose processor may be configured as respective different hardware modules at different times. Software may accordingly configure a processor, for example, to constitute a particular hardware module at one instance of time and to constitute a different hardware module at a different instance of time.

[0071] Hardware modules can provide information to, and receive information from, other hardware modules. Accordingly, the described hardware modules may be regarded as being communicatively coupled. Where multiple of such hardware modules exist contemporaneously, communications may be achieved through signal transmission (e.g., over appropriate circuits and buses) that connects the hardware modules. In embodiments in which multiple hardware modules are configured or instantiated at different times, communications between such hardware modules may be achieved, for example, through the storage and retrieval of information in memory structures to which the multiple hardware modules have access. For example, one hardware module may perform an operation and store the output of that operation in a memory device to which it is communicatively coupled. A further hardware module may then, at a later time, access the memory device to retrieve and process the stored output. Hardware modules may also initiate

comm unications with input or output devices, and can operate on a resource (e.g., a collection of information).

[0072] The various operations of the example methods described herein may be performed, at least partially, by one or more processors that are temporarily configured (e.g., by software) or that are permanently configured to perform the relevant operations. Whether temporarily or permanently configured, such processors may constitute processor-implemented modules that operate to perform one or more operations or functions. The modules referred to herein may, in some example embodiments, comprise processor-implemented modules.

[0073] Similarly, the methods or routines described herein may be at least partially processor-implemented. For example, at least some of the operations of a method may be performed by one or more processors or by processor-implemented hardware modules. The performance of certain of the operations may be distributed among the one or more processors, not only residing within a single machine (having different processing abilities), but also deployed across a number of machines. In some example embodiments, the processors may be located in a single location (e.g., deployed in the field, in an office environment, or as part of a server farm), while in other embodiments the processors may be distributed across a number of locations.

[0074] Unless specifically stated otherwise, discussions herein using words such as "processing," "computing," "calculating," "determining," "presenting," "displaying," or the like may refer to actions or processes on a GPU thread that manipulates or transforms data represented as physical (e.g., electronic, magnetic, or optical) quantities within one or more memories (e.g., volatile memory, non-volatile memory, or a combination thereof), registers, or other machine components that receive, store, transmit, or display information.

[0075] As used herein any reference to "one embodiment" or "an embodiment" means that a particular element, feature, structure, or characteristic described in connection with the embodiment is included in at least one embodiment. The appearances of the phrase "in one embodiment" in various places in the specification are not necessarily all referring to the same embodiment.

[0076] Some embodiments may be described using the expression "coupled" and "connected" along with their derivatives. For example, some embodiments may be described using the term "coupled" to indicate that two or more elements are in direct physical or electrical contact. The term "coupled," however, may also mean that two or more elements are not in direct contact with

each other, but yet still co-operate or interact with each other. The embodiments are not limited in this context.

[0077] As used herein, the terms "comprises," "comprising," "includes," "including," "has," "having" or any other variation thereof, are intended to cover a non-exclusive inclusion. For example, a process, method, article, or apparatus that comprises a list of elements is not necessarily limited to only those elements but may include other elements not expressly listed or inherent to such process, method, article, or apparatus. Further, unless expressly stated to the contrary, "or" refers to an inclusive or and not to an exclusive or. For example, a condition A or B is satisfied by any one of the following: A is true (or present) and B is false (or not present), A is false (or not present) and B is true (or present), and both A and B are true (or present).

[0078] In addition, use of the "a" or "an" are employed to describe elements and components of the embodiments herein. This is done merely for convenience and to give a general sense of the description. This description, and the claims that follow, should be read to include one or at least one and the singular also includes the plural unless it is obvious that it is meant otherwise.

[0079] This detailed description is to be construed as an example only and does not describe every possible embodiment, as describing every possible embodiment would be impractical, if not impossible. One could implement numerous alternate embodiments, using either current technology or technology developed after the filing date of this application.

WHAT IS CLAIMED:

1. A apparatus for evaluating brain health of a subject, the apparatus comprising:

one or more electrodes;

one or more processors;

a computer-readable memory storing non-transient instructions that when executed by the one or more processors cause the apparatus to:

provide, using the one or more electrodes, electrical current to an ocular region of the subject;

sense, using the one or more electrodes, an electrical signal obtained from the ocular region of the subject, and determine a bioimpedance value of the subject from the electrical signal, wherein the bioimpedance value represents a bioimpedance for a conduction path that includes at least a portion of the ocular and brain regions of the subject; and

determine a brain health indicator from the bioimpedance information.

2. The apparatus of claim 1, wherein the brain health indicator indicates at least one of changes (i) in cerebral blood volume (CBV), (ii) cerebral autoregulation (CAR), (iii) intracranial pressure (ICP), (iv) cerebral perfusion pressure (CPP), (v) a perfusion reactivity index (PRx), (vi) cerebral blood flow (CBF), (vii) blood pressure, and (viii) ventilation.

3. The apparatus of claim 1, wherein the computer-readable memory storing non-transient instructions that when executed by the one or more processors cause the apparatus to determine respiration rate, respiration quality, and/or heart rate of the subject.

4. The apparatus of claim 1, further comprising a goggle having a first lens and a second lens, wherein the one or more electrodes are positioned on interior surfaces of the first and second lens, respectively, to provide electrical conduction path from the ocular region of the subject to the brain.

5. The apparatus of claim 4, wherein the first lens comprises current injecting electrodes and the second lens comprises current sensing electrodes.

6. The apparatus of claim 4, wherein the first lens comprises current injecting electrodes and current sensing electrodes, and wherein the second lens comprises current injecting electrodes and current sensing electrodes.

7. A method of evaluating brain health of a subject, the method comprising:

in response to the provision of an electrical signal to an ocular region of a subject and detection of the electrical signal over a conduction path that includes at the ocular region and at least a portion of a brain region, determining an ocular-brain region bioimpedance value of the subject;

determining, from the ocular-brain region bioimpedance value, changes in intracranial pressure over a sample time period, those changes corresponding to changes in cerebral blood volume (CBV);

determining the effects of arterial pressure of the subject on CBV over the sample time period;

determining the effects of mean intracranial pressure over the sample time period and mean arterial pressure over the sample time period on CBV; and

determining a pressure reactivity index value from a correlation of the mean intracranial pressure and the mean arterial pressure, the pressure reactivity index on CBV indicating a brain health of the subject.

8. A method of evaluating brain health of a subject, the method comprising:

receiving mean intracranial pressure data of the subject over a sample time period;

receiving mean arterial pressure data for the subject over the sample time period;

receiving a pressure reactivity index value determined from a correlation of the mean intracranial pressure and the mean arterial pressure, the pressure reactivity index indicating a brain health of the subject;

in response to the provision of an electrical signal to an ocular region of the subject and detection of the electrical signal over a conduction path that includes at the ocular region and at least a portion of a brain region, determining an ocular-brain region bioimpedance of the subject over the sample time period; and

combining the bioimpedance with the pressure reactivity index and producing a brain health indicator, the indicator having a positive value indicating a healthy brain state of the subject and a negative value indicating an unhealthy brain state of the subject.

9. The method of claim 8, wherein combining the bioimpedance with the pressure reactivity index comprises performing a moving Pearson correlation between pressure reactivity index and the bioimpedance and/or a moving Pearson correlation between mean arterial pressure and bioimpedance.

10. A method of treating a brain condition of a subject, the method comprising:

applying, to an ocular region of the subject, a brain-condition affecting treatment to the subject, the brain-condition affecting treatment being a transcranial direct current stimulation (tDCS), a transcranial alternating current stimulation (tACS), a biophotonic stimulation, and/or an acoustic stimulation.

11. The method of treatment of claim 10, further comprising:

measuring an ocular-brain region bioimpedance of the subject over a treatment time of the brain-condition affecting treatment; and

assessing an efficacy of the brain-condition affecting treatment based on changes in the ocular-brain region bioimpedance over the treatment time.

12. The method of treatment of claim 11, wherein measuring the ocular-brain region bioimpedance of the subject over the treatment time of the brain-condition affecting treatment comprises:

providing an electrical signal to an ocular region of the subject through one or more electrodes placed on an outer surface of the subject at the ocular region of the subject;

detecting the electrical signal over a conduction path of the subject, that conduction path including the ocular region and at least a portion of a brain region; and

determining the ocular-brain region bioimpedance from the detected electrical signal.

13. The method of claim 12, wherein assessing the efficacy of the brain-condition affecting treatment based on changes in the ocular-brain region bioimpedance over the treatment time comprises:

determining a brain health indicator from the bioim pedance information, wherein the brain health indicator indicates at least one of changes (i) in cerebral blood volume (CBV), (ii) cerebral autoregulation (CAR), (iii) intracranial pressure (ICP), (iv) cerebral perfusion pressure (CPP), (v) a perfusion reactivity index (PRx), (vi) cerebral blood flow (CBF), (vii) blood pressure, and (viii) ventilation; and

assessing the brain health indicator to determine if the brain health indicator has an acceptable brain health indicator value or an unacceptable brain health indicator value.

14. An apparatus for treating a brain condition of a subject, the apparatus comprising:

a housing configured to engage an ocular region of the subject, the housing having one or more electrodes configured to deliver electrical signals to the ocular region of the subject;

one or more processors;

a computer-readable memory storing non-transient instructions that when executed by the one or more processors cause the apparatus to:

supply, using the one or more electrodes, an electrical signal in the form of a transcranial direct current stimulation (tDCS) and/or a transcranial alternating current stimulation (tACS) to the ocular region of the subject to treat the brain condition.

15. The apparatus of claim 14, wherein the housing is a goggle having a first lens and a second lens, wherein the one or more electrodes are positioned on interior surfaces of the first and second lens, respectively, to provide electrical conduction path from the ocular region of the subject to the brain.

16. The apparatus of claim 15, further comprising a photonic stimulation to provide therapy and/or diagnostic information integrated with the goggle and configured to provide photonic stimulation for therapy and/or diagnostic information to the brain through the ocular region.

17. The apparatus of claim 16, wherein the photonic stimulation is provided during supply of the electrical signal.

18. The apparatus of claim 16, wherein the photonic stimulation does not overlap with the supply of the electrical signal.

19. The apparatus of claim 15, further comprising an acoustic stimulation stage configured to provide acoustic stimulation for therapeutic or diagnostic purposes to the subject.

20. The apparatus of claim 19, wherein the acoustic stimulation stage is configured to provide the acoustic stimulation at the ocular region.

21. The apparatus of claim 19, wherein the acoustic stimulation stage is configured to provide the acoustic stimulation at a region on the subject other than the ocular region.

