Ocular Perfusion Pressure in Spaceflight-Associated Neuro-Ocular Syndrome

by

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Abstract

Purpose

Spaceflight associated neuro-ocular syndrome (SANS) is considered by the National Aeronautics and Space Administration (NASA) as one of the most significant barriers to long term space exploration (Larkin, 2018). Its main features include posterior globe flattening, hyperopic shifts, choroidal and retinal folds, cotton wool spots, and optic disc edema (Lee, Mader, Gibson, Brunstetter, & Tarver, 2018). Currently, it is confined to males and its cause remains unknown (Mader et al., 2011). While there are terrestrial diseases with features similar to SANS, none of them completely match the syndrome. Understanding the mechanisms of these diseases as well as the relationship between IOP, eye size, gravity, ocular and systemic fluid dynamics, and ICP is vital to understand and develop ways to prevent, modulate, and treat SANS. A relatively new and unexplored possible contributor to SANS is ocular perfusion pressure (OPP). The purpose of this thesis is threefold: (1) To explore the effect of head-down tilt (HDT); a popular analog for spaceflight, on OPP, (2) to determine the effect of HDT on IOP, and (3) to determine the effect of sex on OPP and IOP. We hypothesize that OPP and IOP will vary in a statistically significant way with body position and sex.

Methods

The right eye's IOP was measured by Tonopen XL and mean arterial pressure (MAP_{heart}) was measured continuously by the Finapres Nova System's finger cuff which recalculated blood pressure at the brachial artery. To calculate MAP_{eye}, MAP_{heart} and the distance between the heart and eyes were obtained for 10 participants. Measurements were taken in 4 body positions: sitting, supine, 12° HDT and 30° HDT. Participants (19-41 years old) spent 5 minutes in the first two positions and approximately 25 minutes in the last two tilts. OPP was calculated for the various body positions. Additionally, available non-invasive ICP measures for 9 of the participants were examined in relation to OPP and IOP. Data were analyzed through a mixed

ANOVA. Outcome variables were: OPP, IOP, MAP_{heart}, MAP_{eye}, ICP and translaminar pressure difference (TLPD) for the IOP/ICP mismatch.

Results

Six men and four women completed the experiment. OPP & IOP were found to significantly increase with tilt angle *(P*< 0.001) statistically. OPP increased from 55.26 at baseline to 86.7 at 30° HDT while IOP increased from 14.1 to 22.2 at 30° HDT. We also found a statistically significant IOP/ICP mismatch (*p*= 0.013) between 12° HDT and 30° HDT as TLPD decreased by 10.24 at the last tilt. Within the power of our sample sex had no statistically significant effect on any variable (p> 0.05).

Conclusions

Our findings show that OPP increases sufficient to compromise autoregulation do occur with change in body posture indicating a possible mechanism for the observed ocular changes that occur during spaceflight. In addition, it appears that an IOP/ICP mismatch may occur at high levels of tilt. However, as our findings are acute, further investigation is needed to determine long-term effects of HDT on OPP as well as the effects of lower body negative pressure (LBNP) devices and the minimum duration LBNP that would be required to protect the eyes.

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Dedication

To those who have inspired it and will not read it.

Dear parents and grandparents, thank you for always believing in me. May this and all that follows make you proud.

