UNIVERSITY OF CALIFORNIA SAN DIEGO

Effect of Soccer Heading on Intracranial Pressure and Cerebral Perfusion Pressure in Athletes

A Thesis submitted in partial satisfaction of the requirements
for the degree Master of Science

in

Biology

by

Justin Lee

Committee in charge:

Professor Lonnie Petersen, Chair
Professor Laurie Smith, Co-Chair
Professor Randolph Hampton

2020

The Thesis of Justin Lee is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

_____

_____
Co-Chair

_____
Chair

University of California San Diego

2020

EPIGRAPH

We're still pioneers, we've barely begun.
Our greatest accomplishments cannot be behind us,
cause our destiny lies above us.

Cooper

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Intracranial Pressure – (ICP)

Mean Arterial Pressure – (MAP)

Heart Rate – (HR)

Cochlear and Cerebral Fluid Pressure – (CCFP)

Cerebral Perfusion Pressure – (CPP)

Tympanic Membrane Displacement – (TMD)

Head Up Tilt – (HUT)

Head Down tilt (HDT)

Chronic Traumatic Encephalopathy – (CTE)

Traumatic Brain Injury – (TBI)

LIST OF FIGURES

ACKNOWLEDGEMENTS

I would like to acknowledge and thank Dr. Lonnie Petersen for her never-ending support, mentorship, and guidance. Without her, I would not have been able to accomplish many of the things I have achieved during my academic career. I am eternally grateful for the opportunities she has given me through my time working in her lab. I would also like to thank her for serving as my thesis advisor, formulating the hypothesis and serving as the Principal Investigator for this project.

I would like to acknowledge Dr. Casper Petersen for his support and guidance throughout my master's journey and his assistance with the statistical analysis of the data. I would also like to thank Jeremy Sieker, who's guidance in both my research experience and life outside of lab has been invaluable and immeasurable, for his assistance in the drafting and creation of this thesis. In addition, I would like to thank Evan Grace for his part in the data collection of this study and the coauthoring this material along with the assistance and opportunities he has given me in life and in academics.

I would also like to thank and acknowledge Dr. Laurie Smith for her mentorship guidance with my thesis. I would like to thank Dr. Randy Hampton for his help and assistance with my thesis also.

I would like to acknowledge Alan Hargens for allowing us to use his equipment.

Lastly, I would like to thank my sister for picking up my late-night phone calls and Jasmine Rye for graciously giving up her study space during the preparation for this thesis.

This thesis in part is currently being prepared for submission for publication of the material. Lee, Justin; Grace, Evan; Sieker, Jeremy; Petersen, Johan; Petersen, Lonnie. The thesis

author and Evan Grace were responsible for organizing the study, collecting and analyzing data as well as drafting manuscript and coauthors of this material.

ABSTRACT OF THE THESIS

Effect of Soccer Heading on Intracranial Pressure and Cerebral Perfusion Pressure in Athletes

by

Justin Lee

Master of Science in Biology

University of California San Diego, 2020
Professor Lonnie Petersen, Chair
Professor Laurie Smith, Co-Chair

Regular participation in head contact sports is linked to risks of developing neurodegenerative disease. Studies have demonstrated the structural changes that may occur after soccer heading but the effects of soccer heading on intracranial pressure (ICP) in still unknown. In the following study, we tested the hypothesis that repeated soccer heading will cause a transient increase in ICP and a change in cerebral perfusion pressure (CPP).

ICP changes were measured in eight male subjects from the UC San Diego Men's Soccer team by recording acoustical evoked tympanic membrane displacement through a Cerebral Cochlear Fluid Pressure (CCFP) Analyzer (Marchbanks, UK).

Mean arterial pressure (MAP) and heart rate (HR) was recorded using the volume clamp method (Nexfin, Netherlands). ICP and cardiovascular variables were measured before the

soccer heading trial, immediately after soccer heading trial, and 24 hours after the soccer heading trial. During each measurement, ICP and cardiovascular variables were recorded in three different postures, 15° head up tilt (HUT), 0° supine, -15° head down tilt (HDT), in a randomized order.

During the soccer heading trial, a soccer ball was kicked to the subject from 35 yards away and the subject then headed the ball into a soccer goal. This was repeated for a total of 6 headers.

After soccer heading, ICP significantly increased at 15° HUT and 0° supine immediately post heading and returned back to baseline levels after 24 hours. ICP at -15° HDT, and MAP and HR at all positions did not significantly change at any point after soccer heading. This increase in ICP and unchanged MAP points to a decrease in CPP, implying compromised perfusion of cerebral tissue and potentially suggesting a risk in participating in head contact sports like soccer.

Introduction

From initial anecdotal histories and suspected association, increasing amounts of data is now supporting a link between various contact sports and later development of neurodegenerative disease [1]. First reports of neurodegenerative disease in the 1920's were termed "punch drunk" syndrome where career boxers showed symptoms of tremors, speech issues, confusion, slowed movements, and vertigo [2]. This neurodegenerative disease was termed *dementia pugilistica* in 1937 and more recently as chronic traumatic encephalopathy (CTE) [3] [4].

Recent studies implicated mild, but repetitive head trauma from head contact sports as a risk factor for CTE and other various neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS) [5] [6] [7] [8].

Repetitive blows to the head have also been implicated as a risk factor for neuropsychiatric issues. Athletes, who have participated in head contact sports such as tackle football, have been shown to be at a greater risk of depression and anxiety later in life [9] [10]. These athletes also show impaired cognitive function, memory loss, diminished executive function, and psychomotor impairment [11] [12]. Poorer mental health, lower general quality of life, emotional issues, and less satisfaction from relationships and social activities has also been reported at higher levels in former high-level athletes [13].

Recent studies documenting the prevalence of CTE in all levels of football including professional, college, and even high school, along with increased public awareness of the long lasting effects of head contact sports in part to recent high profile suicides of several NFL

athletes have called into question the safety of participating in head contact sports such as American football, boxing, and soccer [14].

In part due to the attention of CTE in American football, there has been less of a focus in the scientific community and mass media on the neurodegenerative risk of soccer despite the fact that soccer remains the world's most popular sport by a wide margin and is currently played worldwide by over 250,000,000 people [15]. Although considered a relatively "safe" sport, a recent study reported that professional soccer players were at a higher risk of dying from neurodegenerative disease and were prescribed dementia-related medications more frequently throughout their lives [16]. However, only a few cases of CTE in soccer players have been reported in the scientific literature. Thus, the frequency of CTE in soccer players and the role of heading the soccer ball may have in the development of neurodegenerative diseases in soccer is still unknown [17].

The role soccer heading may have in any potential health risks is of interest as a soccer player will, on average, perform around 6 of these headers in a single game with over 30% of recorded concussions being the direct result of soccer heading [18] [19] [20] [21].

