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The Relationship Between Optic Nerve Sheath Diameter, Carotid Artery Pulsatility Index, and Blood Pressure in Healthy Adults

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THE RELATIONSHIP BETWEEN OPTIC NERVE SHEATH DIAMETER, CAROTID ARTERY PULSATILITY INDEX, AND BLOOD PRESSURE IN HEALTHY ADULTS

By

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ABSTRACT

Monitoring intracranial pressure (ICP) has become an important practice in patients with elevated ICP (e.g., traumatic brain injury) to improve patient outcome. However, little information exists surrounding chronic, but sub-clinical elevations in ICP, which may stem from classic cardiovascular risk factors, such as elevated blood pressure (BP). The current methods to assess ICP are invasive and costly; but optic nerve sheath diameter (ONSD) and blood flow pulsatility (pulsatility index; PI) are promising non-invasive techniques, both of which have been reported to strongly correlate with invasive measures of ICP in pathology. However, the interactions of BP, ONSD and PI in otherwise healthy adults, remains undetermined. Accordingly, the purpose of this investigation was to determine the relationship between ONSD, PI and BP, and to highlight possible sex differences in a population of young healthy adults. Sixteen participants (6 females) underwent assessment of arterial BP, ONSD (left and right eyes) and PI (left common carotid artery) using ultrasound. There was a strong correlation between mean ONSD (left and right eye combined) and PI ($R=0.735$, $p=0.001$). There was no significant relationship between PI and BP ($R=0.058$, $p=0.832$) or ONSD and BP ($R=0.272$, $p=0.309$). Additionally, there was a significant difference between males and females for mean ONSD, whereby males demonstrated a larger diameter (males=0.486±0.110 vs. females=0.353±0.062cm; $p=0.018$), but there was no significant difference in PI between males and females (males=2.363±0.613 vs. females=1.950±0.196; $p=0.136$). Results of this study confirm the relationship between ONSD and PI in a healthy population. While ICP was not directly assessed in the current study, the strong associations between ONSD and PI suggest that their combined assessment may be employed as a tenable surrogate to non-invasively measure ICP when the invasive measure of ICP is unfeasible.

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LIST OF ABBREVIATIONS

BP	Blood Pressure
BSA	Body Surface Area
CBF	Cerebral Blood Flow
CCA	Common Carotid Artery
CPP	Cerebral Perfusion Pressure
CSF	Cerebrospinal Fluid
CO_2	Carbon Dioxide
CT	Computed Tomography
DBP	Diastolic Blood Pressure
HR	Heart Rate
ICA	Internal Carotid Artery
ICP	Intracranial Pressure
MAP	Mean Arterial Pressure
MRI	Magnetic Resonance Imaging
nICP	Non-invasive Intracranial Pressure
NVC	Neurovascular Coupling
ONSD	Optic Nerve Sheath Diameter
P_aCO_2	Partial Pressure of Arterial Carbon Dioxide
P_aO_2	Partial Pressure of Arterial Oxygen
PI	Pulsatility Index
PP	Pulse Pressure
TBI	Traumatic Brain Injury
SBP	Systolic Blood Pressure
VA	Vertebral Artery

1. INTRODUCTION

Fastidious regulation of the pressure within the skull, the intracranial pressure (ICP), is essential for optimal brain health. An elevated ICP is generally associated with severe cerebrovascular complications, such as a traumatic brain injury (TBI), intracranial tumor, or subarachnoid hemorrhaging (Geeraerts et al., 2007). Research in TBI is particularly important due to its high mortality rate, and costly medical care (Koziarz et al., 2019). Both the severity and duration of elevated ICP have been correlated with fatal outcome TBI, therefore, ICP monitoring has become an increasingly important practice among neurosurgical and neurological patients in order to improve patient prognosis (Evensen & Eide, 2020). Less known, however, are the effects of chronic but sub-clinical elevations in ICP, which may occur from mild TBI such as a concussion (Haider et a., 2019), or classic cardiovascular risk factors, such as elevated blood pressure (BP). Indeed, a sub-clinical but chronically elevated ICP may in part be responsible for the increased prevalence of cerebrovascular events associated with high BP (Rossi et al., 1995). The ability to identify and characterize elevated ICP may therefore be vital for early detection and prevention of cerebrovascular complications.

The conventional determination of ICP is through the invasive insertion of a catheter through the skull into the intraventricular space (Bellner et al., 2004), an approach which is unfeasible (and unethical) in sub-clinical populations. A second option is with the use of brain computed tomography (CT) scans, which is not easily accessible, is expensive, and emits potentially harmful ionizing radiation (Wiest et al., 2002). As such, there has been a recent move towards the use of non-invasive alternatives for estimating ICP. Of those, the two most promising are via ultrasound assessments of the optic nerve sheath diameter (ONSD) and blood flow pulsatility of cerebral vessels (pulsatility index; PI).

Although the PI and ONSD have been demonstrated to correlate with ICP in clinical settings of elevated ICP (e.g., TBI, stroke, subarachnoid hemorrhage; Geeraerts et al., 2007, Birnefeld et al., 2020), there is limited information in otherwise healthy populations. Moreover, it remains unclear whether high cerebral pulsatility is damaging or in fact protective in healthy young adults (Desmidt et al., 2018). Much of this confusion likely stems from the lack of data in different population groups. Indeed, the association between ONSD and PI with classic cardiovascular and cerebrovascular risk factors, such as elevated BP, is unknown. Addressing this gap in the literature will provide insight on the relationship between ONSD, cerebral PI and BP in young adults free of overt cerebrovascular and cardiovascular disease. Collectively, results from this research will provide a starting point for future studies relating to cerebrovascular injury and elevated ICP. The current knowledge on cerebral blood flow (CBF) regulation, ICP regulation, ONSD, cerebral PI and BP, and the link between these systems will be summarized. Special attention will be given to the relationship between ONSD, PI and BP in young healthy adults.

2. REVIEW OF THE LITERATURE

Cerebral Blood Flow Regulation

Cerebral blood flow is one of the most tightly regulated systems in the human body and involves the integration of a myriad of factors, which can be broadly categorized into; 1) blood gases, 2) metabolism, 3) perfusion pressure and 4) neurogenic factors (Willie et al., 2014). These mechanisms work together to precisely control CBF to maintain constant nutrient and oxygen delivery. The following subsections will discuss the aforementioned factors individually with respect to their influence on CBF maintenance.

Blood Gases

The brain is highly sensitive to changes in the concentration and partial pressure of arterial carbon dioxide ($PaCO_2$) and oxygen (PaO_2); for example, on average there is a 3-6% increase and a 1-3% decrease in CBF per millimeter of mercury change in carbon dioxide (CO_2) above and below resting $PaCO_2$ levels, respectively (Sato et al., 2012; Willie et al., 2012). The physiological response, termed cerebrovascular reactivity, reflects the ability of the vessels to dilate or constrict in response to changes in $PaCO_2$ and/or PaO_2 (Ainslie & Duffin, 2009). In conditions of reduced $PaCO_2$ levels (hypocapnia), the cerebral vessels vasoconstrict, resulting in a decreased cerebral vascular compliance, and in turn CBF (MacKay et al., 2016). Alternatively, in conditions of increased $PaCO_2$ (hypercapnia), the cerebral vessels vasodilate, increasing the CBF, in effect increasing the cerebral 'washout' of CO_2 in attempt to maintain brain pH (MacKay et al., 2016). Although the largest influence is generally thought to be at the level of the pial arteries, the cerebral arteries, such as the internal carotid artery (ICA) and vertebral artery (VA), are also sensitive to changes in blood gases (as reviewed in Wille et al., 2012). For instance, Willie and colleagues demonstrated a 20% change in diameter of the ICA between a range of 15-65 millimeters of

mercury $PaCO_2$ (Willie et al., 2012). As such, these large vessels can be considered an integral component within the maintenance of CBF.