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List of Abbreviations

0-G: microgravity

1-G: Terrestrial gravity

BCVA: Best corrected visual acuity

CHI: Coded hemodynamic imaging

$CO_{2:}$ Carbon dioxide

CSF: Cerebral spinal fluid

CWS: Cotton wool spots

DBP: Diastolic blood pressure

DI: Head-out dry immersion

HBR: Horizontal bedrest

HDT: Head-down tilt

HM: Hypotony maculopathy

ICP: Intracranial pressure

ICP_{Supine}: Intracranial pressure while supine

ICP_{12}: Intracranial pressure at 12° HDT

ICP_{30}: Intracranial pressure at 30° HDT

IIH: Idiopathic intracranial hypertension

IOP: Intraocular pressure

IOP_{Sit}: Intraocular pressure while sitting

IOP_{Supine}: Intraocular pressure while supine

IOP_{12}: Intraocular pressure at 12° HDT

IOP_{30}: Intraocular pressure at 30° HDT

ISS: International Space Station

LBNP: Lower body negative pressure

LC: Lamina cribrosa

MAP or MAP_{heart}: Mean arterial pressure/ blood pressure

MAP_{eye}: Mean arterial pressure at eye level

$MAPeye_{Sit}$: Mean arterial pressure at the eye when sitting

$MAPeye_{Supine}$: Mean arterial pressure at the eye when supine

$MAPeye_{12}$: Mean arterial pressure at the eye at 12° HDT

$MAPeye_{30}$: Mean arterial pressure at the eye at 30° HDT

$MAPheart_{Sit}$: Mean arterial pressure at the heart when sitting

$MAPheart_{Supine}$: Mean arterial pressure at the heart when supine

$MAPheart_{12}$: Mean arterial pressure at the heart at 12° HDT

$MAPheart_{30}$: Mean arterial pressure at the heart at 30° HDT

MCA: Middle cerebral artery

MH: Malignant hypertension

NASA: National Aeronautics and Space Administration

nICP: Non-invasive intracranial pressure

OCT: Optical coherence tomography

OD: Right eye Oculus dexter

ON: Optic nerve

ONH: Optic nerve head

ONSD: Optic nerve sheath diameter

OPP: Ocular perfusion pressure

OPP_{12}: Ocular perfusion pressure at 12° HDT

OPP_{30}: Ocular perfusion pressure at 30° HDT

OPP_{Sit}: Ocular perfusion pressure while sitting

OPP_{Supine}: Ocular perfusion pressure while supine

OS: Left eye Oculus sinister

PCOS: Polycystic ovary syndrome

RNFL: Retinal nerve fiber layer

SANS: Spaceflight-Associated Neuro-Ocular Syndrome

SBP: Systolic blood pressure

TCD: The Transcranial Doppler ultrasound

TLPD: Translaminar pressure difference

$TLPD_{Supine}$: Translaminar pressure difference while supine

$TLPD_{12}$: Translaminar pressure difference at 12° HDT

$TLPD_{30}$: Translaminar pressure difference at 30° HDT

USGLP: Ultrasound-guided lumbar puncture

VA: Visual acuity

VIIP: Visual Impairment and Intracranial Pressure

WI: Head-out wet immersion

Chapter 1 Literature Review

1.1 Historical Background and Literature Review

In the last decade, astronauts have been found to be susceptible to a set of symptoms and signs occurring on board the International Space Station (ISS); a habitable artificial satellite, in low Earth orbit. It was in 2003 (debatably 2005 in other sources), however, that choroidal folds were first observed in a returning astronaut, followed by observations of optic disc edema and cotton wool spots (CWS) amongst other signs through 2008 (Larkin, 2018). By 2008, astronauts sent on missions were equipped with reading glasses in preparation for the hyperopic shifts that had been often observed on long-duration flights; missions longer than 30 days (Larkin, 2018). The first report of the abovementioned set of signs, along with others, was published in 2011 (Mader et al., 2011) and Mader referred to them as Vision Impairment and Intracranial Pressure (VIIP). Moderate visual impairment is defined by the WHO as a best corrected visual acuity (BCVA) of 20/70 to 20/200 (World Health Organization, 2015). As returning crewmembers all had a BCVA of 20/20, the definition of visual impairment was inapplicable (Brunstetter, Macias, Smith, & Stenger, 2018). Moreover, the name VIIP is inaccurate as it implies that intracranial pressure is the etiology, which has not been proven to date. Thus, this name was changed into Spaceflight-Associated Neuro-Ocular Syndrome a few years ago.

As many astronauts with SANS have been found symptomless once back on Earth, it is possible that SANS was not an issue in the past when missions were shorter. However, it was found that 29% of short- and 60% of long-duration mission astronauts reported a blur in vision (Stenger et al., 2017) suggesting SANS was indeed also present in the past.

1.2 Signs and Symptoms

SANS is associated with hyperopic shifts, cotton wool spots, retinal and choroidal folds, retinal hemorrhages, posterior globe flattening (presumably contributing to the hyperopic shift), retinal nerve fiber layer (RNFL) thickening, and quite uncommonly, visual field defects like scotoma (Mader et al., 2011). Other signs include optic nerve sheath diameter distention, optic nerve (ON) tortuosity/kinking, and choroidal thickening (Brunstetter et al., 2018). Finally, the characteristic edema of the optic disc (Lee et al., 2018) is the most worrying sign (Brunstetter et al., 2018) because of the possible irreversible visual defects it can cause. These signs have interestingly shown to be more prevalent in the right eye (Mader et al., 2011).

Although SANS has been characterized by the disc edema, around 60% (i.e. 1 in 3) of astronauts (Marshall-Goebel, Damani, & Bershad, 2019) returning from long-duration missions have exhibited at least one of the abovementioned signs over the past decade (Brunstetter et al., 2018; Huang, Stenger, & Macias, 2019). Furthermore, while most signs vanish upon return to Earth, some signs persist for a varied duration of time. For instance, there are cases of globe flattening and refractive error that have persisted for over 7 years (Brunstetter, 2018a). Additionally, in some long-duration mission astronauts, there have been remaining signs of choroidal folds lingering from decades ago (Brunstetter et al., 2018).

When it comes to symptoms, the blur of vision at near (or near and distance) during space missions seems to be the only reported complaint, apart from the one-time report of a scotoma in one astronaut's visual field (Stenger et al., 2017). This blur is suspected to have resulted from the posterior globe flattening found in some astronauts. Nevertheless, the diagnosis of SANS is now based alone on the presence of an optic disc edema of Frisen grade ≥ 1 (an edema extending at least 270^{o} around ONH) through fundoscopy (Brunstetter, 2018a).

1.3 Methods

1.3.1 Methods of Detection and Measurements

In 1989, astronauts were encouraged to report any changes experienced in near or distant vision during their short and long flights (Brunstetter et al., 2018). Many changes have been reported since then, with some through surveys distributed to as many as 300 astronauts (Mader et al., 2011). These reports led NASA to begin trying to find the underlying etiology to these complaints using many ophthalmological techniques (Mader et al., 2011). Astronauts had their clinical findings documented, along with test findings including ultrasound, optical coherence tomography (OCT) imaging, radiographic findings (Lee et al., 2018), and dilated fundus exams with binocular ophthalmoscopy (Stenger et al., 2017). Furthermore, as of 2014, there are currently six instruments being used on board the ISS: a Snellen chart, Acuity Pro software (for distance vision measurements and an Amsler grid), a hand-held tonometer, ultrasound, fundoscope, and an OCT (NASA, 2019).