Concussions are classified as the mildest type of traumatic brain injury (TBI) and result from acceleration of the brain, usually caused by head contact, acceleration of other parts of the body that transfer forces to the brain, or blast injuries from explosions. Symptoms of a concussion generally include headaches, dizziness, confusion, and in some cases memory loss and loss of consciousness [22]

Concussion pathophysiology can be described as a multitude of different neurophysiological processes. The damage to the brain tissue from the mechanical forces results in depolarization of neurons in conjunction with the release of excitatory neurotransmitters.

Disruptions in the neuronal membranes resulting from mechanical shearing forces result in the rapid efflux of intracellular potassium and influx of extracellular sodium and calcium, causing widespread depolarization [23]. This depolarization promotes the release of excitatory neurotransmitters, in particular glutamate, into the extracellular space [24]. The released glutamate then binds to N-methyl-d-aspartate receptors on membrane ion channels, causing further efflux of potassium into the extracellular space and influx of calcium into the cell prolonging membrane depolarization [25].

This increased intracellular calcium reduces energy production by altering typical mitochondrial function and also activates calcium-dependent proteases, resulting in apoptosis, breakdown of the blood brain barrier, neuronal damage, and free radical generation [26].

Membrane ionic pumps then become activated in an effort to restore ionic homeostasis, consuming ATP and increasing neuronal metabolic demands. This hypermetabolic phase is followed by a hypometabolic state, resulting in decreased ATP production, increased production of lactate, neuronal dysfunction, and a reduced cerebral blood flow [27].

The breakdown of the blood-brain barrier leads to an increase in ion and plasma protein concentrations in the extracellular matrix, resulting in increased accumulation of extracellular water. Also, as intracellular sodium concentrations in neurons increase as a result of glutamate release, normal membrane ion pumps become unable to maintain homeostasis, resulting in the increase in accumulation of intracellular water [28].

The increased water content of the neurons raises tissue volume and as the brain tissue swells against the unexpandable compartment of the skull, intracranial pressure (ICP) begins to rise. Normal physiological ICP is below 15 mmHg, and ICP values above is referred to as intracranial hypertension. Elevated ICP can alter the cerebral perfusion pressure (CPP) and

impede typical cerebral blood flow, preventing the proper perfusion of cerebral tissue [29]. CPP is the pressure gradient that drives blood flow into the cerebral tissue and is defined by the following equation: MAP - ICP = CPP [30], where MAP is mean arterial pressure at brain level.

Consequently, increased ICP can lead to cerebral ischemia as the cerebral blood supply is unable to provide enough oxygen and nutrients to keep up with the brain's metabolic needs [31]. Thus, intracranial hypertension is the most common cause of death in patients with traumatic brain injuries and managing this increase in ICP to maintain adequate cerebral perfusion plays a key role in treating and preventing secondary brain injuries after a TBI [32] [33].

Several studies have examined the potential effect soccer has on the brain structure through neuroimaging. Soccer heading has been associated with abnormal white matter microstructure in the brain and disrupted myelination [34] [35]. Former professional soccer players have also been documented with central cerebral atrophy, widened lateral ventricles, and cortical thinning in the inferolateral-parietal, temporal, and occipital cortex [36] [37]. Soccer heading also has been demonstrated to raise serum levels of several brain damage markers such as S-100B, neuron-specific enolase (NSE), nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), choline, and myo-inositol [38] [39] [37].

While previous studies have examined the structural and biochemical effects of soccer heading, limited data exists examining the effects soccer heading may have on intracranial hypertension and cerebral perfusion. Thus, in this study, we tested the hypothesis that repeated soccer headings will cause measurable intracranial hypertension and altered cerebral perfusion pressure.

Methods

Subjects

The protocol was approved by the Institutional Review Board at UC San Diego. All subjects were notified of the purpose and risks of the study and informed consent was obtained through written consent forms. A total of 8 subjects (22.1 ± 1.1 years, 180.91 ± 7.74 kg, 76.81 ± 12.22 cm) were recruited from the UC San Diego NCAA men's soccer team and participated in this study. Requirements to participate in the study included no history of concussions or other serious head trauma within the past 6 months prior to the study and at least 10 years of organized soccer experience. Participants were instructed to avoid any strenuous activity, alcohol consumption, caffeine, or any recreational drugs from 24 hours before the study until the end of the study.

Equipment

Intracranial pressure was estimated non-invasively through the use of a Cerebral Cochlear Fluid Pressure (CCFP) analyzer (Marchbanks, UK). The CCFP measures acoustical evoked tympanic membrane displacement (V_m) to estimate ICP, where a more negative volume displacement is correlated with higher ICP. Acoustic reflex thresholds of individual subjects were first measured with a handheld tympanometer. The CCFP probe was inserted into the participant's left external auditory meatus with a proper seal. A 1 KHz stimulus set to a sound level 5dB above the individual's acoustic reflex threshold was used to evoke tympanic membrane displacement. The CCFP recorded 2 sets of 10 tympanic membrane displacement measurements. These measurements are then automatically averaged to give V_m.

The volume clamp method on the third finger was used to measure mean arterial pressure (MAP) and heart (HR) continuously in subjects throughout the measurement period (Nexfin,

Netherlands). The height adjustment sensor was attached to the patient's chest at heart level for proper calibration. An inversion tilt table was used to tilt subjects at different angles (Exerpeutic Therapeutic Fitness, City of Industry, USA) and an official NCAA approved soccer ball at manufacturer recommended PSI was used in the heading trials.

Study Design

Participants were first explained the study procedure and filled written consent forms prior to the start of the study. Baseline ICP and cardiovascular variables were first recorded. For each measurement, study participants were properly secured onto the inversion table and ICP and cardiovascular variables were recorded in three different postures: 15° head up tilt (HUT), 0° supine, -15° head down tilt (HDT), in a randomized order. Subjects remained in each posture for 5 minutes to allow blood and body fluids to equilibrate prior to the measurements. After ICP, HR, and MAP were measured in one position, the subject was tilted to a new position and procedure was performed again. The inclusion of different postures during the measurements served as a control to determine whether the CCFP was properly measuring ICP, as previous studies have demonstrated measurable increases in ICP due to postural changes in the head down direction [40]

After baseline measurements were taken, the subjects then proceeded with the heading trial. During the heading trial, subjects were instructed to stand 5 yards in front of a soccer goal. A soccer ball was then kicked from 35 yards away at the subject and subjects were instructed to use their head to knock the soccer ball into the goal. This heading trial was repeated 6 times for each subject. Immediately after the heading trial, ICP and cardiovascular variables were recorded at the three aforementioned positions, and these variables were remeasured 24 hours later. A

paired t-test was then performed between these measurements to determine statistically significant changes in ICP, MAP, and HR before and after soccer heading.

