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Research Article

Combined Bio-Impedance and Transcranial Doppler Ultrasonography in Parkinson's Patients and Neurologically Normal Ageing Subjects

Vardy TC[1]*, Moskalenko Yu[2], Mokhov[3] and R Todd Dombroski[4]

[1]*Queensland University of Technology, Brisbane, Australia*

[2]*Osteopathy Department, Mechnikov North-West State Medical University, Saint Petersburg, Russia*

[3]*Institute of Osteopathy, St. Petersburg State University, Saint Petersburg, Russia*

[4]*Department of Mechanical Engineering, University of North Texas, Denton, Texas, United States of America*

***Corresponding Author**: Vardy TC, Queensland University of Technology, Brisbane, Australia.

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Abstract

Objective: Current knowledge of intracranial fluid dynamics in Parkinson's disease patients is limited. Magnetic Resonance Imaging, computerized tomography and Positron Emission Tomography provide important information of cranial fluid changes but are static.

Materials and Methods: 20 Parkinson patients, stage I-III Hoehn and Yahr and 22 age and gender matched neurologically normal subjects were enrolled in a prospective 2 year study. Monitoring consisted of transcranial Doppler, bio-impedance, near infrared, Portapres®, electrocardiogram, chest respiratory band, and galvanic skin response. Transcranial Doppler measured blood flow into each brain hemisphere and the and bioimpedance device measured the volumes of cerebrospinal fluid (CSF) within the cranium. Perturbations were orthostatic and cognitive challenges.

Results: Parkinson patients utilized their right brain hemisphere in contrast to neurologically normal ageing subjects (left hemisphere was dominant) pre and post all cognitive and orthostatic tests, $p = 0.0039$.

Significantly increased diastolic volume of cerebrospinal fluid was measured in the neurologically normal subjects left hemispheres pre and post all orthostatic and cognitive tests compared to the PD patients, $p = 0.0275$.

Conclusion: The left-brain hemisphere is normally associated with analytical reasoning, mathematical calculations and logic and all neurologically normal subjects. In contrast, all Parkinson subjects used their right brain hemispheres for solving the arithmetic cognitive tests.

Keywords: *Cranium; Brain; Blood; Cerebrospinal Fluid (CSF); Bio-Impedance; Parkinson's Disease; Ageing; Doppler; Cognition*

Introduction

Failure in the regulation of the fluid contents of the human cranium, principally blood and cerebrospinal fluid, is of significant importance in the treatment of traumatic brain injury (TBI), subarachnoid haemorrhage, hydrocephalus and stroke patients. Proper regulation is a pivotal mechanism of cranial homeostasis which is better understood in the human body than the cranium. All systems of the body are linked. While operating singularly, they interact with each other. The cardiovascular system continually readjusts to changes in temperature, pressure and posture. In turn this affects the vascular, nervous, endocrine, muscular, fascial and skeletal systems.

Cranial volume regulation is accomplished by the relationship between Cranial Elastance (CCe), control of the volume of blood allowed to enter the cranial cavity via the cranial arteries, venous blood outflow, and the production, volume and outflow of cerebrospinal fluid (CSF)

within the cranium. Added to this activity is the osmotic action through the blood brain barrier (BBB) resulting in both cerebrovascular physical and chemical reactivity (CVR_{phys} and CVR_{chem}). While each of these cranial activities operate autonomously, they interact with each other to create a level of intracranial pressure (ICP). Unlike the body's autoregulation, it is unclear what is the autoregulator for the cranial contents. The competency of cerebrospinal fluid (CSF) in removing waste products from brain tissue has been reported as being essential in neurodegenerative diseases e.g. dementia and Alzheimer's [3,4].

Using a measurement system integrating the waveforms from a transcranial Doppler and a bio-impedance device, we investigated whether analysis of the combined data would provide feasible measurements of intracranial fluids. We also investigated if there was evidence of significantly different fluid volume changes of blood and CSF within the cranium of neurodegenerative adults (Parkinson's patients) and age/gender matched neurologically normal ageing adults.