While OCT and ultrasound instruments are available and frequently used both onboard the ISS and terrestrially, cranial and orbital MRI machines are only available on Earth (Lee et al., 2018). NASA is, continuously looking to find instruments, portable and functional to equip the ISS. Such instruments need to provide reliable measurements in 0-G to gather as much inflight data as possible.

1.3.2 Astronaut Findings

Multiple studies have been conducted on various numbers of astronauts and cosmonauts (Russian astronauts). It was 2011 when the main findings in astronauts were first described after long-duration spaceflight on the ISS (Mader et al., 2011). As summarized again in 2017, complete ocular examinations were taken for seven astronauts pre-and post-mission (Lee, Mader, Gibson, & Tarver, 2017). Optic disc edema, choroidal folds and globe flattening were each noted in five astronauts, RNFL infarcts in three, RNFL thickening and decreased near

vision (hyperopic shift) in six (Lee et al., 2017). Five of these six-affected astronauts experienced a hyperopic shift varying between +0.50 D to +1.75 D (Lee et al., 2017).

In a recent study conducted in long-duration microgravity, the Bruch membrane opening (BMO) was found to be deepened. Amongst other changes, there was an increase in total retinal thickness and RNFL as well as disc edema-like changes found in the morphology of the ONH and surrounding tissue (Patel, Pass, Mason, Gibson, & Otto, 2018). While these results are not inclusive of all astronauts, it is important to note that there is no single, open source database or report that includes all data for all astronauts. Due to the small astronaut sample sizes, it would be relatively easy to determine specifically who is described in such a data set. Therefore, information is carefully published when sample sizes are large enough to permit astronaut confidentiality (Brunstetter, personal communication, March 18, 2019).

1.3.3 Summary of Findings

The abovementioned studies are the oldest study documented, as well as one of the most recent ones completed on astronauts. These comparisons demonstrate that astronauts still are facing relatively the same ocular issues and findings in 0-G across an eight-year period. The syndrome has; therefore, most probably existed from the very beginning of space exploration and was going on unnoticed until approximately the past decade. However, the ambitious destinations planned, and the longer durations of spaceflight today render SANS especially problematic to our time.

1.4 Simulations

1.4.1 Microgravity Simulations/Analogs

In order to better study SANS and general spaceflight, scientists needed to “recreate” microgravity on Earth. The most commonly known microgravity analogs are head-down tilt bed

rest (HDT), head-out water immersion (WI), head-out dry immersion (DI), parabolic flight and horizontal bed rest (HBR; Watenpaugh, 2016). HDT has become by far the most commonly used method, especially for longer studies. The reason for that is HDT studies permit activities of short duration (e.g. short showers in a horizontal posture; Watenpaugh, 2016). Its convenience, affordability, ease of use (relative to WI and DI) and ability to reproduce many 0-G characteristics are contributors to its popularity (Watenpaugh, 2016), regardless of the experimenter's chosen bed tilt value. Parabolic flight recreates a state of 'free-fall', making it the most similar to spaceflight but only for very short durations (Watenpaugh, 2016). The following is a brief description to each analog:

1. Head-down tilt bed rest (HDT): It is preferred over the HBR because of its superior ability to mimic microgravity's fluid distributions (Hargens & Vico, 2016). While HDT angles used usually range anywhere between approximately 4° to 15°, the most commonly used angle of tilt is 6° as it produces a gravitational effect quite close to 0-G (Jordan, Hellweg, Mulder, & Stern, 2020; Watenpaugh, 2016). This analog is also a really good simulator when it comes to observed cardiovascular changes on the ISS (Pandiarajan & Hargens, 2020). However, as mentioned in a paper by Mekjavic et al., Levinsohn's work demonstrated that both it and HBR are not the best for simulating ocular changes including those observed in SANS (Mekjavic, Amoaku, Mlinar, & Jaki Mekjavic, 2020). Moreover, the prone position in that same tilt has been observed to affect the eye more prominently (Mekjavic et al., 2020).

2. Head-out water immersion (WI): It neutralizes gravity forces with buoyancy (Watenpaugh, 2016). In this analog, the water level is most often set at the jugular notch as subjects sit or stand (Watenpaugh, 2016). The water's temperature is usually 34–35°C (Watenpaugh, 2016).

3. Head-out dry immersion (DI): Like in WI, participants are placed in a body of water (Watenpaugh, 2016). However, they are covered by an elastic cloth (thereby keeping

them dry), and the air between the cloth and the participant's skin causes the floating of the individual without any exerted pressure (Watenpaugh, 2016).

4. Parabolic Flight: Used mostly for acute simulation of microgravity, subjects are exposed to free-fall for a duration of about 20 seconds multiple times in order to obtain needed measurements (Karmali & Shelhamer, 2008). These 20-30 seconds of 0-G (microgravity) are then followed by a short burst of 2 Gs (Karmali & Shelhamer, 2008).

5. Horizontal bed rest (HBR): An attempt to mimic microgravity's headward fluid shifts by lying down horizontally and parallel to the ground (Watenpaugh, 2016).