Although cerebrovascular CO_2 reactivity has been the topic of many studies, a conclusive mechanism relating blood gases and CBF has yet to be determined, but it at least in part involves changes in extracellular pH. As noted by Willie and colleagues, cerebrovascular smooth muscle contracts with increased pH (alkalosis) and relaxes with decreased pH (acidosis), decreasing and increasing blood flow, respectively (Willie et al., 2014).

Metabolic Control

The brain is well equipped to ensure appropriate blood supply for a given metabolic demand (Phillips et al., 2016) via a mechanism referred to as neurovascular coupling (NVC). Neurovascular coupling describes the relationship between cerebral metabolism and regional cerebral perfusion (Phillips et al., 2016), and is responsible for the increase in CBF to support greater regional metabolic demands. The neurovascular unit, comprised of pial arteries, pericytes, interneurons and neurons, represents the structural focus for the study of NVC (Phillips et al., 2016). Briefly, excitatory and inhibitory neurons synapse on astrocytes and interneurons, thereby allowing communication and a vasoactive response between vascular smooth muscle cells to local stimuli (Willie et al., 2014). One potential mechanism involves glutamate, a strong neurotransmitter, which causes a cascade (in the presence of oxygen and glucose) ending with the release of nitric oxide at the level of the arterioles causing dilation (Phillips et al., 2016). Neurovascular coupling is thought to occur within a feed-forward mechanism, thereby leading to a greater increase in CBF relative to local metabolic demand (Phillips et al., 2016). Additionally, NVC is known be highly robust, and well maintained under physiological stressors (Phillips et al., 2016).

Neurogenic Control

The cerebrovasculature is highly innervated by the sympathetic nerve fibers; however, controversy remains surrounding the influence of sympathetic nerve activity on the regulation of CBF (Ainslie & Duffin, 2009). It has been hypothesized that the main role of the sympathetic nervous system is to directly regulate vascular tone in order to maintain blood pressure (Peterson, Wang & Britz, 2011). Indeed, influence from the sympathetic neural innervation is the leading tenable theory for cerebral autoregulatory control (i.e., regulation of the CBF with changes in perfusion pressure).

Perfusion Pressure

The CBF is vulnerable to changes in the perfusion pressure (blood pressure), just as is all other vascular tissue in the body. That is, low blood pressure can lead to cerebral hypoperfusion, while high blood pressure can lead to hyperperfusion (Willie et al., 2014). Strictly, the cerebral perfusion pressure (CPP) is calculated as the mean arterial pressure (MAP), minus the ICP. However, because historically there has been a lack of an appropriate non-invasive estimate of ICP, the ICP is often ignored in the estimates of the CPP (discussed later). Unlike the majority of other tissues in the body (e.g., vasculature of the leg), the brain is particularly effective at buffering changes in blood pressure to maintain a relatively steady blood flow – termed cerebral autoregulation. Although well beyond the scope of this literature review, it is generally accepted that the brain is much more effective at buffering long-term changes in blood pressure (e.g., with essential hypertension), versus acute changes in blood pressure (e.g., moving from sitting to standing) (Willie et al., 2014). The mechanisms of cerebral autoregulation are poorly understood, however, are thought to play a protective role in attempt to avoid hemorrhaging (with high blood pressure) or nutrient deprivation (with low blood pressure) (Willie et al., 2014).

Intracranial Pressure Regulation

Intracranial pressure is tightly regulated and influenced by the volume equilibrium within the brain, cerebrospinal fluid (CSF), and blood (Zhang et al., 2017). The relationship between the volume of the brain, blood volume, and CSF can be described by the Monro-Kellie doctrine. This hypothesis states that the sum of volumes between the brain tissue, CSF and blood volume remains constant (Mokri, 2001); thereby, an increase in one component should cause a reciprocal decrease in one or both of the others (Mokri, 2001). Due to brain volume fixed within the bony structures of the skull, blood volume and CSF are thought to be the main factors dictating ICP (Zhang et al., 2017).

CSF Circulation and Blood Volume

The CSF system is a closed circuit and involves two mechanisms; a compliance factor and a resistance factor (Mann et al., 1978). The compliance factor involves distention of the cranial and spinal meninges and their capacity to expand and withstand rapid increases in fluid volume (Mann et al., 1978). This mechanism is operative under all conditions of increased ICP and occurs during the initial phase of rising pressure (Mann et al. 1978). The resistance factor, being the rate at which CSF is absorbed into the venous circulation (Mann et al., 1978), involves the ability of the arachnoid villi to absorb and distribute CSF while achieving steady-state pressure. This mechanism remains constant over a broad range of pressure and is the major compensatory mechanism to prevent neurological damage (Mann et al., 1978). As previously discussed, blood flow to the brain (and therefore volume) remains relatively stable to maintain constant nutrient and oxygen delivery, and removal of waste. If compliance factors and outflow resistance mechanisms fail to compensate for increases in fluid volume, ICP rises rapidly and CBF is compromised (Mann et al., 1978).

Importance of Monitoring ICP

The baseline intracranial pressure is primarily dependent on age, body position, and clinical condition (Czosnyka & Pickard, 2004). In a healthy adult, ICP is maintained in the range of 5-15mmHg, 3-7mmHg in children, and 1.5-6mmHg in infants (Khan et al., 2017). However, a host of dynamic conditions can acutely alter the ICP. For example, postural changes from supine to sitting results in a decrease in pressure (i.e., ICP is greater while supine; Qvarlander et al., 2013; Gergelé & Manet, 2021). A chronically elevated ICP (> 20mmHg; Khan et al., 2017) occurs in a variety of medical conditions including head injury leading to intracranial hematoma or cerebral edema, and disorders of CSF circulation such as hydrocephalus; these conditions can compress and damage brain structures, cause brain herniation, and eventually restrict blood supply to the brain (Czosnyka & Pickard, 2004; Zhang et al., 2017). Therefore, the prevention of compromised CBF is one of the main reasons for measuring ICP (Evensen & Eide, 2020). As such, continuous monitoring and assessment of ICP in these clinical conditions is of utmost importance in order to reduce the risk of subsequent and irreversible neurological damage and/or death.