Results

Intracranial Pressure

At 15° HUT, mean V_m was 37.81±133.21 nL at baseline, -20.82±158.27 nL immediately post soccer heading (P=0.0482, Figure 1), and -27.2±140.6177849 nL at 24 hours after soccer heading (P=0.1738, Figure 2). These trends are analogous to increased ICP immediately post soccer heading but a return to baseline ICP after 24 hours.

At 0° supine, mean V_m was -46.19±178.50 nL at baseline, -84.27±183.55 nL immediately post soccer heading (P=0.0321, Figure 1), and -62.9±135.4429938 nL at 24 hours post soccer heading (P=0.5048, Figure 2). Similar to 15° HUT, ICP increased immediately after soccer heading but there was no significant difference after 24 hours.

At -15° HDT, mean V_m was -148.48±196.07 nL at baseline, -187.02±186.19 nL immediately post soccer heading (P=0.1176, Figure 1), and -151.1±174.8859716 nL at 24 hours post soccer heading (P=0.9329, Figure 2), indicating no significant change at either time point in the head down position.

Cardiovascular Variables

At 15° HUT, MAP was 85.4±7.30 mmHg at baseline, 84.5±5.25 mmHg immediately post soccer heading (P=0.5876, Figure 3), and 77.3±15.6 mmHg at 24 hours after soccer heading (P=0.1354, Figure 4). At 0° supine, MAP was 86.0±8.09 mmHg at baseline, 85.1±7.96 mmHg immediately post soccer heading (P=0.7789, Figure 3), and 78.3±16.7 mmHg at 24 hours post soccer heading (P=0.2220, Figure 4). At -15° HDT, MAP was 87.4±4.07 mmHg at baseline, 83.2±5.63 mmHg immediately post soccer heading (P=0.0687, Figure 3), and 77.8±17.6 mmHg at 24 hours post soccer heading (P=0.1542, Figure 4). These measurements indicate no significant change in MAP at any positions.

At 15° HUT, mean HR was 63.1±12.18 bpm at baseline, 66.3±12.7 bpm immediately post soccer heading (P=0.2356, Figure 5), and 64.9±11.9 bpm at 24 hours after soccer heading (P=0.3236, Figure 6). At 0° supine, mean HR was 61.3±11.2 bpm at baseline, 63.3±10.5 bpm immediately post soccer heading (P=0.3688, Figure 5), and 63.3±13.5 bpm at 24 hours post soccer heading (P=0.2439, Figure 6). At -15° HDT, mean HR was 60.9±12.9 bpm at baseline, 60.04±9.70 bpm immediately post soccer heading (P=0.8463, Figure 5), and 62.5±12.9 bpm at 24 hours post soccer heading (P=0.4281, Figure 6). Similar to MAP, there was no significant change in HR at any positions after soccer heading.

Discussion

Intracranial Pressure and Cardiovascular Variables

After 6 repetitions of standardized and controlled soccer ball heading, estimated ICP significantly increased at 15° HUT and 0° supine immediately post heading and then after 24 hours returned to baseline levels. However, ICP at -15° HDT, and MAP and HR at all positions did not significantly change after soccer heading. This increase in ICP and unchanged MAP results in decreased CPP, indicating altered cerebral perfusion.

The higher mean displacement values observed in the HDT positions relative to HUT and supine positions are expected results of the headward fluid shift observed in HDT [40]. Although a significant increase in ICP was observed at 15° HUT and 0° supine, potential ICP changes due to soccer heading at -15° HDT may have been masked by the already expected increase in ICP associated due to this fluid shift associated with HDT.

These observations potentially reflect what may be increased ICP in response to soccer heading. Soccer heading may cause mechanical damage to the neural tissue and subsequently induce widespread depolarization, glutamate release, and disruptions in the blood brain barrier, resulting in the intracellular and extracellular accumulation of fluid in the neurons. This swelling of the brain then may induce the observed increase in ICP after soccer heading. It is then speculated that ICP returns to baseline levels as the swelling of the cerebral tissue goes down.

While these potential changes in ICP and brain swelling seem to disappear within 24 hours, soccer players at all levels may experience these repeated cycles of increased ICP nonstop for extended periods of time. These cycles of increased ICP could lead to a relatively mild but continuous ischemia in the brain tissue from inadequate cerebral flow, potentially leading to

neuronal dysfunction and brain damage over time. This study implies a potential risk in participating in head contact sports, such as soccer. This could also play a role in the observed risk of neurodegenerative disease and increased rate of neuropsychiatric disorders reported in soccer players.

These results are similar to previous studies that have demonstrated increases in intracranial pressure in response to mild traumatic brain injuries from blows to the head [41] [42] [43] [44]. Research into mild TBIs from blast injuries have also demonstrated a measurable increase in intracranial pressure similar to the increase observed from soccer heading in this study [45]. Previous research in patients with mild TBIs from falls and motor vehicle accidents also showed an increase in intracranial pressure in conjunction with cerebral hemodynamic changes, similar to this studies' implications of soccer heading's effect on cerebral perfusion [46]. Several studies have shown long-term atrophy of brain tissue and subsequent decrease in brain volume in response to mild TBIs [47] [48] Although this study only examined acute changes of intracranial pressure and brain volume up to 24 hours after heading, it is possible that the altered cerebral perfusion from soccer heading may lead to cycles of hypoxia in the brain and contribute to this atrophy and long term decrease in brain volume.

The results of this study are also similar to studies of mild TBIs in other sports. A study in hockey players showed no increases in brain volume from cerebral edema 72 hours after a concussion, which could be comparable to the results of this study where ICP returned to baseline after 24 hours [48]. The effect of soccer heading on cerebral blood flow and perfusion suggested by this study is also comparable to previous research on concussions in football. Previous data in football players have demonstrated decreased cerebral blood flow in response to

football related concussions, which potentially could be the result of increased intracranial pressure from head contact [49] [50].

Limitations & Future Considerations

The use of a CCFP to non-invasively estimate ICP results in some limitations. Although useful at indicating relative changes in ICP, this technique does not provide an absolute ICP measurement in mmHg that more invasive measurement techniques can. The variations in inner ear physiology within the population results in the CCFP only being a viable method for estimating ICP in about 70% of the population, limiting sample size [51]. The also explains the high variation in baseline V_m values observed between subjects and the large standard deviations of mean V_m after soccer heading. Future studies involving more accurate and potentially invasive methods of measuring ICP may provide a clearer picture of the effect's soccer heading may have on intracranial pressure.

It is important to note that the MAP measured in this study was at heart level and not corrected for MAP at the brain level. While a general change in CPP can be determined if MAP at heart level does not change after soccer heading, the extent of this change cannot be determined without making this correction for the distance between the heart and the brain [40]. Thus, in future studies, the distance between the 4^{th} intercostal space and the ear will be recorded to allow us to correct MAP at heart level to brain level for a clearer view of soccer heading's impact on CPP.