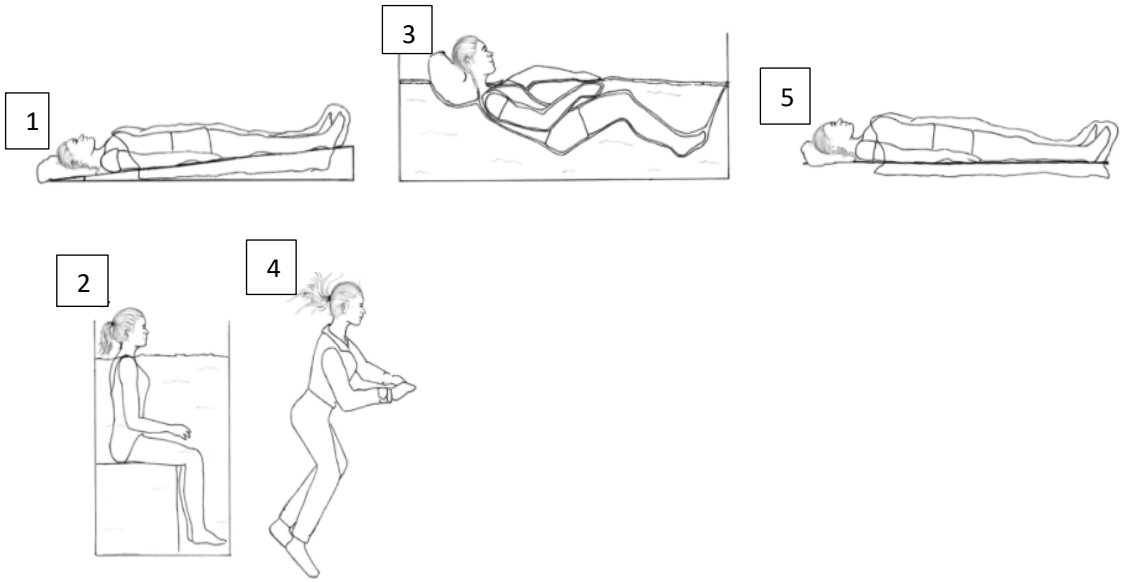

Figure 1. Watenpaugh, Analogs of microgravity: head-down tilt and water immersion, Journal of Applied Physiology, 2016, adapted from the Journal of The American Physiological Society (2016)

While there are multiple differences between these simulation methods and 0-G, they sensibly mimic microgravity responses (Watenpaugh, 2016). To better understand these analogs, however, one must understand a concept involving circadian cycles. Our bodily functions rely greatly upon our wake-sleep state, and with it, the body's axial position relative to gravity. On earth we are switching daily between the upright position when awake (1-G) and recumbent (microgravity) when asleep in the 24 hours of the day. However, these positional changes are not of much effect when in space (Watenpaugh, 2016). Since microgravity challenges the circadian component of this cycle, analogs needed to as well (Watenpaugh, 2016). Despite the limitations of the analogs, it is useful to understand intraocular pressure (IOP) variations when switching from supine to upright postures on Earth (Zhang & Hargens, 2017).

1.4.2 Simulation Findings on SANS

In spaceflight, IOP in two studies increased 20% (i.e. the first IOP measurements taken in spaceflight) and 92% after 44 minutes and 16 minutes of entering microgravity consecutively (Draeger, Schwartz, Groenhoff, & Stern, 1993). These increases surpassed the elevation in pressure seen with acute (Macias, Liu, Grande-Gutierrez, & Hargens, 2014) and chronic (Mader, Taylor, Hunter, Caputo, & Meehan, 1990; Taibbi et al., 2014) HDT. On average, IOP changes of 6.5 mmHg are seen in astronauts during spaceflight (Nelson, Myers, Lewandowski, Ethier, & Samuels, 2020). However, the duration needed for the different findings on the ISS to normalize again varies. Many studies have revealed its return to pre-flight values to usually be within a week of its start (i.e. excluding cases where IOP was maintained high Launch+8 days; Chung et al., 2011).

While multiple studies have taken measurements onboard the ISS, there are also many that were taken with the previously mentioned analogs in attempts to understand SANS. For instance, to better understand the effect of microgravity on IOP, Draeger and Mader (as cited in Taibbi, Cromwell, Kapoor, Godley, & Vizzeri, 2013) each conducted a study in parabolic flight in which they respectively noted a mean 5 mmHg and 7 mmHg increase in IOP, using a handheld

applanation tonometer. These results were similar to another study's approximate IOP change of 5 mmHg also conducted in parabolic flight (i.e. compared to its seated baseline measured in a lab) using a Perkins tonometer (Anderson et al., 2016).

As for IOP findings in HDT, a study using an ICare tonometer compared 14-day HDT to 70-day HDT. It found the slight increase in IOP (i.e. +1.42 and +1.79 respectively) that returned to baseline post-HDT was likely caused by cephalad fluid shifts (i.e. shift of blood towards the head). As seen in the values of IOP increase above, there was no statistically significant difference between 14 days and 70 days in 6° HDT suggesting IOP relatively plateaus before returning to baseline post-HDT (Taibbi, Cromwell, Zanello, Yarbough, & Ploutz-snyder, 2016). This is an agreement with IOP findings on the ISS mentioned above. It is also likely that the IOP increases would have better matched ISS findings should they have been measured within the first few days of the experiment.