Measurement Techniques in Humans

There are several methods of measuring ICP, however, most of the current methods are invasive, expensive, and time consuming (Czosnyka & Pickard, 2004; Khan et al., 2017; Zhang et al., 2017; Evensen & Eide, 2020). The gold standard for measuring ICP involves the insertion of an intraventricular catheter through a burr hole, connected to an external pressure transducer (Khan et al., 2017). Despite being one of the most accurate methods, there are several complications associated with it, including high risk of infection, incorrect and difficulty placing the probe, malposition, and drifting of the “zero” reference pressure level, thus leading to an inaccurate ICP reading (Evensen & Eide, 2020). Other methods include but are not limited to, lumbar puncture,

epidural and subdural pressure sensors, and intraparenchymal devices (Zhang et al., 2017). Due to the invasive nature and possible complications associated with these methods, they are considered unethical in non-emergent conditions. Therefore, researching and developing non-invasive ICP (nICP) monitoring techniques has remained a priority by many clinicians.

Numerous nICP techniques have been proposed to estimate ICP, for example, neuroimaging (CT scan and magnetic resonance imaging (MRI)), transcranial doppler ultrasound, near-infrared spectroscopy, venous ophthalmodynamometry, tympanic membrane displacement and ONSD (Frattalone & Stevens, 2011; Zhang et al., 2017). Several advantages exist with estimating ICP using nICP methodologies including affordability, mobility, the ability to triage or determine a patient's current status, ability to provide on-going and long-term measurement of ICP without having to reinsert a new device, and no risk of complications or infection as seen with invasive probe insertion (Zhang et al., 2017). To assess the accuracy of a non-invasive method, the Association of Advancement of Medical Instrumentation stated when ICP is in a normal range (5-15mmHg), a difference of 2mmHg is acceptable when comparing to an invasive method (Popovic et al., 2009). Although still under consideration, the most promising nICP technique is based on transcranial ultrasonography, specifically, ONSD (Czosnyka & Pickard, 2004; Robba et al., 2017).

Optic Nerve Sheath Diameter

The use of the eye for ultrasound imaging is ideal due its superficial positioning and soft tissue, allowing easy ultrasound beam transduction (Richards & Mathew, 2021). The optic nerve can be easily identified with ultrasound lying posterior to the retina and optic disc (as depicted in Figure 2B). The optic nerve sheath surrounds and protects the optic nerve and is continuous with the dura matter and subarachnoid space (Hansen et al., 2011). With increasing ICP, local CSF around the

anterior portion of the optic nerve is extended due to hydrostatic transmittance of CSF pressure within the subarachnoid space (Hansen et al., 2011); therefore, the ONSD can be used as an indicator for changes in ICP. Importantly, an increase in ICP and dilation of the ONSD is almost instantaneous (Khan et al., 2017; Zhang et al., 2017), thus, ONSD is potentially useful in detecting acute elevations in ICP and determining a patient's status and/or avenue of treatment.

There is limited consensus on the range of ONSD in a healthy population; typically, ONSD between 3.8 – 4.7mm is considered normal, however, can vary with age (Cardim et al., 2020), sex (Goeres et al., 2016; Cardim et al., 2020), and medical history (e.g., history of mild traumatic brain injury; Lyon et al., 2018). Indeed, it has been established that ONSD increases with age (Cardim et al., 2020), and differs between sex whereby males typically demonstrate a larger ONSD (Goeres et al., 2016; Cardim et al., 2020). With varying ONSD values, dependent on the above factors, as well as method of assessment and location of assessment (described in more detail below), establishing a clinical cut-off point to differentiate between normal and elevated ICP has been difficult. Many studies however have denoted a threshold of 5.0mm, whereby anything greater is indicative of elevated ICP (>20mmHg) (Blaivas et al., 2003; Tayal et al., 2007; Goel et al., 2008; Kimberly et al., 2008; Matthews et al., 2020).

Measurement Techniques in Humans

Like ICP, there are several methods to measure ONSD. The current gold standard for measuring ONSD is MRI due to its high spatial resolution, however, the availability and cost of an MRI machine limits its utility (Bäuerle et al., 2013). Thus, research has focused on developing a tool that is accurate, reliable, and cost-effective.

Sonographic assessment of ONSD has proven to be both feasible and valid (Bäuerle & Nedelmann, 2011; Zhang et al., 2017), and can be administered easily at bedside or in the field (Zhang et al., 2017; Koziarz et al., 2019). Additionally, sonographic ONSD has shown to have low inter- and intra-observer variability, as well as robust scan-rescan reproducibility (Bäuerle et al., 2013). In fact, when compared to the gold standard MRI technique, the difference between measures was less than 2 percent, and less than 5 percent between observers (Bäuerle et al., 2013). Furthermore, the location/depth by which ONSD is assessed is important to consider. Specifically, it has been proven that a depth of 3mm posterior to the optic disc is a more accurate and reliable measure compared to 5mm posterior (Bäuerle et al., 2013). Indeed, inter-, and intra-observer variability increases to a difference of almost nine percent when compared to ONSD measures taken at 3mm from the optic disc (Bäuerle et al., 2013). Part of this discrepancy may be explained by the blurring of the optic nerve as it moves posteriorly (as evident in Figure 2B). Additionally, ONSD at 5mm is seemingly overestimated with ultrasound, and is also likely a result of less defined walls of the nerve sheath as you move deeper (Bäuerle et al., 2013). Therefore, and as recommended by Helmke and Hansen, ONSD measures should be taken at 3mm posterior to the optic disc (1996).

Furthermore, sonographic ONSD assessment has proven to be highly accurate at estimating ICP. Indeed, a recent study comparing different techniques for determining ICP against to the gold standard intraventricular method in patients with hypoxic ischemic brain injury, found that ONSD correlated (R=0.53) the closest to the gold standard measure, even better than invasive internal jugular venous cannulation (Cardim et al., 2019). Given that ONSD is highly accurate and reliable compared to other invasive and non-invasive techniques, use at bedside and in non-emergent conditions is warranted for ICP assessment.

Pulsatility Index

Like the ONSD, the pulsatility index (PI) of cerebral vessels may also reflect the ICP. The PI is derived from the difference in systolic and diastolic blood flow velocity divided by the mean blood flow velocity (Bellner et al., 2004), and in turn reflects the downstream resistance to flow, which is impacted by the ICP. Cerebrovascular compliance and cerebrovascular resistance describe the functionality of the arterial system (Holmgren et al., 2020), and reflect the ability to dampen excessively pulsatile CBF (Desmidt et al., 2018). Brain pulsatility seemingly increases with age (Zarrinkoob et al., 2016), and may be indicative of cerebrovascular impairment, likely a result of arterial stiffening (Desmidt et al., 2018). Furthermore, the association between pulsatility and ICP is positive, whereby a high pulsatility (or pulsatile blood flow) is correlated with an elevated ICP (R=0.697) (Kaloria et al., 2020). Indeed, in 81 patients with indwelling intraventricular catheters, a strong correlation was observed between the PI of the middle cerebral artery and the ICP (R=0.938; Bellner et al., 2004). Knowing the detrimental effects of elevated ICP, quantifying pulsatility of the cerebrovasculature may be useful in understanding disease progression and patient prognosis.