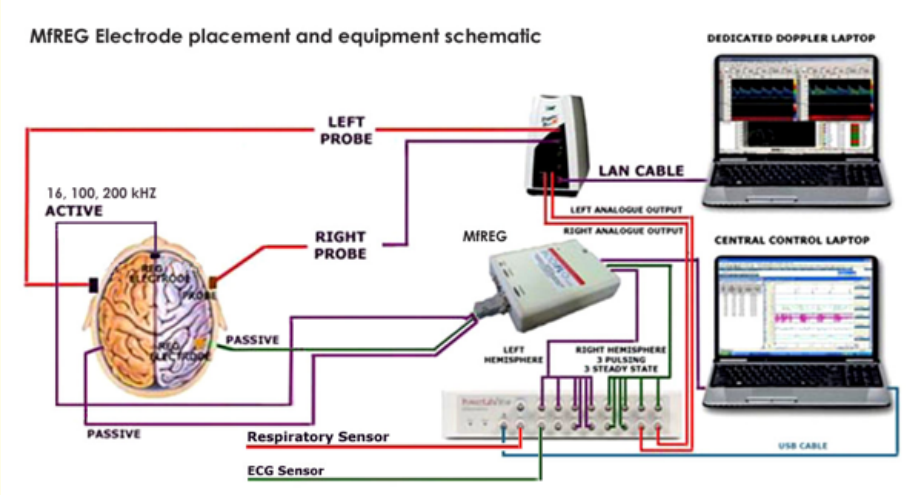


Figure 1: *Schematic diagram of the study devices and laptop complex, positioning of the two Doppler electrode probes and three impedance electrodes for measuring cerebral blood flow (CBF) and cerebrospinal fluid (CSF) volumes for the subjects' brain hemispheres. Analysis was performed using an automated software program (AIS).*

Materials

All participants were measured in a single testing session following an introductory assessment for agreement to participate in the study. In this single blind study, the data collectors were not aware of the analyses to be used or the expected out-comes. As this research involved human subjects, ethical approval was applied for and approved from the Queensland University of Technology (QUT) Human Research Ethics Committee. The scope, nature and risks of the study were fully explained to all subjects prior to any testing or assessments being conducted.

All Health and Safety risks associated with this study were ensured to comply with QUT's Health and Safety requirements.

Methods

Measurements of the cardiovascular status of each subject were conducted with an electrocardiogram (ECG) and whole-body blood pressure unit (Portapres®). The subject's respiratory rate was monitored with a chest respiratory band.

Bioelectrical impedance analysis (BIA) has been used widely in research and clinical applications. BIA is commonly used to determine the fat-free mass (FFM) and total body water (TBW) in subjects, providing they have no significant fluid or electrolyte abnormalities and when appropriate age or pathology-specific exclusions are applied [5]. Excessive hydration or dehydration was discouraged prior to testing.

Indices and Interpretation

The calculated cerebrospinal fluid volume (CSFm) can be interpreted as indicating changes in cerebrospinal fluid pressure. Disturbed CSF circulation certainly causes volume-pressure compensation, and even small changes in intracranial fluid volumes create significant intracranial pressure changes, raised resistance to CSF outflow, high magnitude of slow vasogenic waves and ICP pulse amplitude [6]. Provided that the constituents of the intracranial fluid contents, essentially blood and CSF, remain constant, then theoretically intracranial pressure changes should maintain a parallel relationship to intracranial fluid volume changes. However, should the relative intracranial fluid compositions change, the parallel volume-pressure relationship of increased volume and increased intracranial pressure may not strictly apply. The 'Y' value in all analyses is based on a normalized '0' to allow a comparison from '0' to '1.0'.

For analysis we selected an optimal bio-impedance wave in the recording track, a coincident Doppler wave, and a coincident physiological state of interest e.g. ECG wave. By a series of algorithms, a combined bio-impedance/Doppler wave was created for in-depth analysis. Postural changes on a tilt table and cognitive challenges acted as perturbations to determine if the selected participant groups reacted differently in their intracranial cerebral blood input and cerebrospinal fluid volume. Both the systolic and diastolic cardiac phases were analyzed to ascertain the intracranial fluid differences between the two cardiac phases.