In harmony with the last study's findings, is a study conducted in 2019. It explored the impact of 70 Days of 6° HDT on ocular parameters. Unlike previously mentioned HDT studies, IOP post-HDT remained significantly different from values pre-HDT statistically, albeit less. The statistically significant increase in IOP (i.e. about +1.00-1.50 mmHg) from pre-HDT to all in-HDT and post-HDT time points was thought to be reversible by spending more time out of HDT (Cromwell et al., 2019), probably stemming from the decrease in IOP measures found 2-3 days post-HDT. All being said, none of the findings were "clinically" significant (Cromwell et al., 2019). Regardless of how microgravity was attained, most conducted research reached the same observation; an instantaneous IOP elevation that moderates over time to then decrease below (or equal to) baseline within a week of spaceflight or once the experiment ends (Stenger et al., 2017; Zhang & Hargens, 2017).

Of course, IOP is not the only parameter of interest in ocular studies. One study compared acute HDT of 20 minutes to chronic ISS data. It showed that while acute HDT creates a thickening of the optic nerve sheath diameter (ONSD), this increase is three times less than

what results in space (Sirek et al., 2014). Increases in ONSD have also been observed after 4.5 hours in each of 6°,12° and 18° HDT compared to their supine baseline in a more recent experiment (Marshall-Goebel, Terlević, et al., 2017).

Referring back to Taibbi's study comparing 14-day HDT to 70-day HDT, 70-day HDT induced greater peripapillary retinal thickening than 14-day HDT , demonstrating that time may affect the amount of optic disc swelling (i.e. as noted by the authors), amongst other findings (Taibbi et al., 2016). When looking at ocular parameter changes after 70 days in 6° HDT, Cromwell found the average RNFL thickness to increase significantly from pre-HDT to post-HDT (Cromwell et al., 2019). This is further seen in a study looking at choroidal and peripapillary thickness after both 30 days on the ISS and 30 days in 6° HDT. Both conditions were found to increase peripapillary total retinal thickness (a sign of early disc edema) albeit to a greater extent in HDT (Laurie et al., 2020). Although it seems like some HDT findings might be exaggerated compared to ISS findings, no increase in choroidal thickness was found despite its increase in the astronaut group. These findings are different from the increase found in subfoveal choroidal thickness after both 15 and 30 minutes in 10° HDT in one study (Shinojima et al., 2012) and after an hour in 6° HDT in another (Laurie et al., 2017). It is, therefore, possible that choroidal thickness increases acutely and then returns to baseline in longer durations of HDT.

As for the spherical equivalence and BCVA, Cromwell et al. (2019) found the spherical equivalent to steeply decrease compared to baseline while BCVA noticeably improved at near and distance, the latter likely due to participants' use of a visual chart weekly (Cromwell et al., 2019). Since the decrease in spherical equivalence indicates a myopic shift's occurrence (which seems to be in the wrong direction for SANS), the authors speculated that bed confinement over such a long period might have caused the myopic shift (i.e. through adaptation to near-vision tasks; Cromwell et al., 2019) although this seem unlikely within the time frame. The 14-day to 70-day HDT study also found the changes in "Modified Amsler grid, red dot test,

confrontational visual field, color vision, and stereoscopic fundus photography" to be "unremarkable"(Taibbi et al., 2016).

To summarize, the duration of these studies affects the magnitude of difference between space and its analogs, and analogs amongst themselves. Furthermore, it's important to note that while a six-month study is considered a long-duration one in spaceflight, it can be as low as 5 days in HDT studies (Marshall-bowman, Barratt, & Gibson, 2013). As for short-term studies, the same principle applies; a flight duration of less than approximately two weeks is considered short, whereas it is only minutes to a few hours in HDT (Marshall-bowman et al., 2013). More studies comparing changes between HDT to an equal number of days in spaceflight would be beneficial.

1.4.3 Limitations

While these analogs have provided much-needed information on SANS, they remain far from perfect for multiple reasons. For instance, the currently used Earth-based analogs simply can't remove molecular-level effects of gravity (Watenpaugh, 2016). Thus, one must keep in mind that there is a fair amount of interpretation occurring when comparing the acute effects of analogs to those of long-term space exploration.

For the most part, the inability to rid analogs completely of gravitational influences accounts for much of the differences between microgravity and its analogs; however, other factors are at play (Watenpaugh, 2016). For instance, most analogs are only a representation of the first few hours/days of spaceflight and lack the ability to recreate launch conditions and insertion into orbit (Watenpaugh, 2016). One study (as cited by Watenpaugh, 2016) used centrifugation pre- and post-16 days in HDT to replicate spaceflight launch and landing conditions (Stowe, Yetman, Storm, Sams, & Pierson, 2008). Compared to their ISS mission's data, the study found some immunological and hormonal (originating from the adrenal gland) changes that very much resembled what occurs in spaceflight (Watenpaugh, 2016). However, even with this relatively long period of time spent in HDT, microgravity-induced psychological

stress was one component they could not achieve, for ethical reasons (Watenpaugh, 2016). These 16-day HDT findings were more consistent with what would be seen on a mission of 9 days rather than 16 in spaceflight (Stowe et al., 2008). According to the researchers, this could be due to the difference in how psychological changes were achieved in HDT relative to spaceflight (i.e. while it is due to inactivity in HDT, in spaceflight it results from actual presence in microgravity, sleep deprivation, isolation, etc., Stowe et al., 2008).