Transcranial doppler ultrasound has conventionally been used to assess PI (Holmgren et al., 2020), however, has several nuances including difficulty finding a cranial window through the skull (Desmidt et al., 2018), and high inter- and intra-observer variability (Zhang et al., 2017). Additionally, MRI is often used, however given its utility and high cost, other methods have been employed. Similar to ONSD, the PI is easily and non-invasively determined with the use of doppler ultrasound.

3. STUDY RATIONALE AND HYPOTHESES

There is a well-established link between ONSD and ICP, and PI and ICP, however the relationship between ONSD and PI has yet to be elucidated. The combined assessment of ONSD and PI may prove as an effective method to non-invasively track alterations in ICP throughout treatment programs, or in populations at high risk for a cerebrovascular event. This study contained three distinct, but linked objectives in a population of young healthy adults:

OBJECTIVE 1. Determine if a relationship exists between ONSD and PI.

Hypothesis 1. The ONSD and PI will be positively correlated (i.e., those with a high ONSD will also have a high PI).

OBJECTIVE 2. Determine if a relationship exists between BP and ONSD, and BP and PI.

Hypothesis 2. Both ONSD and PI will be positively associated with BP (i.e., higher BP will correlate with larger ONSD and greater PI).

OBJECTIVE 3. Determine if a relationship exists between sex and ONSD, PI, and BP.

Hypothesis 3. Sex will influence ONSD, PI and BP, with males demonstrating larger ONSD, a higher PI of the carotid artery, and higher resting BP.

4. METHODOLOGY

Ethical Approval

The Kinesiology sub-committee Research Ethics Board for low-risk research at the University of Windsor approved all experimental procedures and protocols in adherence with the principles of the Tri-Council Policy Statement and the University of Windsor Guidelines for Research Involving Human Participants. All participants provided written consent before participation in the study, as well as on going consent prior to data collection during the subsequent visits.

Participants

Sixteen healthy male and female adults (6 female) were recruited from the University of Windsor via poster and email campaigns. All participants were free from overt cardiometabolic, neurologic and respiratory disease, were normotensive (resting seated systolic blood pressure (SBP) <130 and diastolic blood pressure (DBP) <80 mmHg), non-obese and non-smokers (including tobacco, marijuana, and vaping), as determined by pre-screening and a medical history questionnaire. Participants were not on any medications (excluding oral contraceptives) that could influence outcome measures (e.g., beta-blockers, statins, antihypertensive drugs).

Experimental Design

Eligible participants were invited to complete a Protocol Familiarization session and one testing session, separated by at least 48 hours. All testing sessions occurred in the morning (~8:30am) in a temperature-controlled room (22°C). Prior to data collection, all participants were asked to confirm they did not engage in vigorous physical activity or consumed marijuana products (including THC or CBD products) 24 hours prior, did not consume caffeine, alcohol, or over the counter medication 12 hours prior, and had been at least 2 hours fasted. Upon arrival to the

laboratory, basic anthropometric measures were taken (height and weight), using a standard upright medical balance scale. All BP and ultrasound measures (ONSD and PI) were performed with participants in a supine position. Testing procedures involved a measure of 1) BP, 2) CCA PI, and 3) ONSD of the left and right eye. Please refer to Figure 1 for a timeline of the study protocol including the duration of each assessment.

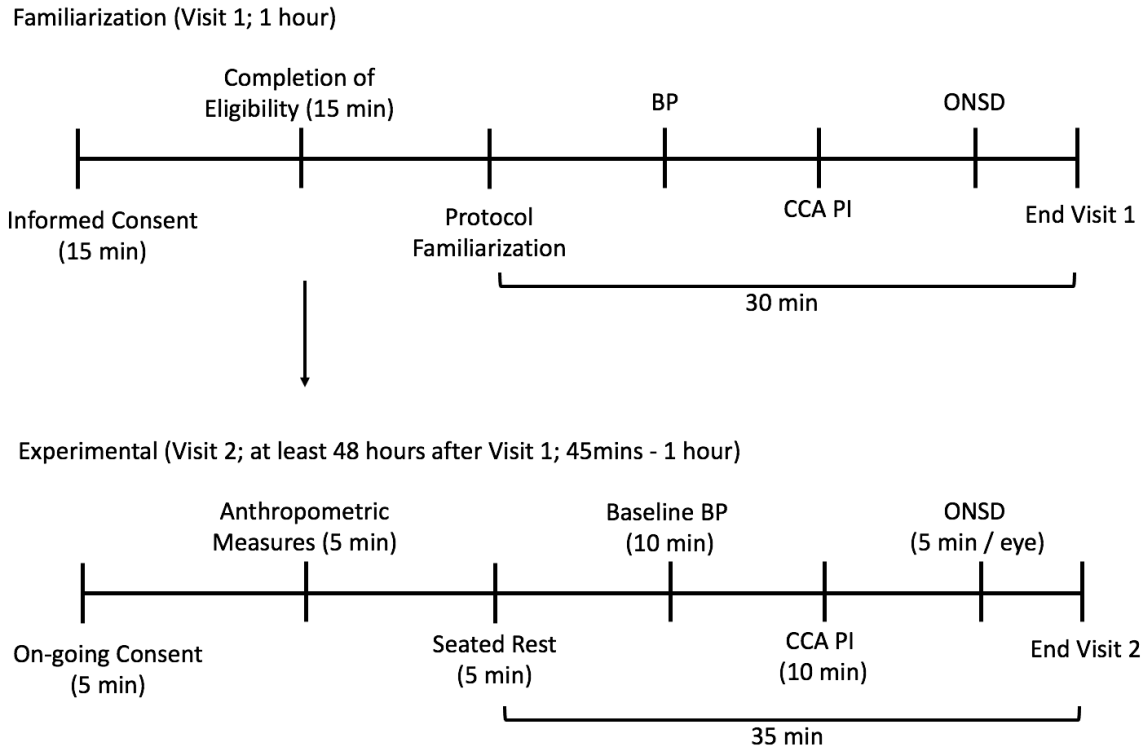

Figure 1. Timeline of study protocol. HR; heart rate, BP; blood pressure, CCA PI; common carotid artery pulsatility index, ONSD; optic nerve sheath diameter.

Measurement Techniques

Resting Blood Pressure

Participants were outfitted with the necessary equipment to assess BP using brachial artery oscillometry (Dinamap, Carescape, v100, Critikon, Tampa, Florida, USA). The participant was asked to lay supine for 5 minutes. Three measures of BP were recorded with 2 minutes between each measure. The Dinamap gave a recording of SBP and DBP. The MAP was then calculated as (1/3 SBP) + (2/3 DBP). The pulse pressure (PP) was calculated as SBP - DBP.