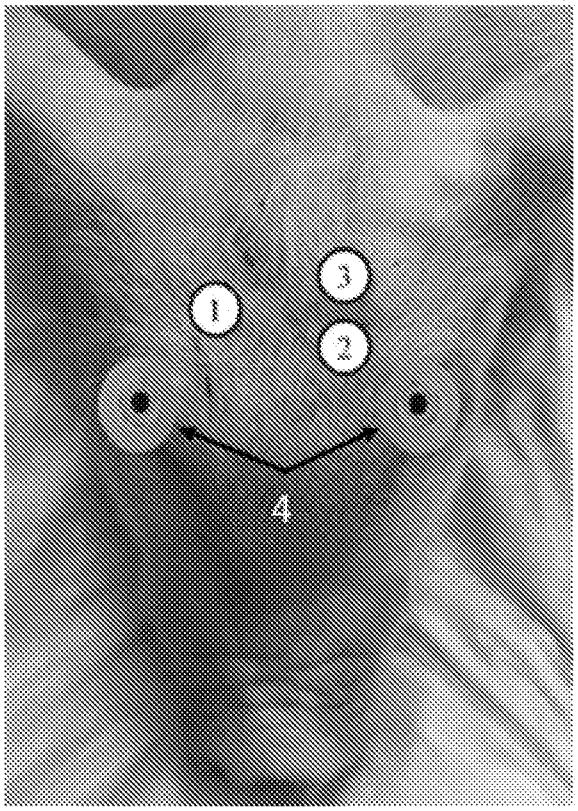


FIG. 1

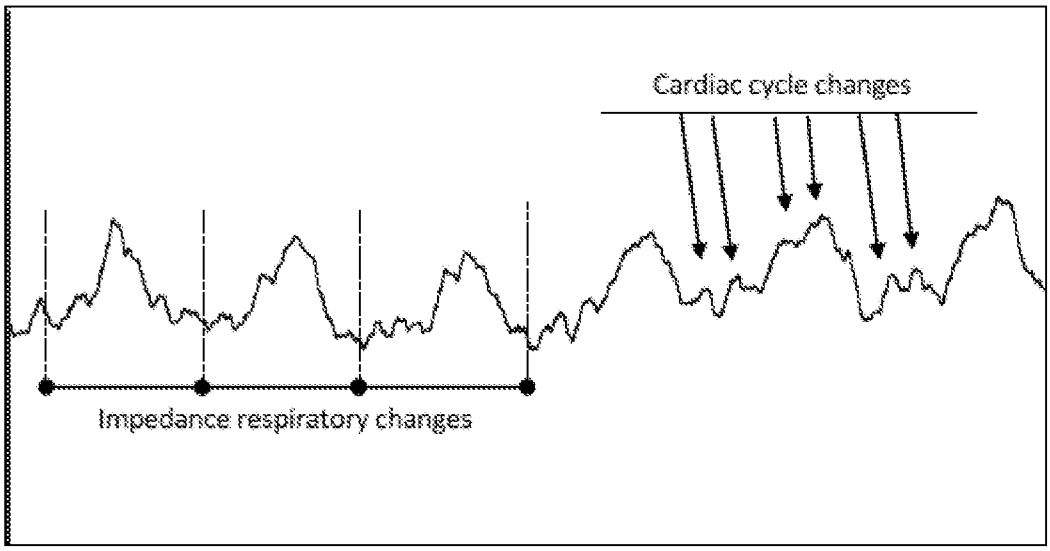


FIG. 2

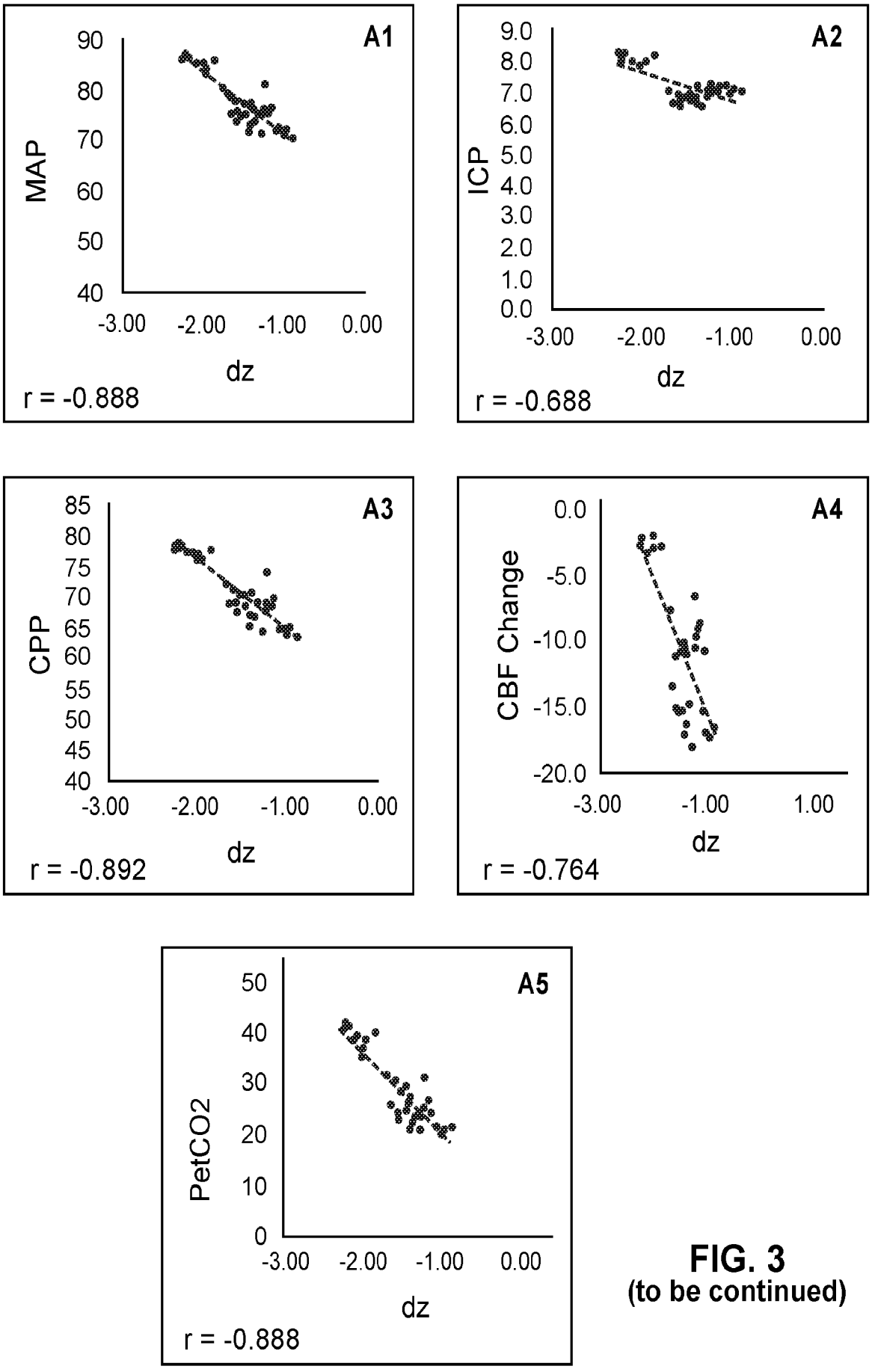


FIG. 3
(to be continued)

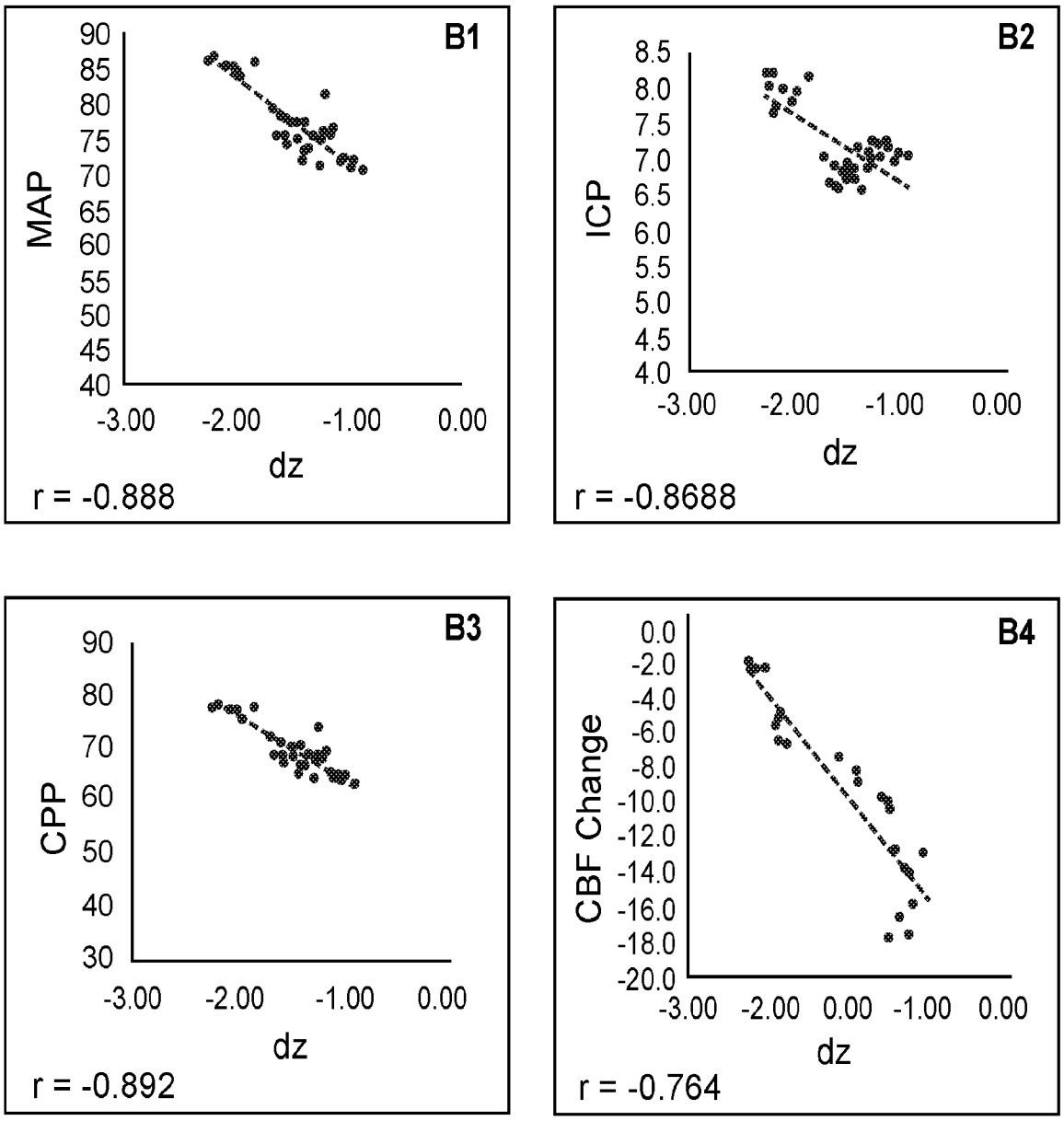


FIG. 3
(to be continued)