Furthermore, the extent at which mental engagement, stress and sensorimotor conditions are triggered pre-flight are very difficult to recreate in earthly analogs (Watenpaugh, 2016). As participants are much more likely to be comfortable and subconsciously aware of the safety of their surroundings, the comparison between analogs and spaceflight is further complicated. A simple demonstration of this can be seen in WI and BR (Lackner, 2014). Axial position isn't of much impact in microgravity, limbs have weight on Earth and none in space, and air is much less movement-resistant than water. Therefore, these analogs can't recreate the motion sickness experienced by some astronauts (Watenpaugh, 2016). In fact, although the closest analog (i.e. parabolic flight) does sometimes elicit motion sickness, even it can't be relied on to depict who will experience this symptom on the ISS (Watenpaugh, 2016). On that note, the misrepresentative short peaks of ~20 seconds in which measurements are taken, are yet another factor making parabolic flight an imperfect analog. Finally, astronauts seldom take part in studies using analogs (Watenpaugh, 2016). This often leads researchers to recruit younger participants and amounts to a misrepresentative population; a significant problem considering the vast difference between responsiveness of the cardiovascular system in the young and the old (Brunstetter et al., 2018).

In a paper by Watenpaugh, HBR, HDT, WI and DI were compared based on a subjective assessment of ground-based analog fidelity and approximate level of evidence for that assessment (Watenpaugh, 2016). Watenpaugh found HDT to replicate cardiovascular function well or “good” and HBR to replicate it “fairly” based on cohort/outcome research. As for sleep/circadian rhythms, both analogs had a subjective “good” score with case control studies as their level of evidence (Watenpaugh, 2016). As these are widely used analogs, this gives an

idea of their reliability in different areas. To summarize, some ocular changes that arise from microgravity simulations will be similar to those occurring in SANS during spaceflight, but none of these analogs are perfect.

1.5 Hypotheses to explain SANS

1.5.1 Intracranial Pressure Variation

1.5.1.1 Increased Intracranial Pressure (ICP)

Likely due to being the earliest and most obvious, one of the most recurrent hypotheses for the cause behind SANS is the bodily fluid shifts that occur in microgravity. When the body is suddenly gravity-deprived (in the ISS for instance), fluids are known to shift upwards towards the brain and are thought to cause, amongst other theories, an increase in ICP. This hypothesis has risen from the experiments conducted that took lumbar puncture measurements (as representative measurements of ICP) pre- and post-flight, all mostly showing an increase in ICP upon landing (Otto, 2017, p. 124; Macias et al., 2014; Mader et al., 2011) . In turn, these findings gave rise to the hypothesis of increased ICP during spaceflight. For the confirmation of such a hypothesis comes the need for in-flight measurements of ICP, a very invasive procedure with many ethical limitations and risks with its performance. Most experiments have thus relied on non-invasive ICP (nICP) representative methods for measurements, including MRI, OCT of the retina, jugular vein ultrasound, middle cerebral artery (MCA) Transcranial Doppler ultrasonography (TCD) and ONSD B-scan ultrasound measurements (Zhang et al., 2017). When invasive options are undoable or risky (as is the case on the ISS) these methods allow the collection of ICP measurements (Zhang et al., 2017).

The gold standard for ICP measurement is the intraventricular catheter, a method performed in parabolic flight for the first and only time in 2017 (Lawley et al., 2017). That study had interesting findings that were a bit different to all the 0-G simulation methods' findings on ICP. It indicated that ICP does not increase in parabolic flight, but rather fails to decrease the way it would when standing (Lawley et al., 2017). Intracranial pressure in zero gravity might be

positioned between what is experienced terrestrially in the supine and upright positions (Lawley et al., 2017). If this finding describes what's truly experienced on-orbit (bearing in mind the acute 20 second bursts of 0-Gs during parabolic flight) and if ICP is a significant factor in SANS pathogenesis, then it's possible that it's the up-down fluctuation of terrestrial ICP that is most critical in preventing optic disc edema (e.g., routine of sleeping/supine then standing for 2/3 of the day; Lawley et al., 2017). Therefore, "complete removal of gravity is not thought to pathologically elevate ICP but does prevent the normal lowering of ICP occurring when upright" (Lawley et al., 2017). This hypothesis is uncertain, and it will require pre-/in-/post-flight ICP data to definitively describe what occurs in microgravity. In short, normal posture changes cause large ICP changes (Lawley et al., 2017).

Moreover, normal ICP values should be less than 10-15 mmHg in adults (Rangel-Castillo, Gopinath, & Robertson, 2008). In these studies, ICP increased to values around 20 mmHg and higher post-flight (Mader et al., 2011). More specifically, these high numbers were found to persist from 6 days to over 2 months postflight (Otto, 2017, p. 124). It is important to note that it is strange for the increased ICP to persist for such a duration and not lower along with its presumed cause (cephalic fluid shift). Although Lawley's findings showed otherwise, the hypothesis of increased ICP is further backed up by the found ON sheath distention in some astronauts; this variable is a good indicator of ICP changes (in the absence of other causes) as high ICP has been associated with ON sheath distention on Earth in the past. However, an ICP that fails to decrease (Lawley et al., 2017) and ON sheath distention might occur independently of each other.

Despite the acute short duration of zero gravity during parabolic flight, there was also no evidence of a progressive rise in ICP due to cephalad fluid shifts with prolonged presence in the HDT position (Lawley et al., 2017). Thus, the authors believed there was no reason to assume their parabolic flight ICP values were higher than what would be seen in spaceflight (Lawley et al., 2017). Of course, these drawn conclusions are based on the assumption that acute data from parabolic flights at least somewhat represents long-term presence in microgravity (Lawley et al., 2017).