Pulsatility Index (PI)

Simultaneous B-mode and Duplex ultrasonography was performed to assess continuous blood velocity recordings of the left common carotid artery (CCA) using a 13-5 MHz linear array probe attached to a high-resolution ultrasound machine (Vivid I, GE Healthcare, Pittsburgh, PA, USA). Left CCA blood velocity was measured at least 2cm proximal from the carotid bifurcation to ensure there is no evidence of turbulent or retrograde flow. The insonation angle was fixed at 60 degrees throughout the entire protocol. Once reliable and consecutive 12 cardiac cycles were obtained, recordings were screen captured and saved for offline analysis. Pulsatility index was subsequently measured from the average difference in peak systolic versus diastolic blood flow velocity, divided by the mean envelope blood flow velocity:

$$PI = (\text{systolic velocity} - \text{diastolic velocity}) / \text{mean velocity} \quad (1)$$

Optic Nerve Sheath Diameter (ONSD)

B-mode ultrasonography was performed to obtain ONSD (Vivid I, GE Healthcare, Pittsburgh, PA, USA). With the participant in the supine position and eyes closed, ultrasound gel

was applied to the outside of the eyelid. Before closing the eye, the participant was instructed to fix their stare on a point directly above on the ceiling. The transducer probe was gently placed horizontally over the eyelid and the participants were instructed keep the stare on the ceiling as best as possible. Three images of the optic nerve from the left and right eyes were obtained. Analysis was performed offline using the integrated software calipers (Vivid I), 3mm behind the retina (see figure 2B). The ONSD was averaged for the three images of each eye. Data is presented as right, left, and mean ONSD (mean of the right and left eye combined).

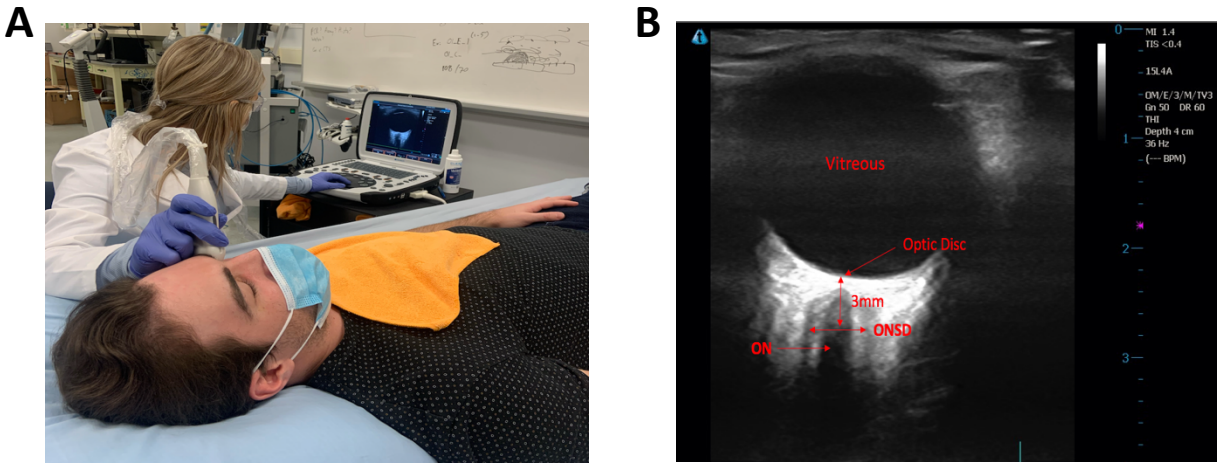

Figure 2. Optic nerve sheath diameter measurement technique with ultrasound (A). Ultrasound image of the left eye and optic nerve (B). ON; optic nerve, ONSD; optic nerve sheath diameter.

Statistical Analysis

Statistical analysis was run offline using SPSS software (Version 25, IBM Corporation, USA), and Prism (Version 9, GraphPad Software, LLC). All data are expressed as mean±SD, with statistical significance set at $p<0.05$. All data were assessed for normality using the Shapiro-Wilk test. Pearson correlations were used to assess the relationships between PI and ONSD (left, right and mean), PI and MAP, and ONSD and blood pressure (SBP, DBP, and MAP). A multivariate analysis of variance was run to determine if sex influenced PI, ONSD, MAP, and PP. Differences

between ONSD left and ONSD right were compared using paired, two-tailed, Student's T-tests. When significant f-values were present, post-hoc analyses were made with Bonferoni adjusted alpha for multiple comparisons.

5. RESULTS

Participants

Demographic data can be found summarized in Table 1. All recruited individuals were deemed eligible to participate and completed the entire protocol.

Table 1. Participant demographics. Values are presented as mean±SD.

	Males (n=10)	Females (n=6)	Combined (n=16)
Age (years)	22.600±4.526	22.667±5.202	22.626±4.617
Height (m)	1.824±0.072	1.603±0.026*	1.741±0.124
Weight (kg)	77.990±6.408	59.467±8.302*	71.044±11.550
BMI (kg/m^2)	23.469±1.789	23.087±2.781	23.326±2.130
SBP (mmHg)	111.900±8.090	97.833±8.232*	106.625±10.551
DBP (mmHg)	62.500±5.778	58.667±8.571	61.063±6.942

*, $p<0.05$ males versus females.

PI and ONSD

Common carotid pulsatility index, ONSD, MAP and PP values are presented in Table 2. The strongest correlations were observed between PI and ONSD right and PI and mean ONSD ($r=0.748$, $p=0.001$; $r=0.735$, $p=0.001$; Figure 3A and 3C, respectively). The PI and ONSD left also showed a relationship ($r=0.667$, $p=0.005$; Figure 3B); however, the relationship was not as strong as for the right and mean ONSD values. Additionally, there was no significant difference between left and right ONSD ($p=0.213$; Figure 6).

PI, ONSD and BP

There was no significant relationship between PI and MAP ($r=0.058$, $p=0.832$; Figure 4A) or ONSD and MAP ($r=0.272$, $p=0.309$; Figure 4B), nor was there a significant relationship

between mean ONSD and SBP (r =0.365, p=0.165; Figure 5A) or mean ONSD and DBP (r= -0.105, p=0.698; Figure 5B).

Table 2. Pulsatility index (PI), optic nerve sheath diameter (ONSD; right, left and mean), mean arterial pressure (MAP), and pulse pressure (PP), separated by sex and combined into one group. Values are presented as mean±SD.

	Males (n=10)	Females (n=6)	Combined (n=16)
PI	2.363±0.612	1.95±0.196	2.208±0.530
ONSD right (cm)	0.475±0.109	0.342±0.058	0.425±0.113
ONSD left (cm)	0.496±0.126	0.365±0.070	0.447±0.124
ONSD mean (cm)	0.486±0.110	0.353±0.062*	0.436±0.114
MAP (mmHg)	79.917±6.564	70.559±8.375*	76.408±8.434
PP (mmHg)	49.4±7.168	39.167±5.845*	45.562±8.270

*, $p<0.05$ males versus females.

Sex Differences

There was no significant difference between males and females with respect to CCA PI (2.363±0.613 vs. 1.950±0.196 for males and females, respectively; p=0.136; Figure 7A). There was a significant difference between males and females for mean ONSD (left and right ONSD combined), whereby males demonstrated a significantly larger diameter (0.486±0.110 vs. 0.353±0.062cm for males and females, respectively; p=0.018; Figure 7B). To account for body size, ONSD was scaled to body surface area (BSA) using the DuBois and DuBois equation (DuBois & DuBois, 1916) where as expected, the BSA was larger in males versus females (1.993±0.110m^2 vs. 1.616±0.110m^2, respectively; $p<0.001$). When scaled to BSA, there was no longer a significant difference in mean ONSD values between sexes (p=0.365). Baseline MAP was significantly higher in males (79.917±6.564mmHg) compared to females

(70.559±8.375mmHg; p=0.026; Figure 7C). Further, PP was significantly higher in males compared to females (49.400±7.168 vs. 39.167±5.845mmHg; p=0.011; Figure 7D).