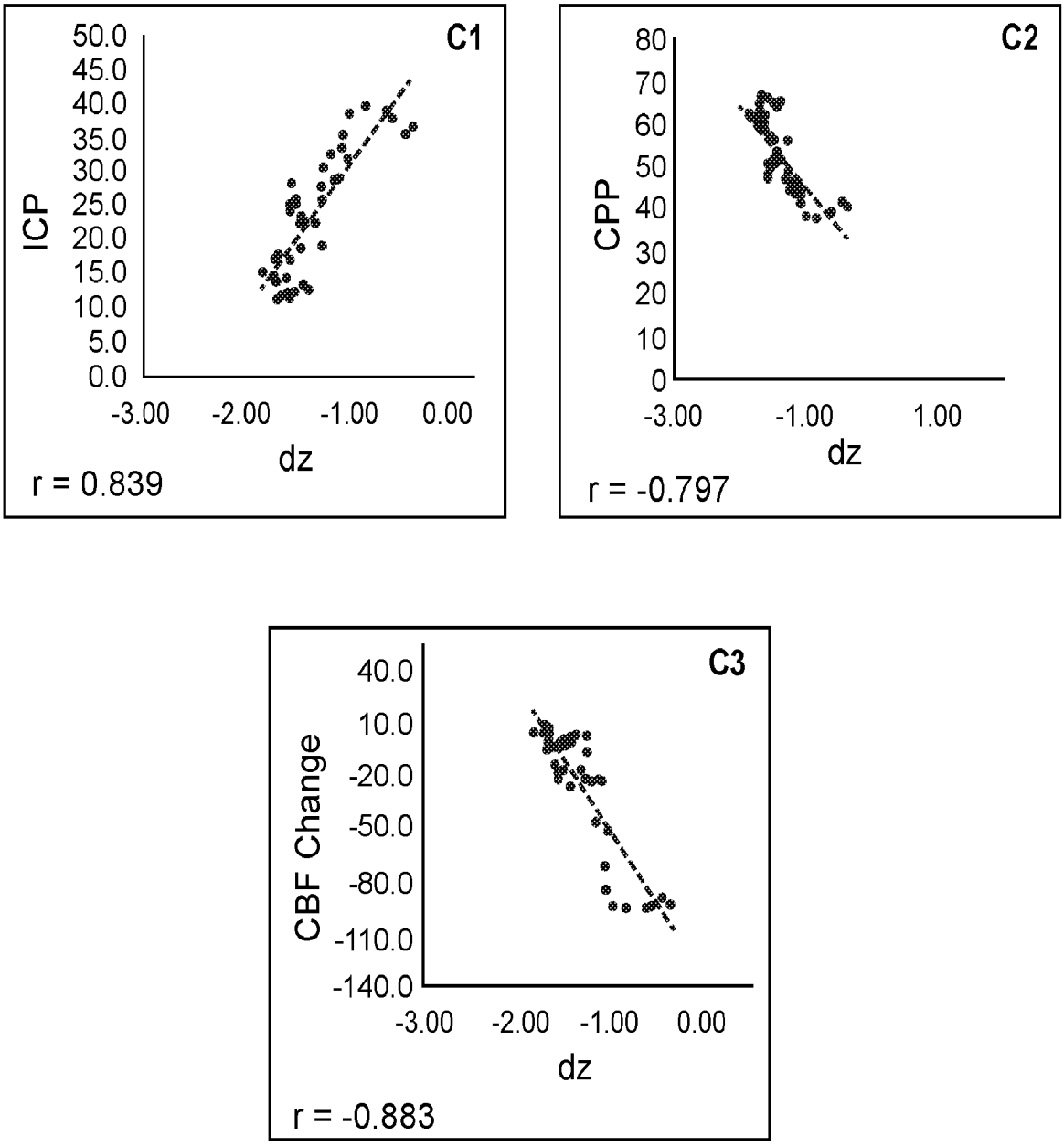


FIG. 3
(to be continued)

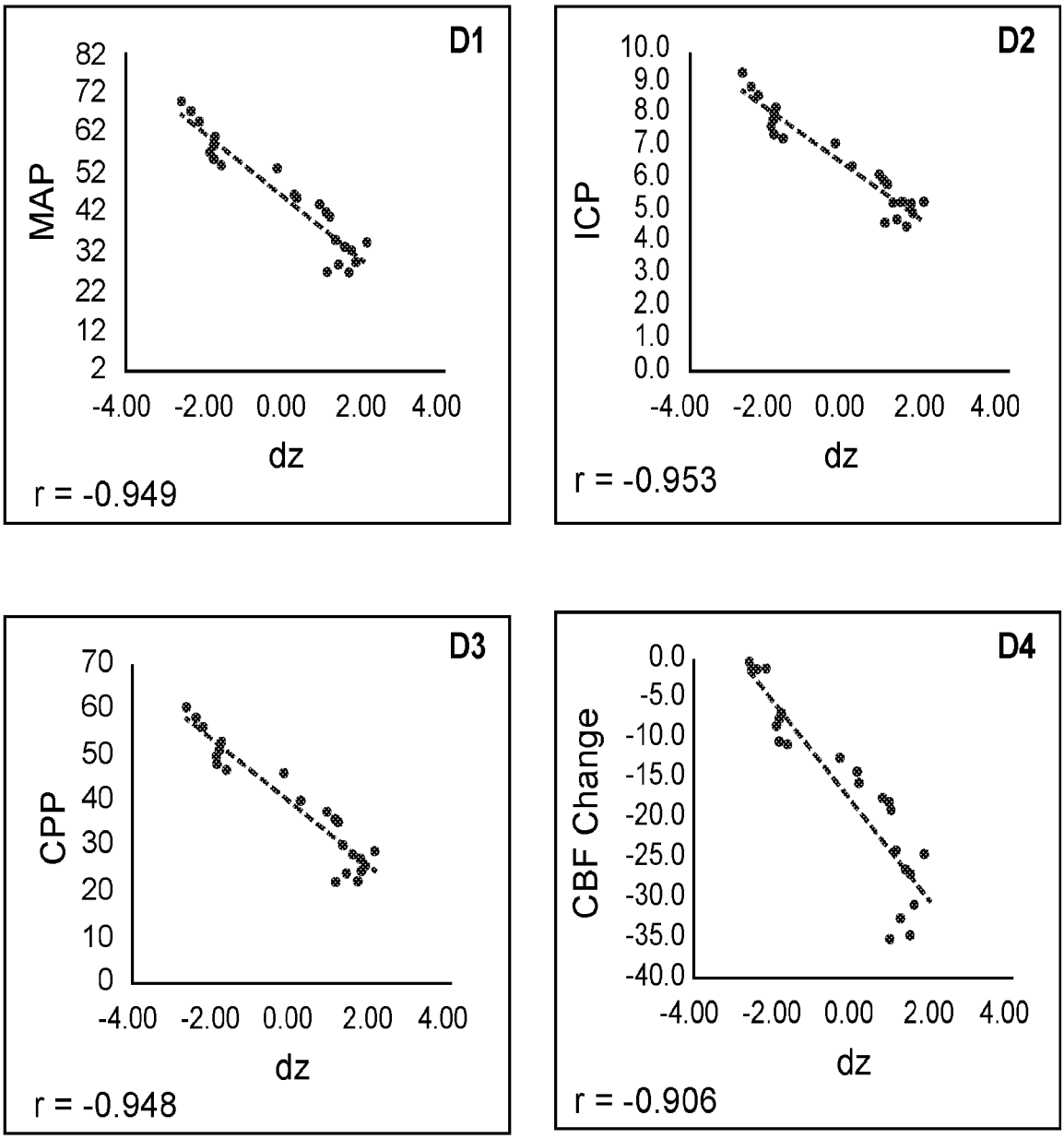


FIG. 3
(continuation)