A mechanism for how raised ICP produces disc edema is found in a study conducted on rhesus monkeys. As orbital and optic nerve blood supply and ON structure are identical to those in humans, the study provided valuable insight. It explored disc edema pathogenesis in raised ICP using inserted space-occupying lesions in monkeys. It became apparent that this pathogenesis is mechanical in nature, starting with a primary rise in cerebral spinal fluid pressure (CSFP). This increase is then transferred into the optic nerve sheath's CSFP which produces axoplasmic flow stasis in the optic nerve fibers in the prelaminar region of the optic disc. The axoplasmic flow then leads to the swelling of the nerve fibers and thus, the optic disc. Finally, this swelling then compresses local fine vasculature leading to both hemorrhage and accumulation of extracellular fluid. In short, vascular changes are secondary, and disc edema in raised CSFP is the result of both swollen nerve fibers and local extracellular fluid (Hayreh, 2016). Based on these findings, one can speculate that any cause for axoplasmic flow stasis could cause disc edema. As parabolic flights provide short term data, this trend of gradually increasing ICP might have been seen in Lawley's findings should it have been a long-term study. However, unlike in SANS, this rhesus monkey study was based on space-occupying lesions as the underlying etiology for raised ICP. In this design, there was a need for continuously increasing ICP to maintain the optic disc edema, which may or may not be the case for SANS.

1.5.1.2 IOP/ICP Mismatch

A literature review presented the previously mentioned different percentages of increase in IOP in short-term spaceflight, parabolic flight and bed rest studies. The percentages varied quite a bit between analogs and between different studies using the same analog (Stenger et al., 2017). Although it seems long-term IOP data on the ISS does not exist, HDT studies have shown a decrease in IOP during the experiment after the initial peak, similar to the somewhat decrease seen after 44 minutes of entry into microgravity (Draeger et al., 1993). Although the way in-flight aqueous humor (AH) accommodates early (within 30 seconds; Mader et al., 2011) IOP alterations in microgravity is unknown, there have been many hypotheses. Amongst these, there is one that proposes that microgravity-induced cephalad fluid shifts lead

to the swelling of veins in the head and neck; the jugular vein distends, and vortex vein pressure increases occur (Mader et al., 2011). As Mader explained, when vortex vein pressures increase, the choroidal blood will fail to drain properly into them at the normal rate, thereby inducing the swelling of the choroid. This swelling creates a retina that is displaced slightly forward, leading to an overall shortened distance between the retina and the crystalline lens (i.e. axial length) and therefore, to hyperopia. Since the hyperopic shift observed within astronauts varies in amplitude, choroidal structure in each crewmember could provide insight on the susceptibility of the individual to this choroidal pooling (Mader et al., 2011). Moreover, this pooling could lead to a sudden increase in choroidal volume; this engorgement would potentially cause the rise in IOP (i.e. choroidal engorgement has the ability to increase IOP within seconds unlike elevations in episcleral vein pressure, which take many minutes) as seen in astronauts on the ISS (Mader et al., 2011).

It's also possible that the etiology of the reduction in IOP after its sudden spike lies within the AH. It is hypothesized that AH reduces in formation and, therefore in volume, in compensation for this IOP increase (Zhang & Hargens, 2017). Furthermore, one might wonder if this decrease in AH could be due to overall dehydration, but such a hypothesis would require data on the duration required in microgravity until dehydration is attained. That data would then be compared to when IOP is found to reduce and a connection could be drawn. Of note, some studies have found IOP to decrease with dehydration (Idu, George, & Obika, 2015), but astronauts do consume special beverages to compensate for dehydration in space (Marlaire, 2018).

Ordinarily, there is a low positive pressure difference between IOP and ICP that helps maintain ocular rigidity/shape on Earth (Zhang & Hargens, 2017). However, during long-duration spaceflight, a slightly increased ICP (i.e. relative to IOP) might occur as a result of the possible persistent mismatch between IOP and ICP (Zhang & Hargens, 2017). This pressure difference is based on a compartmental model where the area in front of the ONH lamina cribrosa (i.e. the area within the eye) contains IOP on its side while ICP is found beyond the ONH counterbalancing IOP. As mentioned by the authors, this combination of a slight increase

in ICP and a moderated IOP decrease for the rest of the flight duration leads to a change in the normal translaminar pressure difference (TLPD) by an altered difference in pressure between compartments on either side of the lamina cribrosa (LC). Also explained is that this pressure gradient increase could be due to an overall increase in ICP or localized to the optic nerve. Furthermore, ONSD increases/distention could be caused by these increases in ICP, as they were found to pressure CSF into the subarachnoid space of the ONH sheath in some terrestrial cases (Zhang & Hargens, 2017). According to Zhang and Hargens (2017), this might lead to both refractive changes and ONH pathologies (e.g. papilledema). As such, an elevated pressure gradient across the lamina cribrosa suggests that the IOP/ICP mismatch is a plausible explanation for SANS, or at least for the optic disc edema that is characteristic of the syndrome (Zhang & Hargens, 2017).