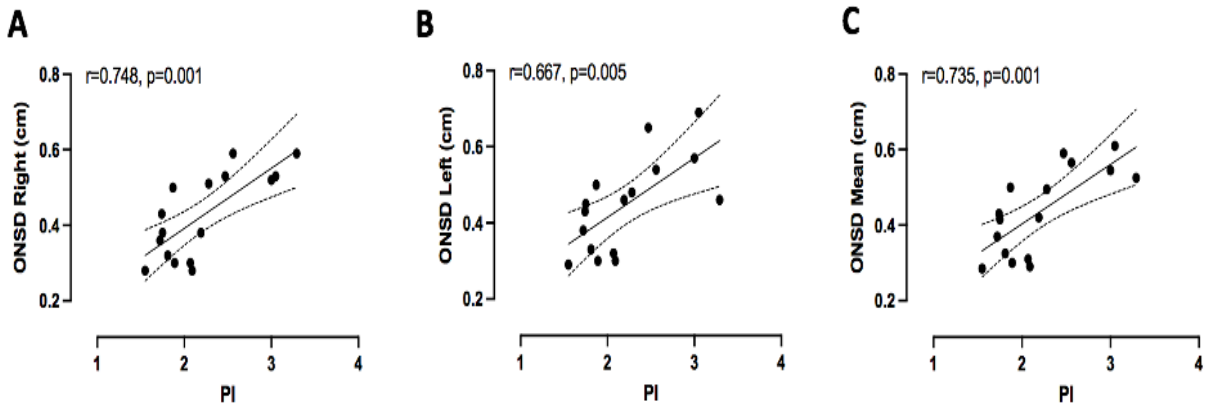

Figure 3. Optic nerve sheath diameter of the right eye (A) and left eye (B), and the mean of the right and left eye combined (C) versus pulsatility index. ONSD; optic nerve sheath diameter, PI; pulsatility index.

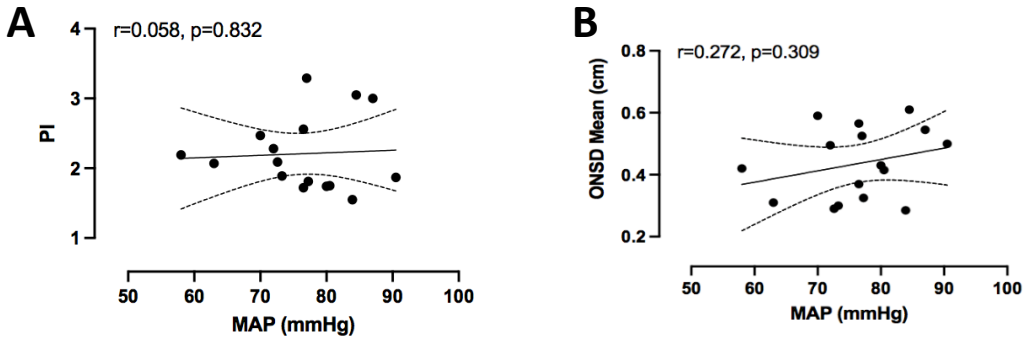

Figure 4. Pulsatility index of the common carotid artery versus mean arterial pressure (A). Mean of the right and left optic nerve sheath diameter combined versus mean arterial pressure (B). MAP; mean arterial pressure, ONSD; optic nerve sheath diameter, PI; pulsatility index.

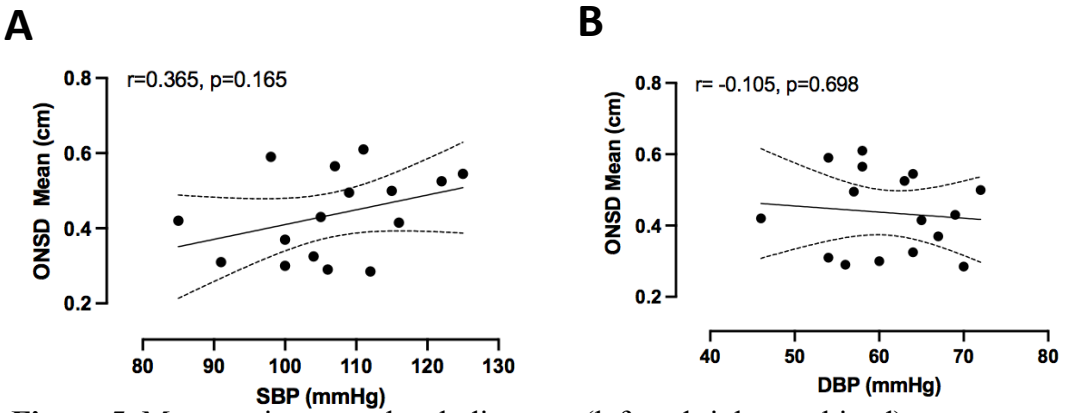

Figure 5. Mean optic nerve sheath diameter (left and right combined) versus systolic blood pressure (A). Mean optic nerve sheath diameter (left and right combined) versus diastolic blood pressure (B). DBP; diastolic blood pressure, ONSD; optic nerve sheath diameter, SBP; systolic blood pressure.

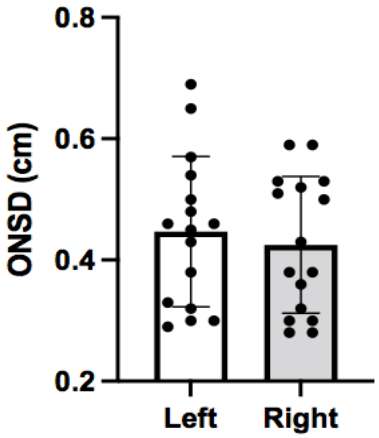

Figure 6. Comparison of optic nerve sheath diameter in the left and right eye. ONSD; optic nerve sheath diameter.