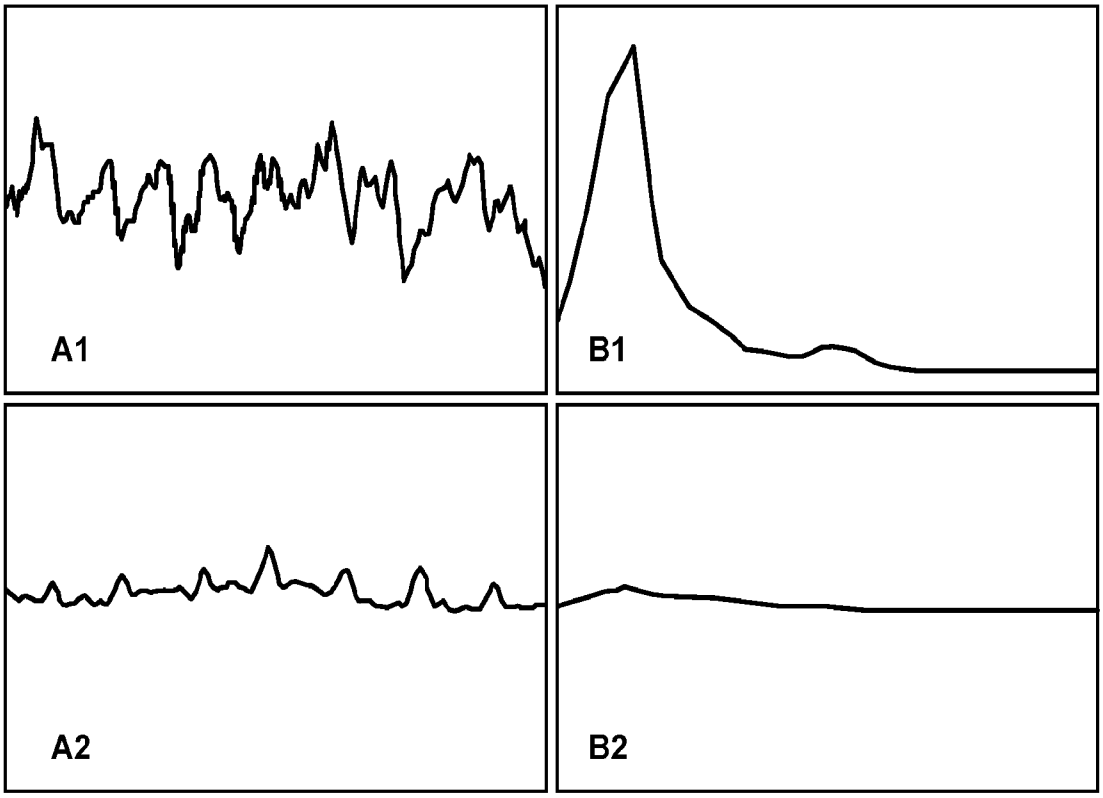


FIG. 4

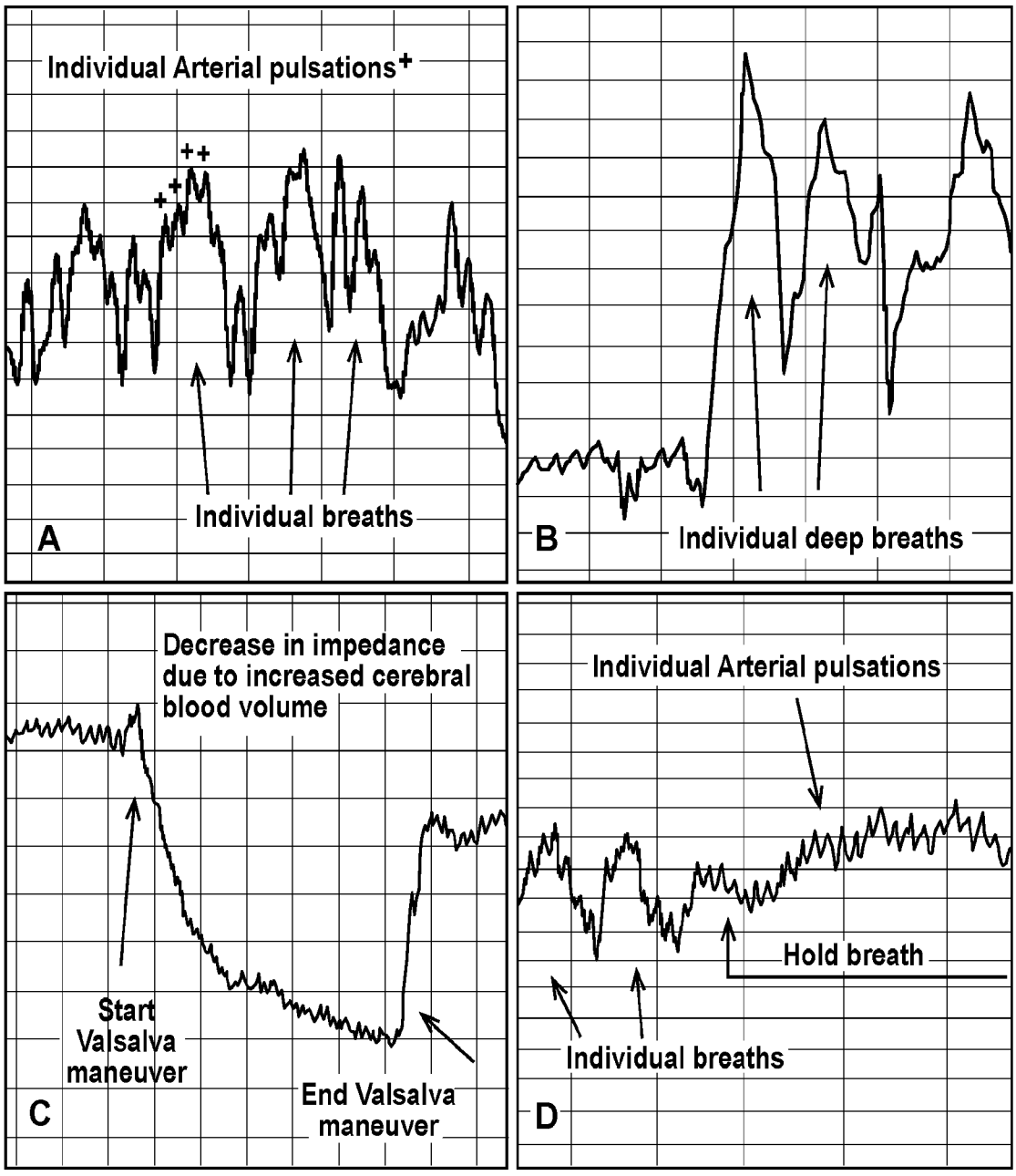
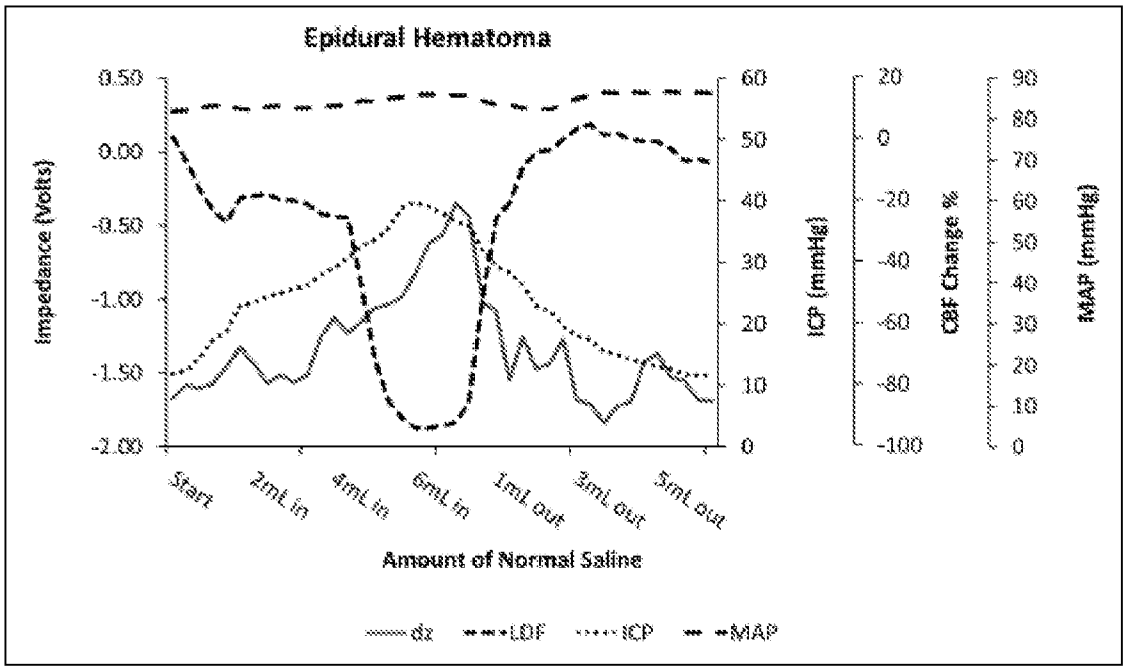

Individual Arterial pulsations+
Individual breaths
A
B
Individual deep breaths
Decrease in impedance due to increased cerebral blood volume
Start Valsalva maneuver
End Valsalva maneuver
C
Individual Arterial pulsations
Hold breath
Individual breaths
D

FIG. 5


Epidural Hematoma
Impedance (Volts)
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0.00
-0.50
-1.00
-1.50
-2.00
60
50
40
30
20
10
0
ICP (mmHg)
20
0
-20
-40
-60
-80
-100
CBF Change %
90
80
70
60
50
40
30
20
10
0
MAP (mmHg)
Start
2mL in
4mL in
6mL in
1mL out
3mL out
5mL out
Amount of Normal Saline
dz
LDF
ICP
MAP

FIG. 6

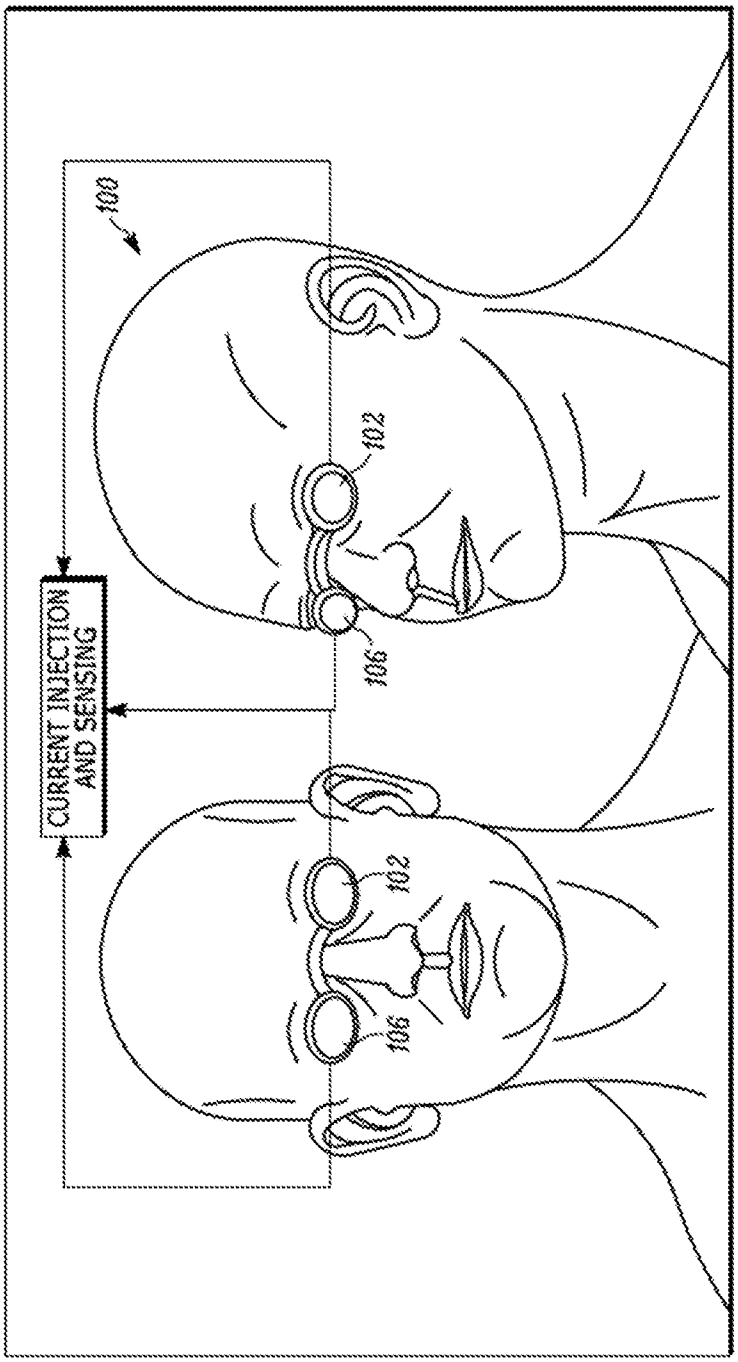
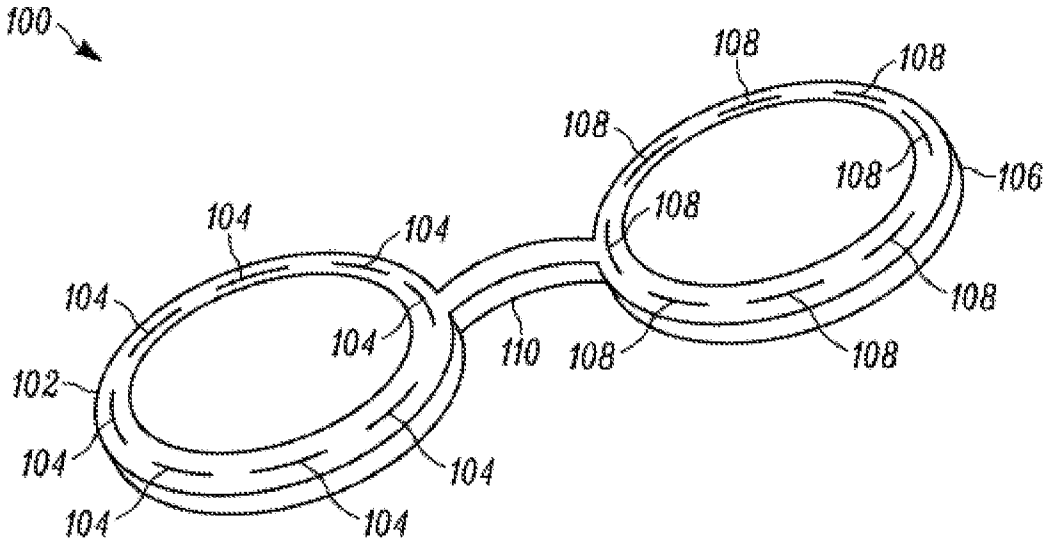