Although the observations of this study may suggest increased ICP and altered CPP, it is important to consider that ICP and CPP are just two elements of the much larger and more complex process of cerebral autoregulation [52]. Although this study provides some valuable

insight into this process, it does not fully explain the effects of head contact on the relatively unknown process of cerebral blood flow regulation.

Unfortunately, it is unknown whether the physical activity associated with soccer, such as running or jumping, by itself was potentially responsible for the observed change in tympanic membrane displacement. Thus, in the future, we plan to investigate the effects of these activities, in the absence of any head contact, on intracranial pressure.

This study simply measured intracranial pressure up to 24 hours after one bout of soccer heading. In the future, we aim to measure intracranial pressure after repeated bouts of soccer heading across a span of multiple days with follow-up measurements taking place across longer periods of time as this will more accurately reflect the actual exposure of the athletes.

Much is still unknown about the short term and long-term effects of soccer heading on the brain and further research must be done to fully understand the risks of participating in soccer. While this study used acoustical evoked tympanic membrane displacement to examine the effects soccer heading has on intracranial pressure, the use of other techniques may help further elucidate other effects soccer heading may have. For example, the use of imaging techniques such as MRI or CT scans may help show the long-term structural changes that occur after soccer heading. EEGs and PET could help examine the effects soccer headings have on brain activity and other techniques such as near-infrared spectroscopy (NIRS) could be used to determine the effects soccer heading may have on brain oxygenation.

Although we only examined intracranial pressure and cerebral perfusion in this study, the results of this study still call into question the safety of participating in soccer and other head contact sports. Further studies that potentially implicate head contact sports as a risk for brain damage will only continue to grow public concern over these sports. This may result in changes

to how these sports are played to reduce the amount of head contact incidents or potentially lead to a gradual shift away from participation in these sports entirely.

Figures

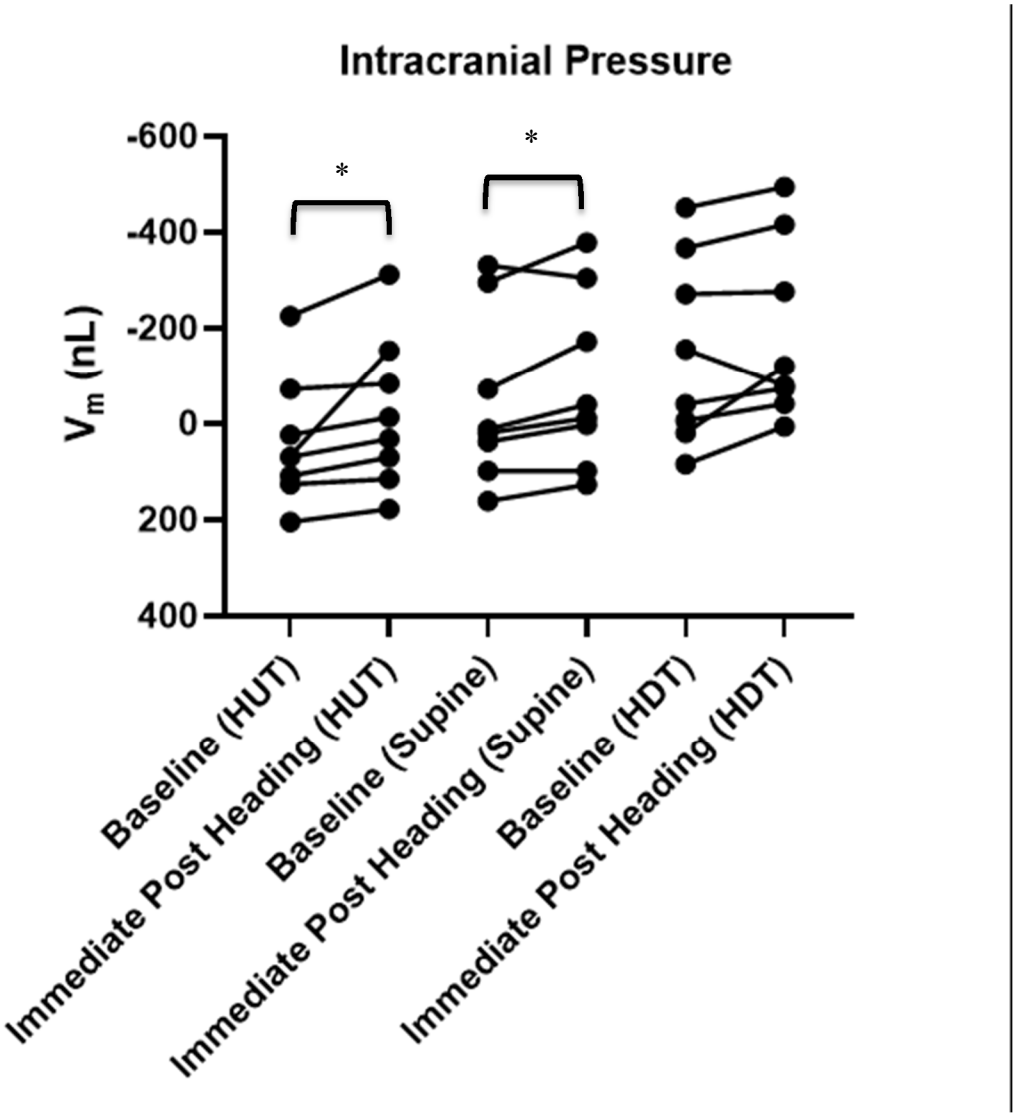

Figure 1. Intracranial Pressure at Baseline vs Immediate Post Heading in 15° head up tilt (HUT), supine and 15° head down tilt (HDT). Individual paired values. Tympanic membrane displacement (V_m) measured in nano liters (nL) is inversely correlated with intra cerebral pressure (ICP).