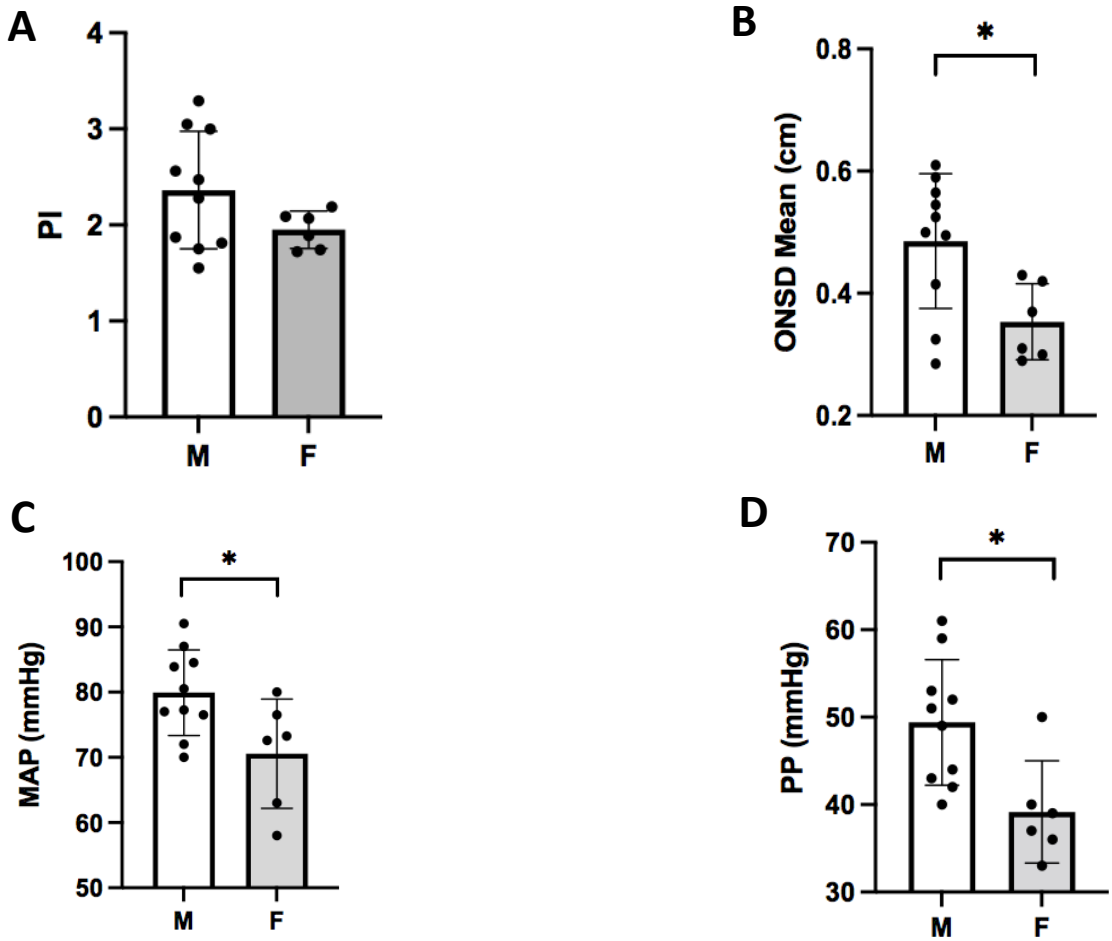

Figure 7. Sex differences between pulsatility of the common carotid artery (A), optic nerve sheath diameter (B), mean arterial pressure (C), and pulse pressure (D). M; males, F; females. MAP; mean arterial pressure, PI; pulsatility index, PP; pulse pressure, ONSD; optic nerve sheath diameter. *, $p<0.05$.

6. DISCUSSION

There are several important findings from this study in a population of young healthy adults. First, in alignment with hypothesis one, the PI of the common carotid artery and ONSD are strongly correlated. Second, in contrast to hypothesis two, BP (MAP, SBP and DBP individually), was not associated with the PI or the ONSD. Lastly, and in partial alignment with hypothesis three, sex had an effect on ONSD and MAP whereby males demonstrated a larger ONSD and greater blood pressure (SBP and MAP) compared to females, but had no influence on PI parameters. Notably however, scaling the ONSD to BSA removed any sex differences.

Relationship between PI and ONSD

The relationships between ONSD and ICP (Bäuerle & Nedelmann, 2011; Maissan et al., 2015; Zhang et al., 2017; Cardim et al., 2019), and PI and ICP (Bellner et al., 2004; Holmgren et al., 2020; Kaloria et al., 2020) are well established in clinical populations. The findings of this study confirm a relationship between ONSD and PI in young healthy adults; these findings are novel in the sense that previous research has focused solely on individuals with elevated ICP, whereby invasive monitoring of ICP was already initiated (Robba et al., 2020; Chang et al., 2021). The results also demonstrate the direction of the relationship between ONSD and PI, whereby a larger ONSD coincides with a greater PI (Figure 2). Given the high accuracy of ONSD and PI to predict elevated ICP individually, a composite score of the two measures may provide the best predictive power. Indeed, a study conducted by Robba and colleagues (2020) assessed sensitivity and specificity of these methods alone and in combination and found ONSD area under the curve (AUC) to be 0.78, PI AUC 0.85, and combined ONSD and PI to be AUC 0.89. Moreover, and

congruent with this study, Robba and colleagues (2020) found a significant correlation between ONSD and PI, although the relationship was weak (R=0.30, p=0.002). Nonetheless, results of this study further validate the use of ONSD and PI for non-invasive assessment of ICP. Importantly, suggest that these measures are sensitive enough to detect even small variations in ICP across young healthy adults. Discussed below, the future utility of ONSD and PI in physiologic research is expansive, for example, for providing more accurate metrics of absolute cerebral perfusion pressure, which is the MAP-ICP.

Relationship between BP, PI and ONSD

The results of this study demonstrate no significant relationship between BP and PI or ONSD in a population of young, normotensive individuals. There is limited research on the relationship between ONSD and BP, except for one notable study that found no association between ONSD and SBP or DBP in healthy individuals (Roque et al., 2012). In contrast however, participants who were hypertensive (criteria = SBP >140mmHg or DBP > 90mmHg), were found to have abnormal ONSD (Roque et al., 2012). Interestingly, the authors found the best cut off point for increased ONSD was 166/82mmHg, thereby concluding individuals with higher BP should be treated more aggressively due to the risk of elevated ICP, which in turn increases the risk for cerebral microvascular damage and ultimately a cerebrovascular event. Furthermore, and similar to ONSD, the relationship between PI and MAP has been elucidated whereby high PI is present in individuals with higher BP (Oughton et al., 2015; Chuang et al., 2016). Given that participants in the present study were all normotensive and below the criteria of SBP <130mmHg and DBP <80mmHg, it is not surprising we found no relationship between ONSD, PI and MAP.

Sex Differences

The finding of a statistically significant difference in ONSD between males and females is consistent with some (Goers et al., 2015; Cardim et al., 2020; Ertl et al., 2020), but not all studies (Bäuerle & Nedelmann, 2011; Bäuerle et al., 2012). In the studies that found sex to influence ONSD, males demonstrated a larger value compared to females. A possible explanation could be related to differences in anatomy and body size, with males typically exhibiting larger body proportions. The findings by Cardim and colleagues (2020) however, demonstrate height and weight to have no influence on ONSD. In the current study, when controlling for BSA, there was no sex difference in ONSD ($p=0.365$). These results thereby indicate that body size (specifically BSA), may, at least in part, explain the sex differences in ONSD. To the best of our knowledge, this is the first study to consider BSA and not just the influence of height or weight alone on ONSD. Conversely, Ertl et al. (2020) proposed a sex-specific response to changes in ICP, which may be related to differences in elasticity of connective tissue (within the dura mater) and fiber size within the optic nerve, and therefore could partially explain the apparent sex differences found herein. Nevertheless, the discrepancy between studies warrants further research between sexes in order to determine the need for sex specific cut-off values for ONSD and the ICP that coincides.