FIG. 7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108
108
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110
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104

FIG. 8

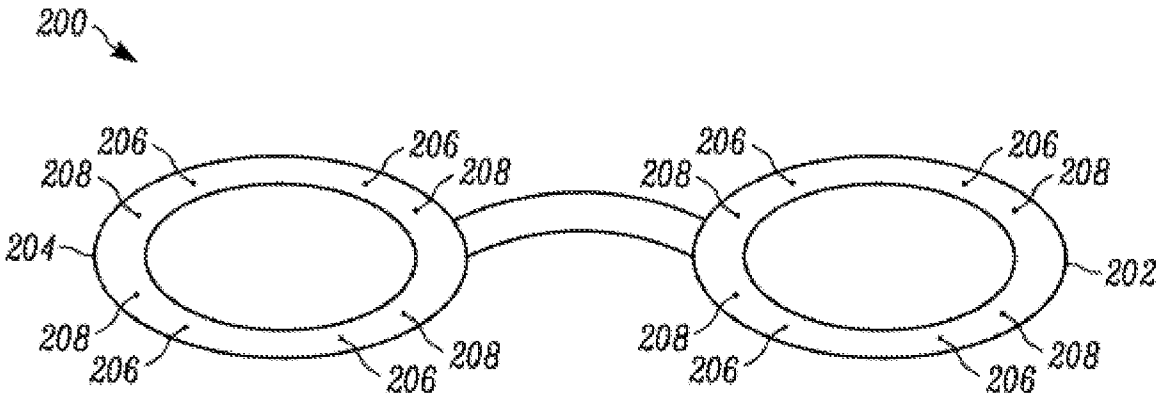
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FIG. 9

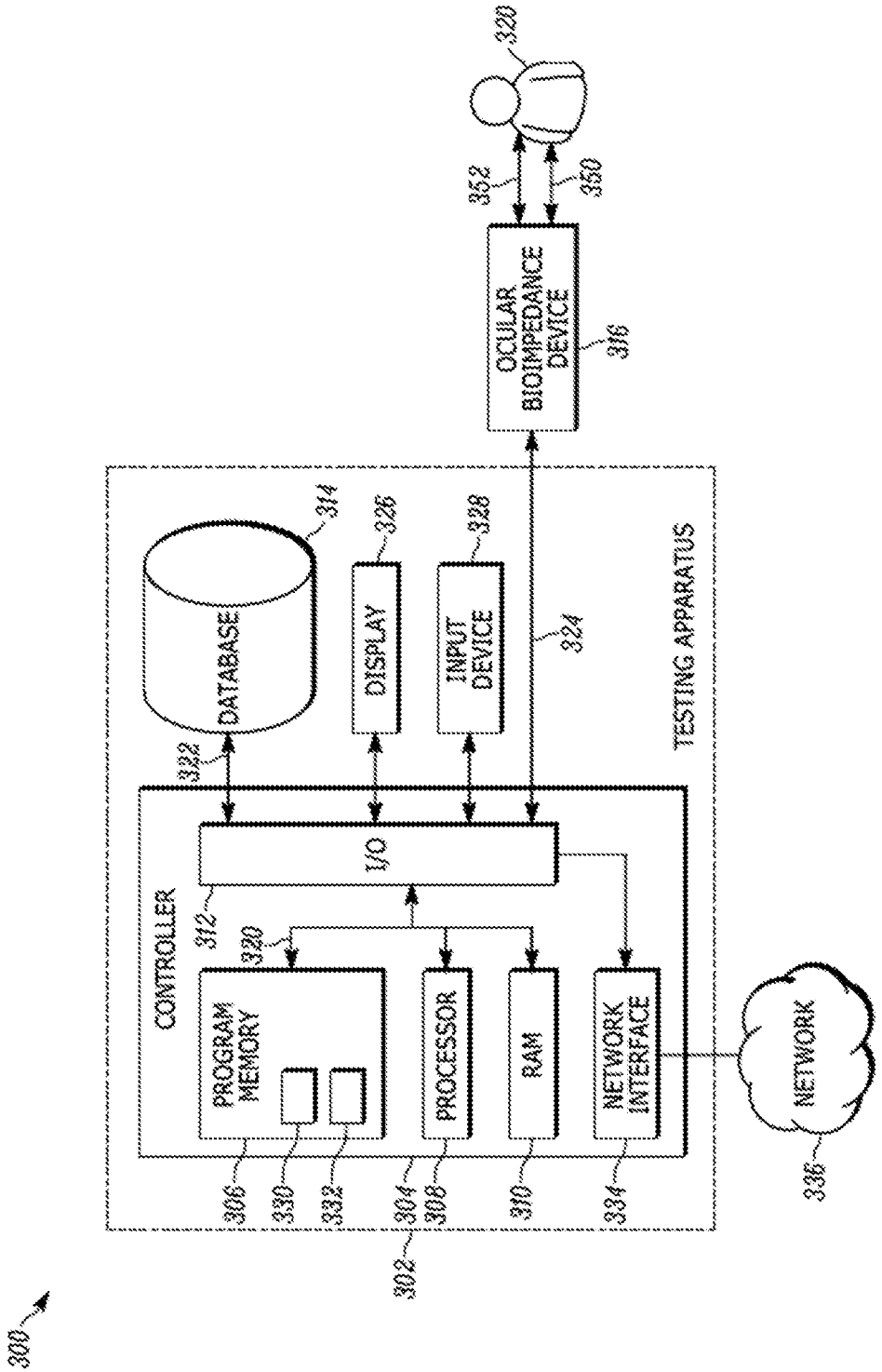
300
302
TESTING APPARATUS
CONTROLLER
I/O
312
320
PROGRAM MEMORY
306
330
332
PROCESSOR
304
308
RAM
310
NETWORK INTERFACE
334
NETWORK
336
DATABASE
314
DISPLAY
326
INPUT DEVICE
328
324
322
OCULAR BIOIMPEDANCE DEVICE
316
352
350
320