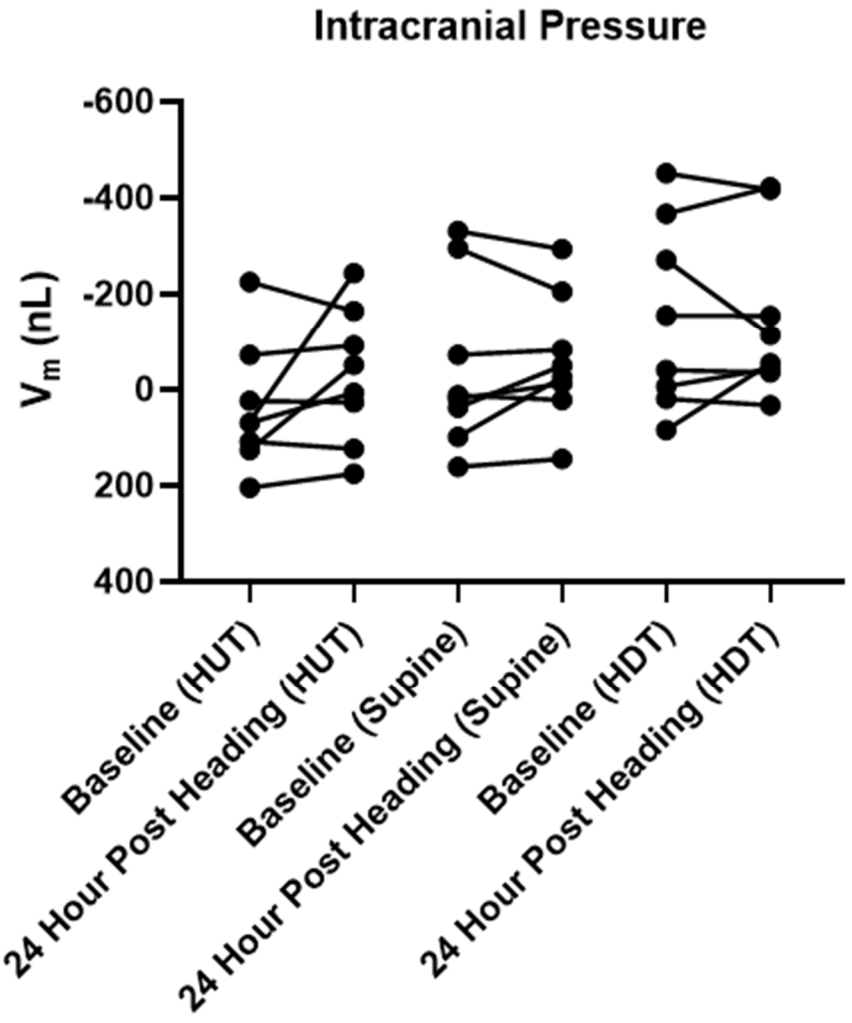

Figure 2. Intracranial Pressure at Baseline vs 24 Hours Post Heading in 15° head up tilt (HUT), supine and 15° head down tilt (HDT). Individual paired values. Tympanic membrane displacemtent (V_m) measured in nano liters (nL) is inversely correlated with intra cerebral pressure (ICP).

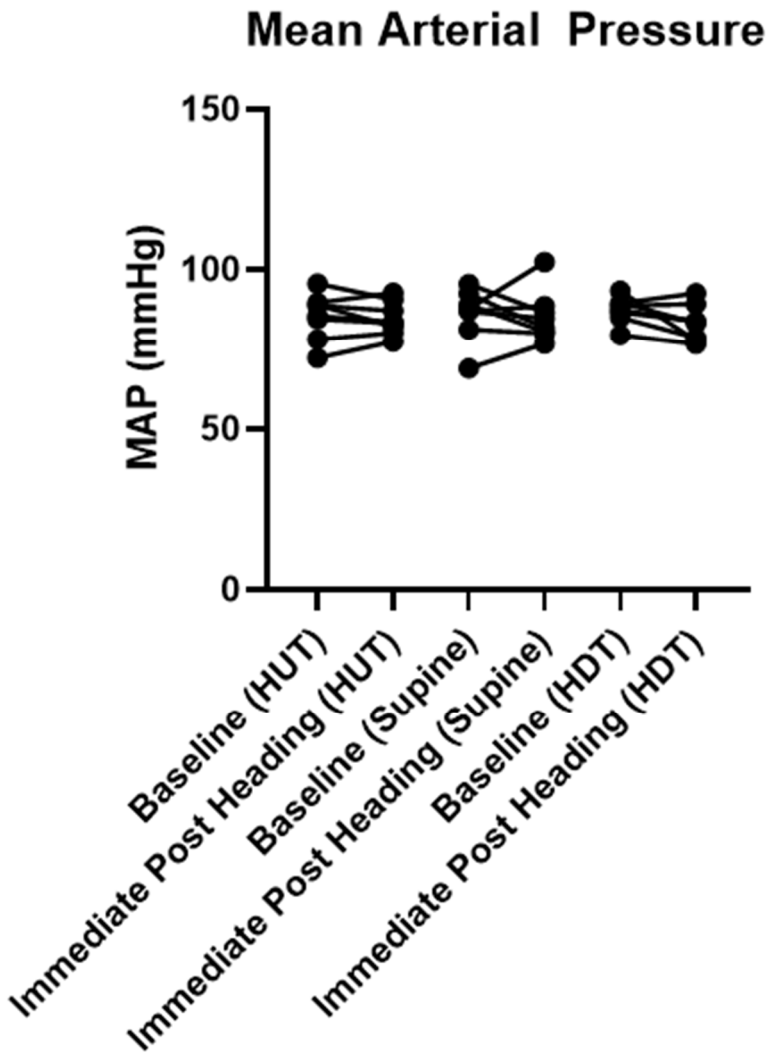

Figure 3. Mean Arterial Pressure (MAP) at Baseline vs Immediate Post Heading in 15° head up tilt (HUT), supine and 15° head down tilt (HDT). Individual paired values.

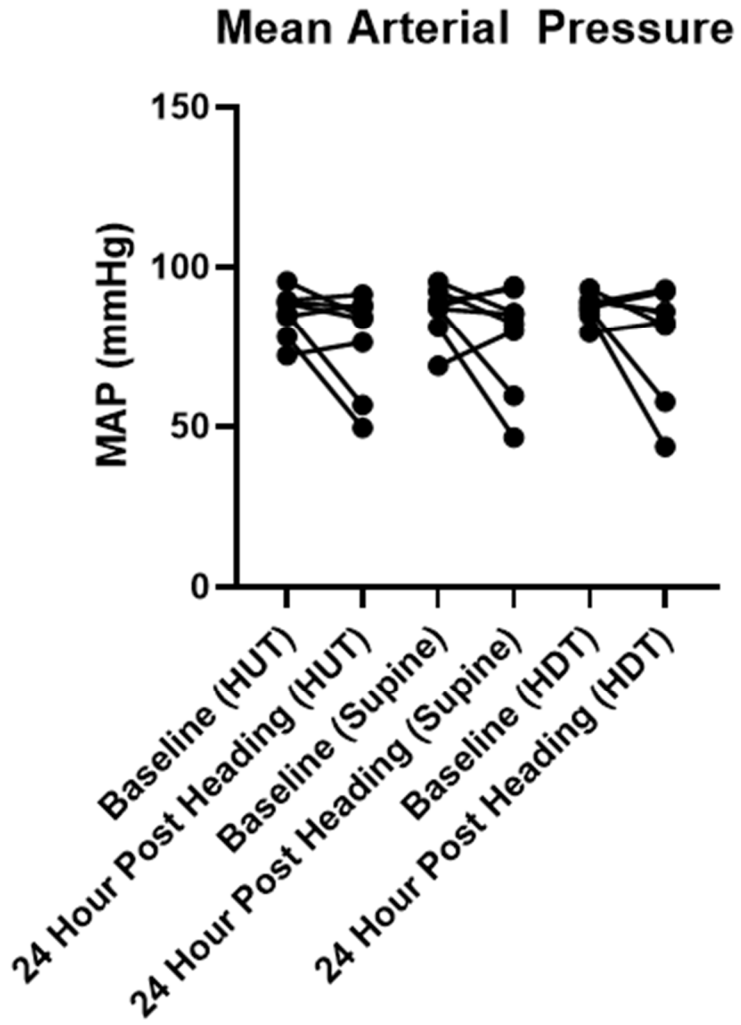

Figure 4. Mean Arterial Pressure (MAP) at Baseline vs 24 Hours Post Heading in 15° head up tilt (HUT), supine and 15° head down tilt (HDT).