Given the statistically significant difference found in ONSD between males and females, it is surprising that there was no difference in PI. However, PI reflects the functionality of the cerebrovasculature and more is related to age than sex (Desmidt et al., 2018). Importantly, higher PI coincides with greater CBF, which in young adults may in fact be neuroprotective. Therefore, PI will not be exaggerated in young (healthy) adults due to high functioning and vascular compliance. In contrast, older adults who demonstrate high pulsatility likely have cerebral

impairment and arterial stiffening, which may hasten the development of cerebral complications like cognitive impairment and stroke (Holmgren et al., 2020).

Despite the lack of relationship between sex and PI, there was a significant difference in PP, whereby males demonstrated a higher PP. Pulse pressure, or the difference between SBP and DBP, is typically lower in females (Skurnick et al., 2009), as was demonstrated in this study. Like PI, PP reflects vascular function and arterial stiffening, therefore, PP typically increases with age (Skurnick et a., 2009). Thereby, in a population of young healthy adults where arterial stiffening may not be a significant factor, PP is more likely related to other cardiovascular factors. Specifically, males tend to have larger hearts and larger stroke volume compared to females, therefore when assessing PP, it will appear higher in males and is likely inflated due to larger stroke volumes and not an indication of vascular dysfunction.

Considerations & Future Research

Nearly all of the research surrounding cerebral autoregulation is hinged on the assumption that MAP is equal to cerebral perfusion; however, it is accepted that CPP = MAP – ICP (Willie et al., 2014; Zhang et al. 2017). As previously mentioned, given the lack of accurate non-invasive methods to assess ICP, it is typically ignored, or assumed to be "fixed" while assessing CPP. Given there are numerous conditions that alter ICP, including insignificant changes in posture and acute changes in CBF, considering both MAP and ICP (using ONSD and PI as a metric) while assessing CPP may deepen the knowledge surrounding the mechanisms of cerebral autoregulation.

The results from this study further confirm the accuracy of ONSD assessment in young healthy adults. Given that ONSD is a quick, effective and easy to learn modality for monitoring and estimating ICP, it has high utility for use in the field. There is an alarming number of sport-

related, diagnosed concussions (Rao et al., 2021). However, the effect of sub-concussive impact exposure is unknown and because symptoms are not immediate, athletes often continue to participate and risk subsequent injury (Rao et al., 2021). Because ONSD can detect subtle but clinically meaningful gradations in ICP, applying this assessment within the return-to-play framework may better evaluate an athlete's condition and alleviate the risk of further injury than the current methods employed on the sidelines. Indeed, current methods rely heavily on self-reporting symptoms (Anderson et al., 2021). Moreover, there is significant evidence to suggest that athletes often go without disclosing symptoms of concussion, or play down the severity of symptoms, in order to avoid losing playing time and disappointing both their team and coaches (Anderson et al., 2021). Given the risk of subsequent concussions and irreversible neurological damage, developing a concrete physiological assessment that can be performed immediately on the field, and does not rely on self-reporting or ability to manipulate responses, is essential.

Importantly, there are known differences in ONSD dilation between individuals with history of mild TBI (i.e., concussion) compared to those with no history of TBI (Lyon et al., 2018). Specifically, after transiently increasing ICP via a Valsalva maneuver, participants who had previously suffered a concussion had significant dilation of the ONSD immediately post-Valsalva and remained significantly dilated five minutes post-Valsalva. Dilation of the ONSD was not observed immediately post- nor five minutes post-Valsalva in healthy participants. These findings demonstrate a clear association between history of mild TBI and ONSD dilation after Valsalva. A possible explanation may relate to structural damage surrounding the optic nerve following head injury, therefore allowing more distention of the ONSD in response to small changes in ICP (Lyon et al., 2018). Further, it is possible that cerebral autoregulation is impaired following head injury; considering Valsalva decreases venous outflow, arterial resistance (pressure) should increase in

response to maintain cerebral perfusion. Given the response of the ONSD in individuals with history of mild TBI, it is evident that ICP is less stable, or less regulated, meaning mechanisms maintaining cerebral perfusion are impaired (Lyon et al., 2018). Nonetheless, this association may thereby warrant the use of ONSD and Valsalva to detect current mild TBI, and with the use of ultrasound, can easily be applied in a field setting.

Furthermore, results of this study are in agreement with the literature in terms of ONSD measurements falling within the normal range of ~3.7-4.7mm. Interestingly, we found no significant difference between left and right eye ONSD. In contrast to our study, others have found asymmetry between ONSD in the left and right eye, which may lead to inaccurate or undiagnosed elevated ICP if assessed in only one (Naldi et al., 2019). Importantly, this asymmetry was prevalent in both healthy individuals and in patients with intracranial hypertension (Naldi et al., 2019), thereby confirming anatomical differences irrespective of clinical condition. Although no significant difference was found in the present study, it is likely to be very small and only detectable with a large sample set. Indeed, a post-hoc analysis of our data (using G*Power®), suggests that a sample size of n=309 is necessary to reveal significant differences in right and left ONSD, at a power of 0.9. However, given the possibility of asymmetry even in healthy populations, it is important that future investigations use binocular assessment to more accurately estimate ICP.

Despite the findings of this study, a few considerations should be made. First, this study was limited to a relatively small population (n=16) and was not balanced for sex (ten males versus six females). However, the study was significantly powered to observe sex differences in most variables. Additionally, it is important to note that menstrual cycle was not accounted for. Given that assessment only took place during one visit and not during different stages of the cycle, as

well as having demonstrated values of ONSD, PI and MAP that are consistent with the literature, it is believed accounting for menstrual cycle would not alter the results, at least within the present study design. If assessment were to occur on more than one occasion (i.e., multiple visits), it may be important to consider menstrual cycle and differing hormone levels within the female participants.

Lastly, the data acquired for this study was collected by multiple sonographers. Additionally, the coefficient of variation (or scan-rescan repeatability) of the sonographers is unfortunately unknown. Although ONSD measurements herein are consistent with the normal range, discrepancies may be explained by examiner experience and analysis. Thereby, including the scan-rescan repeatability may help strengthen the validity of the results. Nevertheless, the analysis of ONSD, PI and MAP were done independently thus blinding the observer to a subconscious bias, for example by calculating a higher ONSD in males or in those with a higher PI. Moreover, ONSD was averaged over three consecutive measures, thereby limiting test-retest error.

7. CONCLUSION

This study confirms a relationship between ONSD and PI in young healthy adults. Importantly, it is shown that ONSD and PI assessment via ultrasound is an accurate and reliable technique, even in sub-clinical populations. Thereby, the combined assessment of ONSD and PI can be employed as a method to track alterations in ICP and could be used as a surrogate to non-invasively measure ICP throughout treatment programs and in non-emergent conditions. Additionally, seen as there is an apparent sex difference in ONSD, it may be important to consider sex-specific thresholds for determination of an elevated ICP. Moreover, the measures of ONSD and PI should be incorporated in all research involving cerebral blood flow dynamics to alterations in CPP (e.g., cerebral autoregulation). Lastly, given its relatively easy administration and mobility, ONSD and PI assessment may be useful in field settings to determine an individual's status, or in clinical settings for triage where prompt recognition of elevated ICP and subsequent treatment are essential.

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