FIG. 10

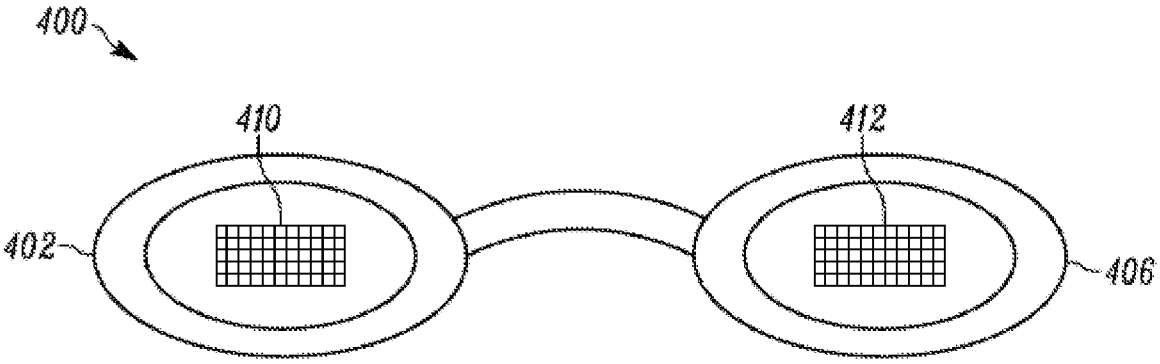

FIG. 11

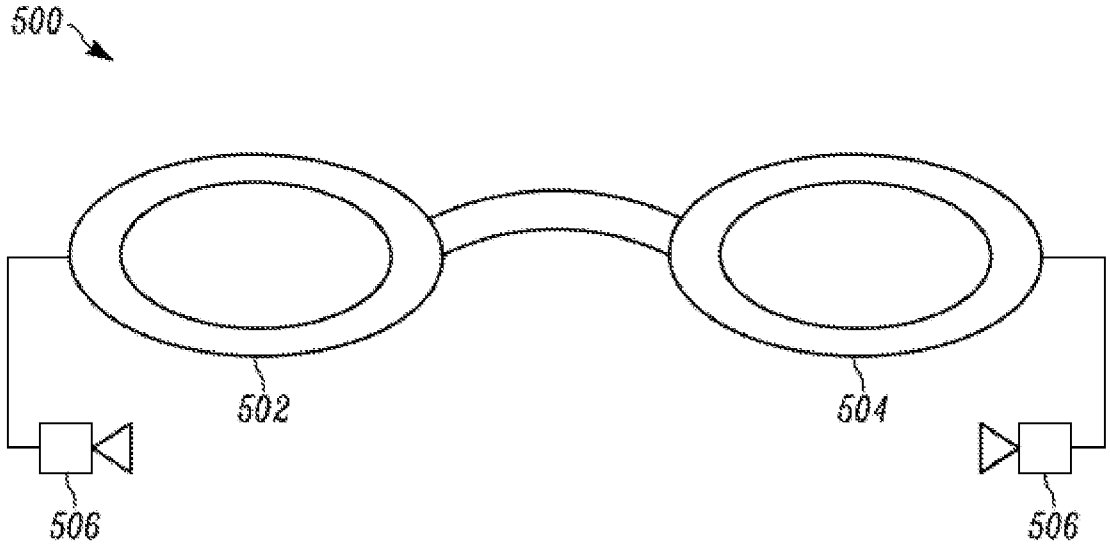

FIG. 12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US20 18/032984

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61N 1/36; A61B 5/00; A61N 1/362; A61N 1/37 (2018.01)
CPC - A61N 1/36; A61B 5/00; A61B 5/0042; A61N 1/37 (2018.05)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 607/45; 600/544; 607/2 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2008/0200787 A1 (SHAPIRA et al) 21 August 2008 (21.08.2008) entire document	1-3
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Y		4-9, 11-21
X	US 2010/0189698 A1 (WILLIS) 29 July 2010 (29.07.2010) entire document	10
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Y		11-13, 16-18
Y	US 2004/0176820 A1 (PAUL) 09 September 2004 (09.09.2004) entire document	4-6, 11b-21
Y	US 2013/0190632 A1 (BARUCH et al) 25 July 2013 (25.07.2013) entire document	7
Y	US 2014/0371545 A1 (BEN-ARI et al) 18 December 2014 (18.12.2014) entire document	8, 9
Y	US 2010/0030054 A1 (BARUCH et al) 04 February 2010 (04.02.2010) entire document	9
Y	US 2011/0245734 A1 (WAGNER et al) 06 October 2011 (06.10.2011) entire document	14-21

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search
20 July 2018

Date of mailing of the international search report
03 AUG 2018

Name and mailing address of the ISA/US
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Form PCT/ISA/210 (second sheet) (January 2015)

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Education and Training

Education

09/1985-09/1991	MD, Medicine, Damascus University, Damascus, Syrian Arab Republic
10/2013-04/2015	MS, Clinical Research Design and Statistical Analysis, University Of Michigan, Ann Arbor, MI

PostDoctoral Training

10/1991-08/1992	Internship, Intern in General Medicine, Ministry of Health Hospitals and Alshifa Hospital, Damascus, Syrian Arab Republic

Academic, Administrative, Clinical, Research and Military Appointments

Academic Appointments

07/2012-08/2016	Research Investigator in Emergency Medicine - Adult, University of Michigan - Ann Arbor, Ann Arbor, Michigan
09/2016-present	Research Assistant Professor in Emergency Medicine - Adult, University of Michigan - Ann Arbor, Ann Arbor, Michigan

Administrative Appointments

06/1994-09/1994	Observership and research assistant, Receiving Hospital, Wayne State University, Detroit, MI
01/1995-05/1995	Observership, Good Samaritan Hospital, Dayton, OH
02/1996-04/1998	Volunteer Research Assistant, Tufts University, Boston, MA
06/1998-05/2000	Senior Quality Control and Production Chemist, Owl Separation System, Portsmouth, New Hampshire
06/2000-05/2010	Life/Phys Science Research Associate, Virginia Commonwealth University, Richmond, Virginia
05/2010-06/2012	Laboratory and Research Manager, Virginia Commonwealth University, Richmond, Virginia

Research Interests

- Development of large animals models to study critical care illness and injury
- Development of non-invasive technologies to evaluate intravenous volume status in critically ill patients using bioimpedance
- Development of non-invasive technologies to evaluate cerebrovascular autoregulation using ocular bioimpedance
- Development of non-invasive spectroscopic technologies to monitor tissue oxygenation using Resonance Raman Spectroscopy (RRS)
- Development of resuscitation Fluids, hemoglobin and non-hemoglobin oxygen carriers
- Development of closed-loop feedback CPR devices
- Development of hemorrhage control materials and devices

Grants

Current Grants

Swine-Sepsis and ARDS MICHR
Co-I with Effort (Principal Investigator: Robert Dickson and Kathleen Stringer)
09/2018-08/2019. $100,000 ($100,000)

Intracranial Pressure Monitor Enhancement for Cerebral Hemodynamic Monitoring The Massey Family Foundation
Co-I with Effort (Principal Investigator: Kenn Oldham)
07/2018-06/2019. $104,433 ($104,433)

Real-Time, Non-Invasive Brain Metabolism The Massey Family Foundation
Co-I with Effort (Principal Investigator: Oliver D. Kripfgans)
07/2018-06/2019. $143,666 ($143,666)

DM160299: Gastroesophageal Resuscitative Occlusion of the Aorta (GROA) Dept. of the Army -- USAMRAA- 16-PAF08148
Co-I with Effort (Principal Investigator: Ward, Kevin Ralph)
02/2018-01/2021. $2,995,616

DM160294: Development and Testing of New Noninvasive Monitoring Tools for Prolonged Field Care Goal-Directed Therapy Dept. of the Army -- USAMRAA
Co-I with Effort (Principal Investigator: Kevin Ward)
01/2018-12/2020. $2,999,754 ($969,599)

DM160225: Novel Noninvasive Methods of Intracranial Pressure and Cerebrovascular Autoregulation Assessment: Seeing the Brain through the Eyes Dept. of the Army -- USAMRAA- 17-PAF00214
Tiba, Mohamad Hakam, PI
01/2018-12/2020. $1,481,538

5 R01 HL133129-04: ECPR After Prolonged Cardiac Arrest: Targeting Mechanisms of the No-Reflow NIH-DHHS-US- 16-PAF07624
Co-I with Effort (Principal Investigator: Neumar, Robert;Bartlett, Robert Hawes)
07/2017-06/2022. $3,894,128

Submitted Grants

Resonance Raman Spectroscopy for Tissue Oxygenation Monitoring in Sepsis SubK-NIH-DHHS-US through a consortium with Pendar Medical, LLC- 19-PAF02234
Co-I with Effort (Principal Investigator: Ward, Kevin Ralph)
01/2019-12/2019. $349,726

Dynamic Respiratory Impedance Volume Evaluation (DRIVE) for Sepsis SubK-NIH-DHHS-US through a consortium with New Vital Signs, Inc.- 19-PAF02230
Tiba, Mohamad Hakam;Ward, Kevin Ralph, PI
01/2019-12/2019. $350,170

ART-123 (recombinant human thrombomodulin alpha) in porcine cardiac arrest Zoll Foundation- 19-PAF01707
Co-I without Effort (Principal Investigator: Greineder, Colin F)
12/2018-11/2019. $47,773

Past Grants

Novel Noninvasive Method of Cerebrovascular Blood Volume Assessment Using Brain Bioimpedance The Massey Family foundation
Tiba, MH and Ward, KR, Co-PI
07/2017-09/2018. $130,565 ($130,565)

Systolic Target Assessment Tool (STAT) for TBI Management The Massey Family Foundation
Co-I (Principal Investigator: Hackenson)
07/2017-09/2018. $73,975 ($73,975)

Redox POC Platform for Evaluation and Treatment of Sepsis, Septic Shock, and Multiple Organ Dysfunction
Michigan Translational Research and Commercialization Program
Co-I with Effort (Principal Investigator: Rodney C. Daniels)
02/2016-01/2017. $155,435 ($155,435)

15-PAF06146: Comparison of Respiratory Induced Limb Bioimpedance Changes With Inferior Vena Cava Diameter Changes to Assess Intravascular Volume Status in Patients Undergoing Hemodialysis Renal Research Institute, LLC
Co-I with Effort (Principal Investigator: Michael Heung)
06/2015-12/2016. $42,830 ($42,830)

G016123: Novel Noninvasive Methods of Intracranial Pressure Assessment: Seeing the Brain Through the Eyes
Massey Family Foundation
Co-I with Effort (Principal Investigator: Krishna Rajajee and Kevin Ward)
02/2015-02/2016. $106,262 ($106,262)

Comparison of Respiratory Induced Limb Bioimpedance Changes with Inferior Vena Cava Diameter Changes to Assess Intravascular Volume Status Baxter Healthcare Corporation- 15-PAF03360
Tiba, Mohamad Hakam;Ward, Kevin Ralph, PI
01/2015-06/2015. $150,476

N017668: Dynamic Respiratory Impedance Volume Evaluation (DRIVE) Michigan Translation and Commercialization (MTRAC) for Life Sciences Program
Mohamad Hakam Tiba, PI
02/2014-01/2015. $92,958 ($92,958)

14-PAF05256: Multi-laboratory Study of Epinephrine in Experimental Cardiac Arrest St. Michaels Hospital
Robert Neumar Mohamad Hakam Tiba, Co-PI
11/2013-12/2015. $10,000

Honors and Awards

Regional

2010	Mentorship Award, Goldwater Scholarship committee. For mentorship of Elizabeth Proffitt, a Goldwater Scholar
2016	Outstanding Poster Award. Massey Regional TBI Conference

Institutional

2014	Spoor Memorial Scholarship Award
2015	First place in the poster competition award. The Eighth Annual Symposium, A. Alfred Taubman Medical Research Institute.

Memberships in Professional Societies

2012-present	Member, The Shock Society
2013-present	Member, American Association for the Advancement of Science
2013-present	Member, Society for Academic Emergency Medicine
2013-present	Member, Society of Critical Care Medicine
2014-present	Member, American Heart Association

Editorial Positions, Boards, and Peer-Review Service

Study Sections

National

2015-present	Peer review panel of the 2015 Combat Casualty Care Research Program (CCCRP) for the Department of Defense U.S. Army Medical Research and Materiel Command (MRMC).

2018-present	Autonomous and Unmanned Medical Capability (AUMC-1) peer review panel of the 2017 Defense Medical Research and Development Program (DMRDP) Joint Program Committee-1 (JPC-1) for the Department of Defense Congressionally Directed Medical Research Programs (CDMRP).