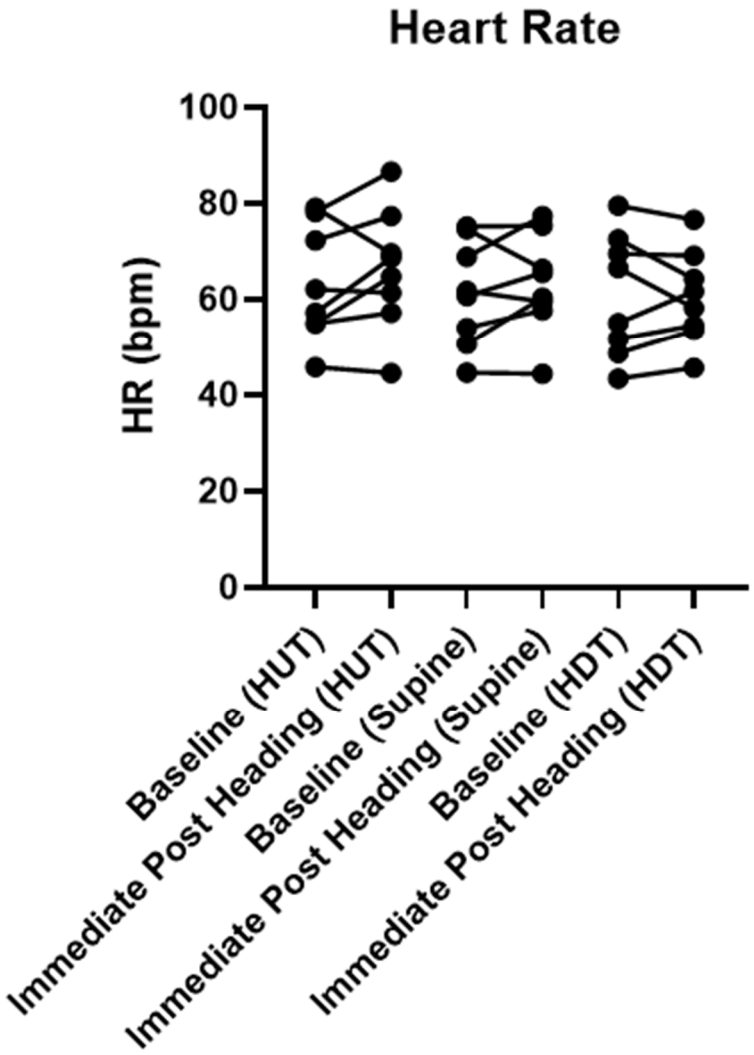

Figure 5. Heart Rate (HR) at Baseline vs Immediate Post Heading in 15° head up tilt (HUT), supine and 15° head down tilt (HDT).

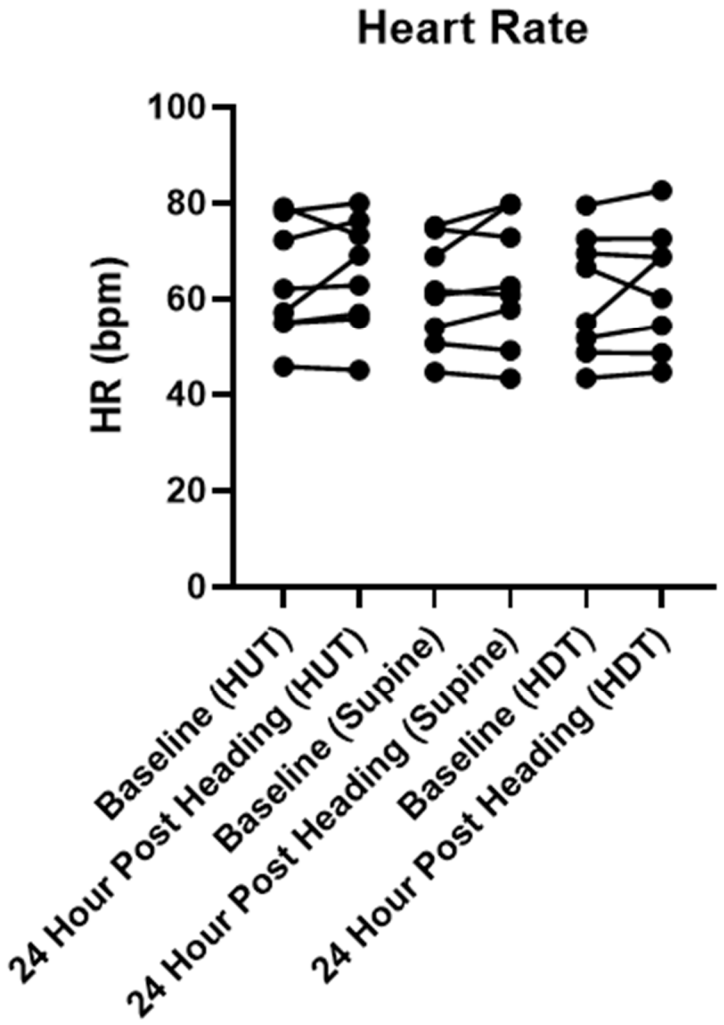

Figure 6. Heart Rate (HR) at Baseline vs 24 Hours Post Heading in 15° head up tilt (HUT), supine and 15° head down tilt (HDT).

This thesis in part is currently being prepared for submission for publication of the material. Lee, Justin; Grace, Evan; Sieker, Jeremy; Petersen, Johan; Petersen, Lonnie. The thesis author and Evan Grace were the primary investigators and coauthors of this material.

References

[1] Lehman EJ, Hein MJ, Baron SL, Gersic CM. Neurodegenerative causes of death among retired National Football League players. Neurology. 2012;79(19):1970-1974. doi:10.1212/WNL.0b013e31826daf50

[2] Martland HS. PUNCH DRUNK. *JAMA*. 1928;91(15):1103-1107. doi:10.1001/jama.1928.02700150029009

[3] Millspaugh JA. Dementia pugilistica. *US Naval Med Bull*. 1937;35(297):e303.

[4] Critchley M. Punch-drunk syndromes: the chronic traumatic encephalopathy of boxers. *Hommage a Clovis Vincent (ed) Maloine, Paris*. Published online 1949.