The bio-impedance system in this study utilized a 100 kilohertz (kHz) frequency, and an electrical current of 0.5 millivolts (+/- 0.15 mV). The transcranial Doppler device consisted of a DWL twin probe device to measure cerebral blood flow (CBF).

It was expected that the combination of bio-impedance and Doppler would provide accurate data for analyzing the intracranial fluid dynamics within the semi-finite confines of the cranium. Additionally, that there would be a clear indication that there are different intracranial fluid volumes in the brain hemispheres of Parkinson's patients and ageing neurologically normal subjects when cognitively and orthostatically challenged.

Results

Averaged values of measured parameters are given in table 1 (Parkinson's patients) and table 2 (normally ageing participants)

Table 1 and 2 are the mean of the Pre-tests for 5 Parkinson and 5 Ageing participants. Cranial Compliance (CCe- cranial flexibility), Angle (Ascending slope of systolic wave), Delta V (calculated intracranial volume), Delta T (Time between the peak of the Doppler wave and the peak of the bio-impedance wave), systolic cardiac input phase calculated volume (S.SCFm), diastolic cardiac phase calculated volume (D.CSFm) for left and right brain hemispheres.

PD Participants	CCe^{deg}		Angle^{deg}		DeltaV$^{\%}$		DeltaT^{secs}		S.CSFm in^2		D.CSFm in^2	
	L	R	L	R	L	R	L	R	L	R	L	R
At Rest Supine Pre 1st SST Test	0.338	0.316	18.20	17.27	0.761	0.761	0.274	0.288	0.166	0.376	0.758	0.688
At Rest Supine Post 1st SST Test	0.456	0.368	23.82	19.37	0.717	0.800	0.186	0.266	0.342	0.300	0.626	0.632

Table 1

Ageing Participants	CCe^{deg}		Angle^{deg}		DeltaV$^{\%}$		DeltaT^{secs}		S.CSFm in^2		D.CSFm in^2	
	L	R	L	R	L	R	L	R	L	R	L	R
At Rest Supine Pre 1st SST Test	0.436	0.546	23.45	28.39	0.742	0.752	0.178	0.182	0.21	0.524	0.566	0.466
At Rest Supine Post 1st SST Test	0.392	0.347	20.92	18.502	0.813	0.696	0.210	0.218	0.184	0.482	0.762	0.676

Table 2

Mean cranial compliance (CCe - cranial flexibility or elastance) of the ageing subjects at rest supine pre their 1st SST challenge compared to their post 1st SST challenge is lower in both hemispheres while the Parkinson patients increased their CCe in both hemispheres in this orthostatic position pre and post the 1st SST challenge $p > 0.05$ not significant.

The Angle degree measurements support the CCe observed changes in these subjects pre and post the 1st SST challenge with similar decreases and increases in Angle measurements of their right and left-brain hemispheres. Ageing (L) 20.92 < 23.45 (R) 18.502 < 18.39 PD PD (L) 18.20 < 23.82 (R) 17.27 < 19.37 $p < 0.05$ not significant.

Delta V (calculated intracranial volume). Parkinson patients had a decreased Delta V in their left hemispheres but increased intracranial volume in their right hemispheres pre and post the 1st SST test supine. L = 0.761 > 0.717 R = 0.761 < 0.800 In contrast the Ageing subjects had increases in their left hemispheres and decreases of Delta V in their right hemispheres. L = 0.742 < 0.813 R = 0.752 > 0.696 $p > 0.05$ not significant.

Delta T Parkinson patients took less time in both hemispheres to autoregulate pre and post the 1st SST test. L = 0.274 > 0.186 R = 0.288 > 0.266 Ageing subjects L = 0.178 < 0.210 R = 0.182 < 0.218 $p = 0.0181 < 0.05$.