Journal Reviewer

2016-present	American Journal of Emergency Medicine (Ad Hoc)

Teaching

Clinical Fellow

10/2018-10/2020	Yub Raj Sedhai, MD, Spectrum system, Grand Rapids, MI

Graduate Student

06/2013-12/2015	Barry Belmont, MS, Biomedical Engineering, University of Michigan
10/2014-04/2015	Brandon Cummings, MS, The Undergraduate Research Opportunity Program (UROP). University of Michigan

Medical Student

06/2015-08/2015	Spencer Thompson, BS, Summer Biomedical Research Proposal. University of Michigan
06/2015-08/2015	Shawn Kache, BS, Summer Biomedical Research Proposal. University of Michigan
08/2015-11/2015	Isaac Ezra Perry, BS, Edward Via College of Osteopathic Medicine
06/2017-08/2017	Alexander Khouri, BS, Summer Biomedical Research Proposal, University of Michigan.

Undergraduate Student

01/2006-01/2010	Elizabeth K. Proffitt, Virginia Commonwealth University
10/2013-05/2014	Eman Hejab, The Undergraduate Research Opportunity Program (UROP). University of Michigan
10/2015-04/2016	Justine Garfinkel, The Undergraduate Research Opportunity Program (UROP). University of Michigan
10/2015-04/2016	Mambwe C. Lupiya, The Undergraduate Research Opportunity Program (UROP). University of Michigan
05/2016-08/2016	John Soukar, University of Michigan
07/2016-05/2017	Stephen Dowker, University of Michigan
10/2016-04/2017	Stephanie Francalancia, The Undergraduate Research Opportunity Program (UROP). University of Michigan
10/2017-04/2018	Alysha Loraff, The Undergraduate Research Opportunity Program (UROP). University of Michigan
10/2017-04/2018	Tessa Magsoudi, The Undergraduate Research Opportunity Program (UROP). University of Michigan
10/2017-04/2018	Varisha Essani, The Undergraduate Research Opportunity Program (UROP). University of Michigan
10/2017-04/2018	Benjamin Koehler, The Undergraduate Research Opportunity Program (UROP). University of Michigan

Visiting Scholars

09/2015-08/2016	Jae Hyuk Lee, MD, Seoul National University Bundang Hospital, South Korea

Teaching Activity

Institutional

08/2013	Surgery concentration. Surgical techniques training session for University Laboratory Animal Medicine (ULAM) veterinary residents
08/2014	Surgery concentration. Surgical techniques training session for University Laboratory Animal Medicine (ULAM) veterinary residents

08/2016	Surgery concentration. Surgical techniques training session for University Laboratory Animal Medicine (ULAM) veterinary residents
08/2018-09/2018	Surgery concentration. Surgical techniques training session for University Laboratory Animal Medicine (ULAM) veterinary residents

Committee and Administrative Services

Committee Services

National

2014-2015	Task force to evaluate animal research publications' compliance with ARRIVE reporting standards. Shock Society, Member

Institutional

2013-present	Institutional Animal Care and Use Committee (IACUC), Member
2014-2016	Large Animals Working Group, Member
2015-2016	IACUC Subcommittee for eRAM Online Protocol Changes and Updates, Member
2015	IACUC Subcommittee for Standard Operating Procedures (SOP) Approval, Member
2016-2017	IACUC Task Force for Review of PI Managed Space Request Application, Member
2017-present	Animal Care and Use Faculty Advisory Committee. ACU-FAC, Chair
2018-present	Strategic Advisory Committee to the UM Animal Care and Use Program (ACUP)., Member

Administrative Services

Volunteer

2015-present	Judge, The Undergraduate Research Opportunity Program (UROP), University of Michigan, Ann Arbor, The Undergraduate Research Opportunity Program's Annual Research Spring Symposium

Visiting Professorships and Extramural Invited Presentations

Extramural Invited Presentations

1. Mohamad H. Tiba, H. Mowafi, G. Gawor, R. W. Barbee, R. Ivatury, K. R. Ward. Preliminary Studies of a New Impedance Based Measure to Noninvasively Determine Central Venous Pressure, Advanced Technologies Applications in Combat Casualty Care, August 2003, St. Pete Beach, Florida. (Poster Presentation)
2. Mohamad H. Tiba, T. A. Timmons, R. W. Barbee, R. R. Ivatury, B. D. Spiess, P. S. Reynolds, and K. R. Ward. Bispectral Index Monitoring of Intubated Trauma Patients Indicates Inadequate Sedation, Advanced Technologies Applications in Combat Casualty Care, August 2004, St. Pete Beach, Florida. (Poster Presentation)
3. Mohamad H. Tiba, Kate Proffitt; R. Wayne Barbee, Gerard Draucker, Rao R. Ivatury, Kevin R. Ward. Noninvasive Bioimpedance Base for Central Venous Pressure Measurement, Advanced Technologies Applications in Combat Casualty Care, August 2005, Pete Beach Florida. (Poster Presentation)
4. Mohamad H. Tiba, G. T Draucker, R. W. Barbee, J. Terner, I. P. Torres Filho, K. R. Ward. Performance of Tissue Hemoglobin Oxygen Saturation as Measured by Resonance Raman Spectroscopy and Near Infrared Spectroscopy Compared to Mixed Venous Hemoglobin Oxygen Saturation and Systemic Lactate Levels During Hemorrhage, 36th Annual Conference on Shock, June 2013, San Diego, California. (Poster Presentation)
5. Mohamad H. Tiba, G. T. Draucker, B. M. McCracken, K. R. Ward. Controlling Pelvic Hemorrhage using a Novel Pressure Garment, 37th Annual Conference on Shock, June 2014, Charlotte, North Carolina. (Poster Presentation)
6. Mohamad H. Tiba, G. T. Draucker, B. M. McCracken, H. B. Alam, J. L. Eliason, K. R. Ward. Testing of a novel Pelvic Hemostasis Belt to Control Lethal Pelvic Arterial Hemorrhage, American Heart Association. Resuscitation Science Symposium, November 2014, Chicago, Illinois. (Poster Presentation)
7. Mohamad H. Tiba, Barry Belmont, Nik Theyyunni, Robert Huang, David F. Barton, Amanda J. Pennington, Gerard T. Draucker, Albert J. Shih, Kevin R. Ward. Coparison of Respiratory Induced Inferior Vena Cava Diameter Changes With Limb Bioimpedance Changes to Assess Intravascular Volume Status, 38th Annual Conference on Shock, June 2015, Denver Colorado. (Poster Presentation)

8. Evaluation of Intravascular Volume Status Using Dynamic Respiratory Induced Bioimpedance of the Limb, Society for Academic emergency Medicine, May 2016, New Orleans, LA. (Oral Presentation)
9. Mohamad H. Tiba, Barry Belmont, Michael Heung, Nik Theyyunni, Robert Huang, Christopher D. Fung, Amanda J. Pennington, Kevin R. Ward: Comparison of Respiratory Induced Inferior Vena Cava Diameter Changes with Limb Bioimpedance Changes In dialysis and mechanically ventilated patients, Thirty-Ninth Annual Conference on Shock, June 2016, Austin, Texas. (Poster Presaentation)
10. Mohamad H. Tiba, Amanda Pennington, Kyle Gunnerson, Kevin R. Ward. Monitoring of Tissue Microvasculature Oxygenation using Resonance Raman Spectroscopy, Thirty-Ninth Annual Conference on Shock, June 2016, austin, Texas. (Poster Presentation)
11. Mohamad H. Tiba, Brendan McCracken, Gerard Draucker, Hasan Alam, Jonathan Eliason, Kevin Ward: Use of a Novel Pelvic Hemostasis Belt to Control Lethal Arterial Hemorrhage, The 2016 Military Health System Research Symposium (MHSRS), August 2016, Orlando, Florida. (Poster Presntation)
12. Mohamad. Tiba, Michael Heung, Nik Theyyunni, Barry Belmont, Robert Huang, Ross Kessler, Christopher Fung, Amanda Pennington, Brandon Cummings, Kevin Ward: Development of a Novel Non-Invasive Technologies to Evaluate Intravascular Volume Status Using Bioimpedance, The 2016 Military Health System Research Symposium (MHSRS), August 2016, Orlando, Florida. (Poster Presentation)
13. Mohamad H. Tiba, Robert Barbee, James Terner, Ivo. Torres Filho, Kevin Ward: Measurement of tissue hemoglobin oxygen saturation using Resonance Raman Spectroscopy in a large animal model of hemorrhage, The 2016 Military Health System Research Symposium (MHSRS), August 2016, Orlando, Florida. (Poster Presentation)
14. Mohamad Hakam Tiba; Brendan McCracken; Sardar Ansari; Venkatakrishna Rajajee; Kevin Ward. Novel Noninvasive Method of Cerebrovascular Autoregulation Assessment: Seeing the Brain through the Eyes., Fortieth Annual Conference on Shock., June 2017, Fort Lauderdale, Florida. (Poster Presentation)
15. Novel Noninvasive Method of Cerebrovascular Autoregulation Assessment, Military Health System Research Symposium (MHSRS), August 2017, Kissimmee, Florida (Oral Presentation)
16. A Novel Large Animal Model of Sepsis, Forty-First Annual Conference on Shock., June 2018, Scottsdale, Arizona. (Poster Presentation)
17. Monitoring Traumatic Brain Injury Patients using Transocular Brain Impedance (TBI)., Military Health System Research Symposium (MHSRS), August 2018, Orlando, Florida. (Poster Presentation)
18. Use of Resuscitative Balloon Occlusion of the Aorta in a Swine Model of Prolonged Cardiac Arrest., American Heart Association. Resuscitation Symposium. (Poster Presentation), November 2018, Chicago, IL

Other

1. DRIVE Performance and update, Baxter Healthcare, March 2015, Chicago, Illinois
2. Mohamad H. Tiba, Barry Belmont, Spencer Thompson, Michael Heung, Nik Theyyunni, Robert Huang, Christofer Fung, Amanda Pennington, Gerard Draucker, Kevin R. Ward. Development of a Novel Non-Invasive Technologies to Evaluate Intravascular Volume Status Using Bioimpedance, Eighth Annual Symposium, A. Alfred Taubman Medical Research institute. University of Michigan., October 2015, Ann Arbor, Michigan. (Poster Presentation)
3. Mohamad H. Tiba, Shawn Kache, Brandon Cummings, Amanda Pennington, Kyle Gunnerson, Kevin R. Ward. Monitoring of Tissue Microvasculature Oxygenation using Resonance Raman Spectroscopy, Eighth Annual Symposium, A. Alfred Taubman Medical Research institute. University of Michigan., October 2015, Ann Arbor, Michigan. (Poster Presentation)
4. Mohamad H. Tiba. Sample Size and Power Analysis: What Do We Need to Know, Institutional Animal Care and Use committee (IACUC). A presentation as part of the training protocol for IACUC members, February 2016, Ann Arbor, MI
5. Mohamad H. Tiba, MD, MS; Nik Theyyunni, MD; Barry Belmont, PhD; Michael Heung, MD, MS; Robert Huang, MD; Christopher Fung, MD; Amanda Pennington, MS; Brandon Cummings; Gerard Draucker, EMT; Kevin R. Ward, MD. Comparison of Respiratory Induced Inferior Vena Cava Diameter Changes with Limb Impedance Changes in Hemodialysis Patients., First Annual William G. Barsan Emergency Medicine Research Forum. (Poster Presentation), April 2016, Ann Arbor, Michigan
6. Mohamad H. Tiba, MD; Amanda Pennington, MS; Gerard Draucker, EMT; Brandon Cummings; Kyle Gunnerson, MD; Kevin R. Ward, MD. Monitoring of Tissue Microvasculature Oxygenation using Resonance Raman Spectroscopy, First Annual William G. Barsan Emergency Medicine Research Forum. (Poster Presentation), April 2016, Ann Arbor, Michigan