[5] Corsellis JA, Bruton CJ, Freeman-Browne D. The aftermath of boxing. *Psychol Med*. 1973;3(3):270-303. doi:10.1017/s0033291700049588

[6] Jafari S, Etminan M, Aminzadeh F, Samii A. Head injury and risk of Parkinson disease: A systematic review and meta-analysis. *Movement Disorders*. 2013;28(9):1222-1229. doi:10.1002/mds.25458

[7] Li Y, Li Y, Li X, Zhang S, Zhao J, Zhu X, Tian G. Head Injury as a Risk Factor for Dementia and Alzheimer's Disease: A Systematic Review and Meta-Analysis of 32 Observational Studies. *PLoS One*. 2017;12(1). doi:10.1371/journal.pone.0169650

[8] Blecher R, Elliott MA, Yilmaz E, Dettori J, Oskouian R. Contact Sports as a Risk Factor for Amyotrophic Lateral Sclerosis: A Systematic Review. *Global Spine J*. 2019;9(1):104-118. doi:10.1177/2192568218813916

[9] Kerr ZY, Marshall SW, Herndon P. Harding J, Guskiewicz KM. Nine-Year Risk of Depression Diagnosis Increases With Increasing Self-Reported Concussions in Retired Professional Football Players: *The American Journal of Sports Medicine*. Published online August 24, 2012. doi:10.1177/0363546512456193

[10] Guskiewicz KM, Marshall SW, Bailes J, McCrea M, Harding H, Matthews A, Mihalik J, Cantu R. Recurrent concussion and risk of depression in retired professional football players. *Med Sci Sports Exerc*. 2007;39(6):903-909. doi:10.1249/mss.0b013e3180383da5

[11] Cunningham J, Broglio SP, O'Grady M, Wilson F. History of Sport-Related Concussion and Long-Term Clinical Cognitive Health Outcomes in Retired Athletes: A Systematic Review. *J Athl Train*. 2020;55(2):132-158. doi:10.4085/1062-6050-297-18

[12] Randolph C, Karantzoulis S, Guskiewicz K. Prevalence and characterization of mild cognitive impairment in retired national football league players. *J Int Neuropsychol Soc*. 2013;19(8):873-880. doi:10.1017/S1355617713000805

[13] Plessow F, Pascual-Leone A, McCracken CM, Baker J, Krishnan S, Baggish A, Connor A, Courtney T, Nadler L, Speizer F, Taylor H, Weisskopf M, Zafonte R, Meehan W. Self-Reported Cognitive Function and Mental Health Diagnoses among Former Professional American-Style Football Players. *J Neurotrauma*. 2020;37(8):1021-1028. doi:10.1089/neu.2019.6661

[14] Mez J, Daneshvar DH, Kiernan PT, Abdolmohammadi B, Alvarez V, Huber B, Alosco M, Solomon T, Nowinski C, McHale L, Cormier K, Kubilus C, Martin B, Murphy L, Baugh C, Montenigro P, Chaisson C, Tripodis Y, Kowall N, Weuve J, McClean M, Cantu R, Goldstein L, Katz D, Stern R, Stein T, McKee A. Clinicopathological Evaluation of Chronic Traumatic Encephalopathy in Players of American Football. *JAMA*. 2017;318(4):360-370. doi:10.1001/jama.2017.8334

[15] Nitrini R. Soccer (Football Association) and chronic traumatic encephalopathy: A short review and recommendation. *Dement Neuropsychol*. 2017;11(3):218-220. doi:10.1590/1980-57642016dn11-030002

[16] Mackay D, Russell E, Stewart K, MacLean J, Pell J, Stewart W. Neurodegenerative Disease Mortality among Former Professional Soccer Players. *New England Journal of Medicine*. 2019;381. doi:10.1056/NEJMoa1908483

[17] Kunz M. A large-scale FIFA survey involving its then 207 member associations shows that football has strengthened its position as the world's number one sport since the last Big Count in the year 2000. Among the most pleasing signs is the continuing growth of the women's game. Published online 2006:3.

[18] Jordan SE, Green GA, Galanty HL, Mandelbaum BR, Jabour BA. Acute and chronic brain injury in United States National Team soccer players. *Am J Sports Med*. 1996;24(2):205-210. doi:10.1177/036354659602400216

[19] Covassin T, Swanik CB, Sachs ML. Epidemiological considerations of concussions among intercollegiate athletes. *Appl Neuropsychol*. 2003;10(1):12-22. doi:10.1207/S15324826AN1001_3

[20] O'Kane JW, Spieker A, Levy MR, Neradilek M, Polissar NL, Schiff MA. Concussion among female middle-school soccer players. *JAMA Pediatr*. 2014;168(3):258-264. doi:10.1001/jamapediatrics.2013.4518

[21] Comstock RD, Currie DW, Pierpoint LA, Grubenhoff JA, Fields SK. An Evidence-Based Discussion of Heading the Ball and Concussions in High School Soccer. *JAMA Pediatr*. 2015;169(9):830-837. doi:10.1001/jamapediatrics.2015.1062

[22] Mullally WJ. Concussion. *The American Journal of Medicine*. 2017;130(8):885-892. doi:10.1016/j.amjmed.2017.04.016

[23] Katayama Y, Becker DP, Tamura T, Hovda DA. Massive increases in extracellular potassium and the indiscriminate release of glutamate following concussive brain injury. *J Neurosurg*. 1990;73(6):889-900. doi:10.3171/jns.1990.73.6.0889

[24] Giza CC, Hovda DA. The Neurometabolic Cascade of Concussion. *J Athl Train*. 2001;36(3):228-235.

[25] Osteen CL, Giza CC, Hovda DA. Injury-induced alterations in N-methyl-D-aspartate receptor subunit composition contribute to prolonged 45calcium accumulation following lateral fluid percussion. *Neuroscience*. 2004;128(2):305-322. doi:10.1016/j.neuroscience.2004.06.034

[26] Raghupathi R. Cell death mechanisms following traumatic brain injury. *Brain Pathol*. 2004;14(2):215-222. doi:10.1111/j.1750-3639.2004.tb00056.x

[27] Yoshino A, Hovda DA, Kawamata T, Katayama Y, Becker DP. Dynamic changes in local cerebral glucose utilization following cerebral conclusion in rats: evidence of a hyper- and subsequent hypometabolic state. *Brain Res*. 1991;561(1):106-119. doi:10.1016/0006-8993(91)90755-k

[28] Unterberg AW, Stover J, Kress B, Kiening KL. Edema and brain trauma. *Neuroscience*. 2004;129(4):1021-1029. doi:10.1016/j.neuroscience.2004.06.046

[29] Rangel-Castilla L, Rangel-Castillo L, Gopinath S, Robertson CS. Management of intracranial hypertension. Neurol Clin. 2008;26(2):521-541, x. doi:10.1016/j.ncl.2008.02.003

[30] Mount CA, M Das J. Cerebral Perfusion Pressure. In: *StatPearls*. StatPearls Publishing; 2020. Accessed August 17, 2020. http://www.ncbi.nlm.nih.gov/books/NBK537271/

[31] Marmarou A. Increased intracranial pressure in head injury and influence of blood volume. *Journal of neurotrauma*. 1992;9 Suppl 1:S327—32.