Systolic cerebrospinal fluid volume(S.CSFm) for the PD patients increased in the L hemisphere L = 0.166 < 0.342 but decreased in their R = 0.376 > 0.300 pre and post 1st SST test. In contrast the Ageing subjects decreased in both their L = 0.21 > 0.184 and their R = 0.524 < 0.482

Diastolic cerebrospinal fluid(D.CSFm) decreased in both hemispheres for the PD patients L = 0.758 > 0.626 R = 0.688 > 0.632 but increased in both hemispheres for the Ageing subjects L = 0.566 > 0.762 R = 0.466 < 0.676 pre and post the 1st SST challenge.

There were a total of 20 PD and 22 age and gender matched neurologically normal ageing participants in the overall study. The following Mean data display was created for comparisons between the 5 Parkinson's (PD) subjects.

Following serial subtraction cognitive challenges in a supine and almost vertical (75 degrees to vertical), the Parkinson subjects exhibited increased right brain hemispheric fluid activity. In contrast, the matched neurologically normal ageing subjects showed increased left-brain hemispheric fluid activity following these same cognitive challenges.

The Ageing subjects achieved a significantly larger intracranial fluid volume in a shorter period of time in their systolic cardiac phase.

The Parkinson patients have to recruit more blood and cerebrospinal fluid in both hemispheres to problem solve. This would support the total body cardiovascular measurement differences between the two subject groups found with our tilt table challenges where the Parkinson patients could not upregulate their blood pressure to accommodate for the orthostatic movement from supine to near vertical. The PD subjects took more time - 130.24 seconds to reach their maximum ECG level compared to 123.98 seconds for the ageing subjects on the TILT table test.

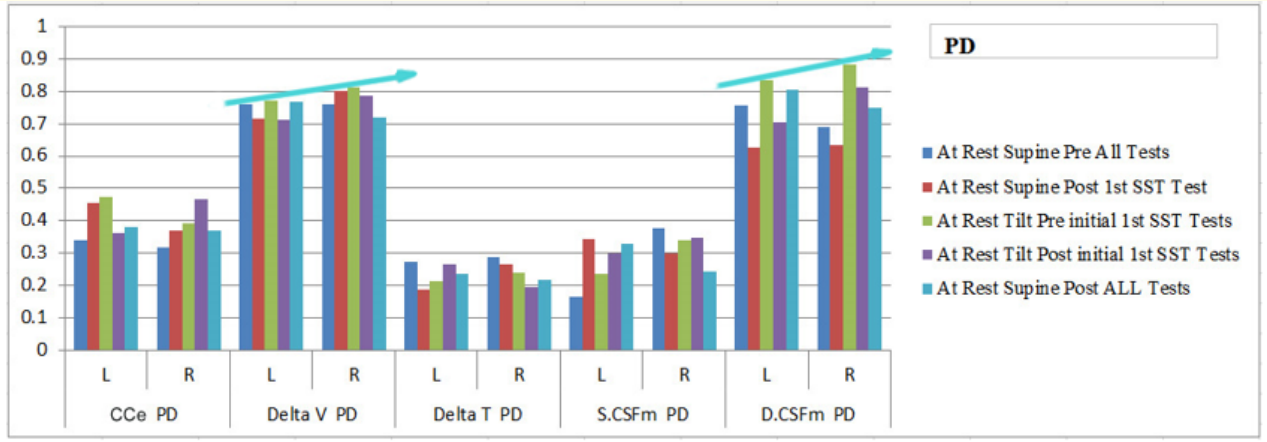


Figure 2: *The mean average comparison of the 5 PD participants displayed a tendency for increased right and left diastolic Delta V and diastolic CSF calculated volume (D.CSFm) during the tilt table and at rest body positions pre the 1st SST-7 and post all orthostatic and cognitive challenges. Both Delta V and D.CSFm are congruent fluid increases, show slightly different values, but display the same trend of increased right hemispheric fluid activity.*