7. Mohamad H. Tiba, MD; Gerard T. Draucker, EMT-P; Brendan M. McCracken, BS; Hasan B. Alam, MD; Jonathan L. Eliason, MD; Kevin R. Ward, MD. Controlling Pelvic Hemorrhage Using a Novel Pressure Garment, First Annual William G. Barsan Emergency Medicine Research Forum. (Poster Presentation), April 2016, Ann ARbor, Michigan
8. Novel Noninvasive Method of Cerebrovascular Autoregulation Assessment: Seeing the Brain through the Eyes, University of Michigan / Massey Foundation, October 2016, Ann Arbor, MI. (Oral Presentation)
9. Mohamad H. Tiba, MD, MS; Brendan McCracken, BS; Sardar Ansari, PhD; Ashwin Belle, PhD; Kevin Ward, MD. Novel Noninvasive Method of Cerebrovascular Autoregulation Assessment: Seeing the Brain through the Eyes, Second Annual William G. Barsan Emergency Medicine Research Forum. (Poster Presentation), April 2017, Ann Arbor, Michigan
10. Noninvasive Assessment of Cerebrovascular Blood Volume and Autoregulation Using Bioimpedance, Massey Foundation Second TBI Summit. (Oral Presentation), October 2017, Ann ARbor, Michigan
11. Monitoring Traumatic Brain Injury Patients using Transocular Brain Impedance (TBI). Grand Challenge Experience., The Massey Foundation TBI Grand Challenge, March 2018, Ann Arbor, Michigan
12. Trans-Ocular Brain Impedance: Novel Non-invasive Monitoring of the TBI Patient, 2018 Massey TBI Regional Conference. Oral Presentation), October 2018, Ann Arbor, MI

Seminars

1. Tissue Hemoglobin Oxygen Saturation in the critically ill, as Measured by Resonance Raman Spectroscopy, University Laboratory Animals Medicine (ULAM) Fall Seminar Series, November 2013, Ann Arbor, Michigan
2. Emergency Department Tour and Description of Two Non-Invasive Monitoring Modalities, University of Michigan. The Undergraduate Research Opportunity Program (UROP) Seminar Series, December 2015, Ann Arbor, Michigan
3. Bolus Versus Continuous Epinephrine Infusion In a Large animal model of Cardiac Arrest: A Multicenter Trial, MCIRCC/OSCAR CONFERENCE, March 2016, Ann Arbor, MI
4. Large Animal Model of Sepsis, University Laboratory Animals Medicine (ULAM) Fall Seminar Series, November 2017, Ann Arbor, Michigan

Patents

Application in Process

EVALUATING CARDIOVASCULAR HEALTH USING INTRAVASCULAR VOLUME, 20150031966, Co-inventor, Submitted on 07/2014

Ocular Impedance-Based System for Brain Health Monitoring, Co-inventor, Submitted on 05/2017

Bibliography

Peer-Reviewed Journals and Publications

1. Torres LN, Torres Filho IP, Barbee RW, Tiba MH, Ward KR, Pittman RN: Systemic responses to prolonged hemorrhagic hypotension Am. J. Physiol. Heart Circ. Physiol. 286(5 55-5): H1811-H1820, 2004. PM14726303
2. Smith L, Tiba MH, Goldberg ME, Barbee RW: Chronic implantation of transit-time flow probes on the ascending aorta of rodents Lab. Anim. 38(4): 362-370, 2004. PM15479550
3. Torres LN, Torres Filho IP, Barbee RW, Tiba MH, Ward KR, Pittman RN: Continuous peripheral resistance measurement during hemorrhagic hypotension Am. J. Physiol. Heart Circ. Physiol. 287(5 56-5): H2341-H2345, 2004. PM15256369
4. Ward KR, Torres Filho I, Barbee RW, Torres L, Tiba MH, Reynolds PS, Pittman RN, Ivatury RR, Terner J: Resonance Raman spectroscopy: A new technology for tissue oxygenation monitoring Crit. Care Med. 34 (3): 792-799, 2006. PM16521273
5. Ward KR, Tiba MH, Barbee RW, Ivatury RR, Arrowood JA, Spiess BD, Hummel R: A new noninvasive method to determine central venous pressure Resuscitation 70(2): 238-246, 2006. PM16820258
6. Ward KR, Barbee RW, Reynolds PS, Filho IP, Tiba MH, Torres L, Pittman RN, Terner J: Oxygenation monitoring of tissue vasculature by resonance Raman spectroscopy Anal. Chem. 79(4): 1514-1518, 2007. PM17297949

7. Evans MC, Diegelmann RF, Barbee RW, Tiba MH, Edwards E, Sreedhar S, Ward KR: Protein synthesis inhibition as a potential strategy for metabolic down-regulation Resuscitation 73(2): 296-303, 2007. PM17250947
8. Ward KR, Tiba MH, Holbert WH, Blocher CR, Draucker GT, Proffitt EK, Bowlin GL, Ivatury RR, Diegelmann RF: Comparison of a new hemostatic agent to current combat hemostatic agents in a swine model of lethal extremity arterial hemorrhage J Trauma 63(2): 276-283, 2007. PM17693824
9. Ward KR, Tiba MH, Draucker GT, Proffitt EK, Barbee RW, Gunnerson KJ, Reynolds PS, Spiess BD: A novel noninvasive impedance-based technique for central venous pressure measurement Shock 33(3): 269-273, 2010. PM19487978
10. Ward KR, Tiba MH, Ryan KL, Filho IP, Rickards CA, Witten T, Soller BR, Ludwig DA, Convertino VA: Oxygen transport characterization of a human model of progressive hemorrhage Resuscitation 81(8): 987-993, 2010. PM20418009
11. Leong B, Reynolds PS, Tiba MH, Holbert WH, Draucker GT, Medina JA, Barbee RW, White NJ, Ward KR: Effects of a combination hemoglobin based oxygen carrier-hypertonic saline solution on oxygen transport in the treatment of traumatic shock Resuscitation 82(7): 937-943, 2011. PM21497981
12. Tiba MH, Draucker GT, Barbee RW, Terner J, Filho IT, Romfh P, Vakhshoori D, Ward KR: Tissue oxygenation monitoring using resonance Raman spectroscopy during hemorrhage J Trauma Acute Care Surg 76(2): 402-408, 2014. PM24378619
13. Tiba MH, Draucker GT, McCracken BM, Alam HB, Eliason JL, Ward KR: Use of pelvic hemostasis belt to control lethal pelvic arterial hemorrhage in a swine model. The journal of trauma and acute care surgery 78(3): 524-9, 2015. PM25710422
14. Tiba MH, Belmont B, Theyyunni N, Heung M, Huang RD, Fung, CM, Pennington AJ, Cummings BC, Draucker GT, Shih AJ, Ward KR: Dynamic Limb Bioimpedance and Inferior Vena Cava Ultrasound in Patients Undergoing Hemodialysis ASAIO J 62(4): 463-9, 2016. PM26919184
15. Tiba MH, McCracken BM, Ansari S, Belle A, Cummings BC, Rajajee V, Patil PG, Alam HB, Ward KR: Novel Noninvasive Method of Cerebrovascular Blood Volume Assessment Using Brain Bioimpedance. J Neurotrauma 34(22): 3089-3096, 2017. PM28657491
16. Daniels RC, Jun H, Tiba H, McCracken B, Herrera-Fierro P, Collinson M, Ward KR: Whole Blood Redox Potential Correlates With Progressive Accumulation of Oxygen Debt and Acts as A Marker of Resuscitation in A Swine Hemorrhagic Shock Model. Shock 49(3): 345-351, 2018. PM28658006 /PMC5745311
17. Belmont B, Kessler R, Theyyunni N, Fung C, Huang R, Cover M, Ward KR, Shih AJ, Tiba M: Continuous Inferior Vena Cava Diameter Tracking through an Iterative Kanade-Lucas-Tomasi-Based Algorithm. Ultrasound Med Biol 44(12): 2793-2801, 2018. PM30213669
18. Coute RA, Shields TA, Cranford JA, Ansari S, Abir M, Tiba MH, Dunne R, O'Neil B, Swor R, Neumar RW, SaveMiHeart Consortium and the CARES Surveillance Group.: Intrastate Variation in Treatment and Outcomes of Out-of-Hospital Cardiac Arrest. Prehosp Emerg Care 22(6): 743-752, 2018. PM29624088
19. Sando IC, Plott JS, McCracken BM, Tiba MH, Ward KR, Kozlow JH, Cederna PS, Momoh AO: Simplifying Arterial Coupling in Microsurgery-A Preclinical Assessment of an Everter Device to Aid with Arterial Anastomosis. J Reconstr Microsurg: 2018. PM29452442

Abstracts

1. Ward KR, Barbee RW, Tiba, MH, Arrowood J, Ivatury RR, Lyders E, Spiess BP.: A Noninvasive Method of Determining Central Venous Pressure, 25th Annual Conference on Shock, Big Sky, Montana, Shock, 17, Supplement 1, 15, 2002.
2. Carr M, Kenawy E, Layman G, Wnek G, Ward KR, Barbee W, Tiba MH.: Development of The BioHemostat- A Treatment Modality for High Pressure Bleeding Based on Super Absorbent Polymers, 25 th Annual Conference on Shock, Big Sky, Shock, 17, Supplement 1, 54, 2002.
3. Barbee RW, Ward KR, Terner J, Torres I, Tiba MH, Torres L, Ivatury R, Spiess B, Pittman R.: Noninvasive Tissue Oxygenation Monitoring Using Resonance Raman Spectroscopy (RRS), 25th Annual Conference on Shock, Big Sky, Montana, Shock, 17, Supplement 1, 58, 2002.
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