[32] Shen L, Wang Z, Su Z, Qui S, Xu J, Zhou Y, Yan A, Yin R, Lu B, Nie X, Zhao S, Yan R. Effects of Intracranial Pressure Monitoring on Mortality in Patients with Severe Traumatic Brain Injury: A Meta-Analysis. *PLoS One*. 2016;11(12). doi:10.1371/journal.pone.0168901

[33] Groom R, Oakley PA. Secondary brain injury: mechanisms and prevention. *Current Anaesthesia & Critical Care*. 1997;8(6):248-253. doi:10.1016/S0953-7112(97)80002-6

[34] Lipton ML, Kim N, Zimmerman ME, Kim M, Stewart WF, Branch CA, Lipton RB. Soccer Heading Is Associated with White Matter Microstructural and Cognitive Abnormalities. Radiology. 2013;268(3):850-857. doi:10.1148/radiol.13130545

[35] Rubin TG, Catenaccio E, Fleysher R, Hunter LE, Lubin N, Stewart WF, Kim M, Lipton RB, Lipton ML. MRI-defined White Matter Microstructural Alteration Associated with Soccer Heading Is More Extensive in Women than Men. Radiology. 2018;289(2):478-486. doi:10.1148/radiol.2018180217

[36] Sortland O, Tysvaer AT. Brain damage in former association football players. An evaluation by cerebral computed tomography. Neuroradiology. 1989;31(1):44-48. doi:10.1007/BF00342029

[37] Koerte IK, Mayinger M, Muehlmann M, Kaufmann D, Lin AP, Steffinger D, Fisch B, Rauchmann BS, Immler S, Karch S, Heinen FR, Ertl-Wagner B, Reiser M, Stern RA, Zafonte R, Shenton ME. Cortical thinning in former professional soccer players. Brain Imaging Behav. 2016;10(3):792-798. doi:10.1007/s11682-015-9442-0

[38] Stålnacke B-M, Tegner Y, Sojka P. Playing soccer increases serum concentrations of the biochemical markers of brain damage S-100B and neuron-specific enolase in elite players: a pilot study. Brain Inj. 2004;18(9):899-909. doi:10.1080/02699050410001671865

[39] Bamac B, Tamer GS, Colak T, Colak E, Seyrek E, Duman C, Colak S, Ozbek A. Effects of repeatedly heading a soccer ball on serum levels of two neurotrophic factor of brain tissue, BDNF and NGF, in professional soccer players. Biology of Sport. 2011;28:177-181. doi:10.5604/959284

[40] Petersen LG, Petersen JCG, Andresen M, Secher NH, Juhler M. Postural influence on intracranial and cerebral perfusion pressure in ambulatory neurosurgical patients. *Am J Physiol Regul Integr Comp Physiol*. 2016;310(1):R100-104. doi:10.1152/ajpregu.00302.2015

[41] Bolouri H, Säljö A, Viano DC, Hamberger A. Animal model for sport-related concussion; ICP and cognitive function. Acta Neurol Scand. 2012;125(4):241-247. doi:10.1111/j.1600-0404.2011.01614.x

[42] Lumba-Brown A, Harley J, Lucio S, Vaida F, Hilfiker M. Hypertonic Saline as a Therapy for Pediatric Concussive Pain. Pediatr Emerg Care. 2014;30(3):139-145. doi:10.1097/PEC.0000000000000084

[43] Donovan V, Bianchi A, Hartman R, Bhanu B, Carson MJ, Obenaus A. Computational analysis reveals increased blood deposition following repeated mild traumatic brain injury. Neuroimage Clin. 2012;1(1):18-28. doi:10.1016/j.nicl.2012.08.001

[44] Lewelt W, Jenkins LW, Miller JD. Autoregulation of cerebral blood flow after experimental fluid percussion injury of the brain. J Neurosurg. 1980;53(4):500-511. doi:10.3171/jns.1980.53.4.0500

[45] Säljö A, Bolouri H, Mayorga M, Svensson B, Hamberger A. Low-level blast raises intracranial pressure and impairs cognitive function in rats: prophylaxis with processed cereal feed. J Neurotrauma. 2010;27(2):383-389. doi:10.1089/neu.2009.1053

[46] Pomschar A, Koerte I, Lee S, Laubender RP, Straube A, Heinen F, Ertl-Wagner B, Alperin N. MRI Evidence for Altered Venous Drainage and Intracranial Compliance in Mild Traumatic Brain Injury. PLoS One. 2013;8(2). doi:10.1371/journal.pone.0055447

[47] Zhou Y, Kierans A, Kenul D, Ge Y, Rath J, Reaume J, Grossman RI, Lui YW. Mild Traumatic Brain Injury: Longitudinal Regional Brain Volume Changes. Radiology. 2013;267(3):880-890. doi:10.1148/radiol.13122542

[48] Jarrett M, Tam R, Hernández-Torres E, Martin N, Perera W, Zhao Y, Shahinfard E, Dadachanji S, Taunton J, Li DK, Rauscher A. A Prospective Pilot Investigation of Brain Volume, White Matter Hyperintensities, and Hemorrhagic Lesions after Mild Traumatic Brain Injury. Front Neurol. 2016;7. doi:10.3389/fneur.2016.00011

[49] Wang Y, Nencka AS, Meier TB, Guskiewicz K, Mihalik JP, Alison Brooks M, Saykin AJ, Koch KM, Wu YC, Nelson LD, McAllister TW, Broglio SP, McCrea MA. Cerebral blood flow in acute concussion: preliminary ASL findings from the NCAA-DoD CARE consortium. Brain Imaging Behav. 2019;13(5):1375-1385. doi:10.1007/s11682-018-9946-5

[50] Wang Y, Nelson LD, LaRoche AA, Pfaller AY, Nencka AS, Koch KM, McCrea MA. Cerebral Blood Flow Alterations in Acute Sport-Related Concussion. J Neurotrauma. 2016;33(13):1227-1236. doi:10.1089/neu.2015.4072

[51] Finch LC, Marchbanks RJ, Bulters D, Birch AA. Refining non-invasive techniques to measure intracranial pressure: comparing evoked and spontaneous tympanic membrane displacements. *Physiol Meas*. 2018;39(2):025007. doi:10.1088/1361-6579/aaa9f8

[52] Petersen LG, Ogoh S. 2019 Gravity, intracranial pressure, and cerebral autoregulation. *Physiol Rep.* 7(6):e14039.