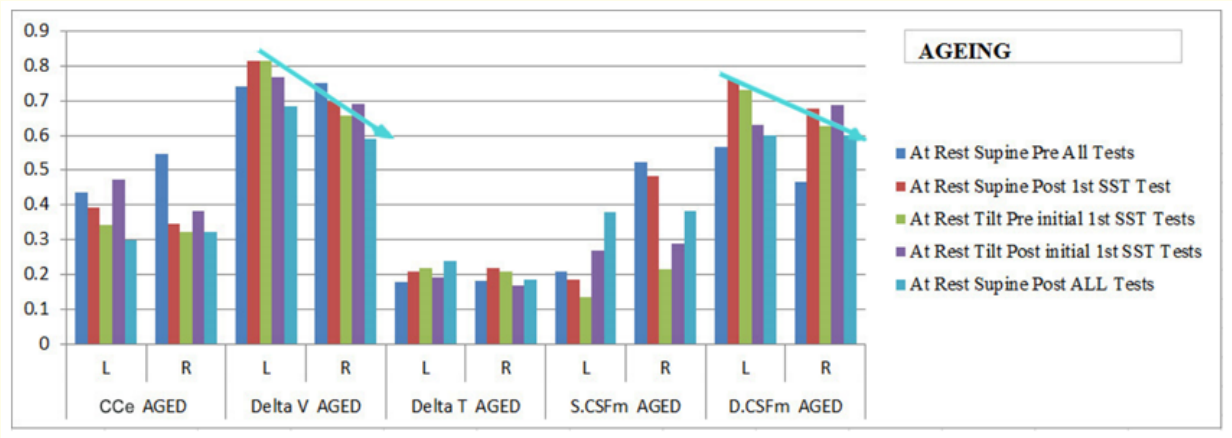


Figure 3: *The mean average comparison of the 5 Ageing participants displays a reversal of the Parkinson's (PD) subjects' hemispheric activity, with increased activity in their left-brain hemisphere for Delta V and D.CSFm pre the 1st cognitive SST challenge and post all challenges. There is a decline in the fluid volume in the Right brain hemispheres of the normal ageing participants and an increase in their Left brain hemisphere of both Delta V and diastolic D.CSFm volumes.*

Each group was allowed 30 seconds for their answers in each cognitive response session.

Both groups had similar accuracy scores in their ability to answer mathematical questions from the cognitive tests.

Delta V was at a higher level for the 10 Parkinson participants in their right brain hemisphere and for the 10 ageing participants their left-brain hemisphere following the cognitive challenges, either after a single cognitive challenge or multiple cognitive challenges.

Discussion

The Parkinson patients have to recruit more blood and cerebrospinal fluid in both brain hemispheres to problem-solve but predominantly used their right hemisphere. This is opposite to the traditional right/left brain function where mathematical calculations are made by the left- brain hemisphere. Increased oxygenated blood available to brain regions provides for better cognitive capacity. It is unclear when measuring the total intracranial fluid volume what part of this fluid volume is blood and what is cerebrospinal fluid. This is further complicated by the current knowledge of cerebrospinal fluid production, function, and when this production occurs.

There are currently two models for CSF production. The traditional model or hypothesis postulates that CSF is formed inside the brain ventricles, mostly by secretion from the choroid plexuses. A more recent hypothesis is that CSF production is determined by a microcirculatory/micro-vessel mechanism [7]. The microcirculatory/micro vessel hypothesis suggests that CNS micro-vessels are instrumental in fluid filtration and reabsorption inside the brain and spinal cord parenchyma, as well as inside the CSF system itself [7]. There are other factors affecting the volume of intracranial fluids, such as intracranial pressure (ICP), osmosis through the cell membranes, cerebrovascular reactivity physical and chemical (CVR_{phy}, CVR_{chem}), blood brain barrier (BBB) permeability, CSF production, cranial blood inflow, lymphatic drainage from the cranium, brain tissue activity and other complex protein synthesis and chemical changes.

The Cranial Compliance (CCe) or boney elastance of the ageing participants is of a higher level than that of the Parkinson's patients. More blood was allowed into the cranium and available for cognitive decisions. The patient's biomechanical ability to pump cerebrospinal fluid from the cranium and remove metabolic waste is critically important in traumatic brain injury (TBI) and neurodegenerative diseases, where there is an accumulation of harmful proteins and protein tangles affecting neuronal connectivity. Microdialysis of the CSF using a catheter alongside the frontal lobe bolt in head injured ICU patients measuring glucose levels, lactate, pyruvate, lactate/pyruvate ratio (anaerobic/aerobic metabolism), glycerol (for cell membrane breakdown) and glutamate in future studies may answer a number of questions in this area. Combining the Cambridge ICM+ monitoring system with the Doppler/Impedance system would add significantly to our knowledge of the overall physiological state of patients.

Unmedicated PD patients using fMRI scans exhibit different and compensatory cortical activity compared to normal ageing subjects when executive processing due to cognitive challenges [8]. A study by Monchi indicated that medications may affect the caudate nucleus and in turn the prefrontal cortex, posterior cortical areas and the parietal and prestriate cortex [8]. As many previous Parkinson's studies have subject groups who were medicated due to their disease, studies prior to Monchi's study may have had measurements that were misleading as to actual brain function.

From the current brain measurement devices of computerized tomography (CT), functional magnetic resonance imagery (fMRI) and positron emission tomography (PET), we have some measurements of fluid volumes and cranial fluid dynamics. The contrast agents used may, however, introduce their own effects [9]. Intracranial Volume/Pressure dependence are both initiated by the median cranial artery (MCA) arterial pressure pulsations.

A number of previous studies have demonstrated the reliability of the combined ultrasound and bio-impedance system [10,11]. Pilot studies had demonstrated a < 1% difference between analyses of the same research subject using the AIS software program used in this study compared to manual analyses of the same data.

Other researchers have used different monitoring devices to those used in this study, usually magnetic resonance imagery (MRI), to support their findings. The capability of the Parkinson patients to recruit a different brain hemisphere to that of the neurologically normal ageing people may indicate the human organism's ability to compensate for neuronal networking inadequacies by providing the necessary oxygenated blood to the brain tissue in whatever region of the brain can best provide a decision-making solution for that particular

human host. This would require an autoregulation at the highest level in a period of time of 2 - 3 seconds for the complex metabolic (chemical) changes and 8 - 12 seconds required for these physiological changes [12]. Previous research papers indicate that Parkinson patients exhibit different cortical activity than a neurologically normal control group [13]. These may also indicate a compensatory brain hemispheric activity and support our findings.

Monchi used functional magnetic resonance imaging (fMRI) to study the specific role of the caudate nucleus in the executive processes of Parkinson's patients during a card sorting challenge. Their subject groups were very similar, consisting of early-stage Parkinson's disease patients (Hoehn and Yahr stages 1 and 2 with a mean age of 62 years) and matched gender/age subjects. Monchi's event-related fMRI study showed a pattern of cortical activation in Parkinson's disease characterized by either reduced or increased activation. These findings are not in agreement with the traditional model, which proposes that the nigrostriatal dopamine depletion results in decreased cortical activity. While Monchi observed bilateral brain activity in a number of brain areas, as we did of increased fluid activity, of significance was the activity in the right posterior cingulate cortex and the right posterior parietal cortex. Similar to our findings.

The Doppler/Impedance combination of devices in our study is non-intrusive with no reported harmful effects. Monchi's study required the Parkinson patient subjects to discontinue their medications to obtain an accurate measurement of brain function. We did not require our Parkinson subjects to discontinue any medications. This has significant implications for emergency treatment of Parkinson's and dementia patients admitted to the intensive care unit (ICU) due to brain trauma or stroke, as we can continue to accurately monitor the medicated patient.

Gerrits' study had different modelling, methodology and protocol, but the conclusion of compensatory brain activity with Parkinson patient subjects is similar [14].

"The Parkinson patients, compared with the controls, showed increased task-related activation of their bilateral inferior parietal cortex, and their right superior frontal gyrus, and decreased activation of their right ventrolateral prefrontal cortex during set-shift trials. Our findings suggest that, despite decreased task-related activation of the right ventrolateral prefrontal cortex, these early-stage un-medicated patients with Parkinson's disease do not yet suffer from set shifting deficits due to compensatory hyper-activation in the inferior parietal cortex and the superior frontal gyrus".

Limitations of the Study

The total testing period was up to 2.5 hours per subject and included a Near Infrared (NIRS) device. The Doppler/Impedance study normally takes 45 minutes per subject. As a result, there may have been a fatigue factor. The data collection staff were not always available resulting in issues with inserting the correct timeline with data collection. Future studies require two assigned data collectors for each test session. The omission of the 200kHz bio-impedance frequency removed the measurement of extracellular and intracellular volume changes, critical ICU measurements for managing traumatic brain injury.

Conclusion

A combined Doppler/Bio-impedance system to measure intracranial fluids non-invasively offers better critical care of traumatic brain injury, stroke patients and research into neurodegenerative diseases such as Parkinson's and Dementia. The contrasting use of brain hemispheres by the Neurologically Normal Ageing subjects compared to the Parkinson patients is a significant finding for compensatory brain mechanisms. More studies are needed to determine if this compensation is restricted to Parkinson's disease or is a mechanism related to other neurodegenerative diseases.

Appendix

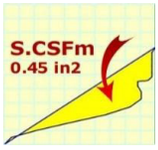
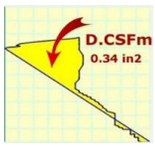
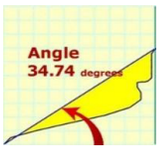
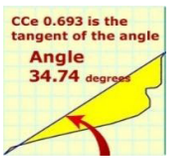
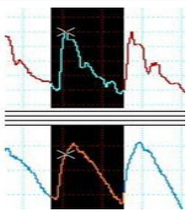
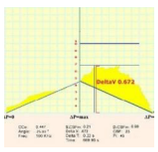
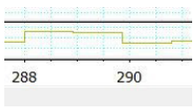
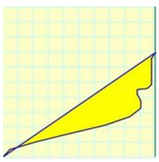
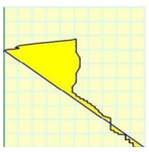
Systolic cerebrospinal fluid volume (S.CSFm)		S.CSFm is the calculated volume (inch^2) of the Systolic Cerebrospinal Fluid Example 0.45 in^2
Diastolic cerebrospinal fluid volume (D.CSFm)		CSFm is the calculated volume (inch^2) of the Diastolic Cerebrospinal Fluid Example 0.34 in^2
Angle		Angle in degrees of the Systolic calculated from a tangent table Example 34.74 degrees
Freq	16 kHz, 100 kHz or 200 kHz	The specific frequency of the Multi-frequency bio-impedance device in Kilohertz (kHz). 100kHz frequency was used in this study.
CCe		CCe is the capacity of the Cranial System to accept an additional fluid volume ie. the flexibility or elastance of the skull bio-mechanical system. This is calculated in degrees from the Tangent of the Angle of the Systolic cardiac phase. Example 0.693 degrees
Delta T		Delta T is derived from the time difference (in seconds) between the Doppler wave at maximum value and the bio-impedance wave at maximum value and can be + or -. When Delta T is Negative CCe must be calculated from the real Doppler voltage value (before normalization) divided by the bio-impedance voltage
Delta V		Delta V (volume in % of 100% of the template created) is derived from the value of the bio-impedance at its maximum value Example 0.672 %
Time		Time signature in seconds from Lab Chart recording at the beginning of selected wave capture Example "at 288 to 290 seconds"
Systolic		The Active portion or systolic phase of the cardiac wave as blood pressure is increasing with arterial input
Diastolic		The Passive portion or diastolic phase of the cardiac wave as blood pressure is decreasing with cerebrospinal fluid input increasing

Table A1: *Descriptions of the Doppler/Bio-impedance intracranial fluid measurements provided by the combining the waves of the Doppler and Bio-impedance devices.*

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