1.5.2 Venous Congestion

Another theory involves venous congestion. The hypothesis revolves around the concept of venous drainage. Should anything obstruct or prevent venous drainage at the level of the ophthalmic veins, the results would be felt at the ocular level. For instance, if the ophthalmic veins were experiencing high pressure (likely from locations preceding their own being transmitted to them), this would exhibit a chain-like effect on the veins connecting to them. These include the central retinal veins (which feed into both retinas), vortex veins (feeding into the choroid), anterior ciliary veins (drain ciliary body), episcleral veins (a pathway that helps drain AH), and so on. These veins would all congest because of their reduced drainage via the ophthalmic veins (Stenger et al., 2017). Therefore, elevated pressure in these ocular veins could cause a congested choroid that shortens the axial length of the eye (i.e. leading to hyperopia), as well as an increased IOP (either through the now congested choroid or through the episcleral veins and trabecular meshwork's impaired AH drainage). Increased ICP can also be transmitted to the eye in similar ways, as well as through the direct effect of CSF on the subarachnoid space, leading to ON sheath distention (Stenger et al., 2017). It should also be kept in mind that the process of obtaining repeated IOP measurements could lead to increased

IOP drainage through stimulation of the trabecular meshwork as this might artificially decrease IOP overall.

Moreover, jugular vein distension due to cephalad fluid shifts has been well documented in astronauts and is usually an indication of venous stasis within and above the neck (Mader et al., 2011). Since ICP is partly determined by CSF, it is crucial that CSF drains properly to maintain normal ICP. Since CSF drainage is thought to depend on the pressure difference between the venous system and itself, drainage would be compromised in the presence of venous stasis and lead to an increase in ICP. It is this same venous congestion in the neck and head that could lead to the rise in vortex vein pressure and thus affect IOP as described above.

Of note, the compensatory decrease in IOP that remains for most of the flight could also be interacting with the "failing to decrease" ICP. This IOP/ICP mismatch would lead to the optic disc edema, as mentioned earlier. The following diagram summarizes clearly the possible mechanisms of action for different hypotheses (the gray boxes contain some of the SANS findings in astronauts). In this diagram, many of its hypotheses rely on ICP increases to explain SANS, which as will be further clarified below, appears to be unlikely.

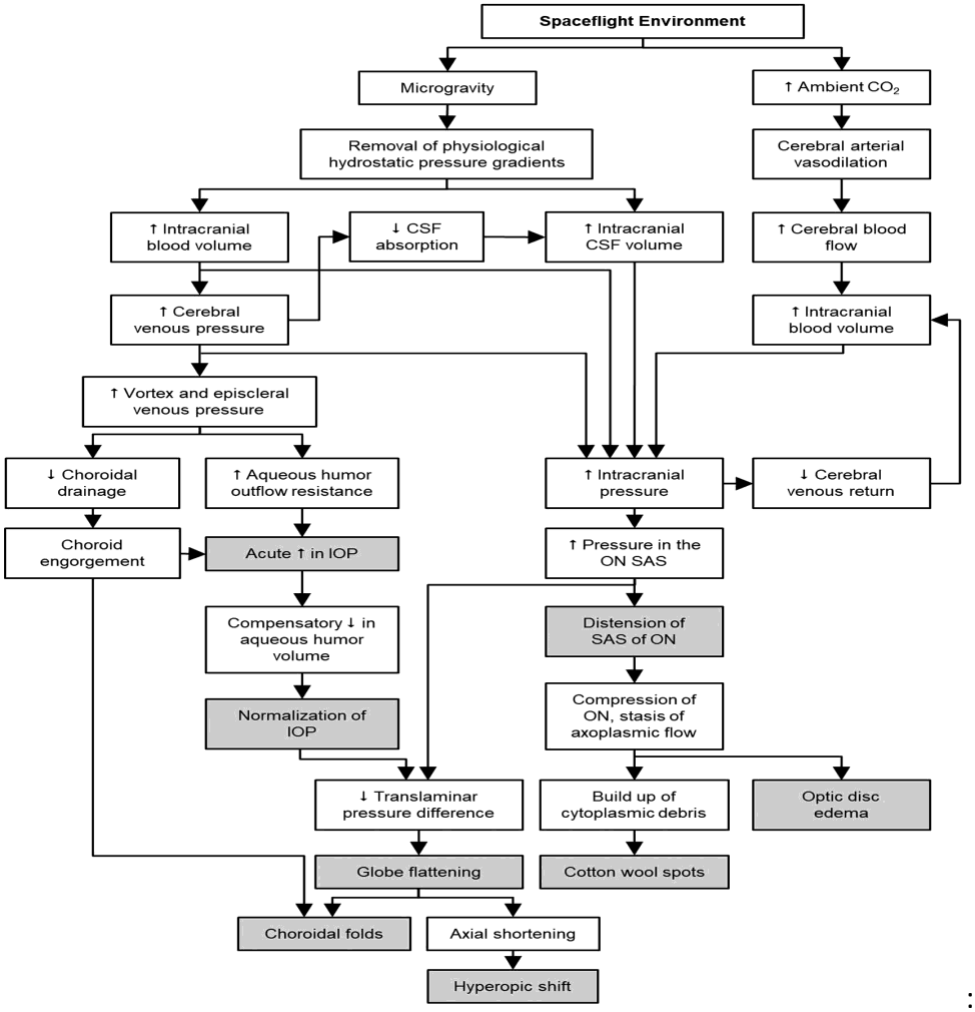

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Figure 2. Marshall-Goebel, Karina, Damani, Rahul & Bershad, Eric, Brain Physiological Response and Adaptation During Spaceflight, Clinical Neurosurgery, 2019, Volume 85, Issue 5, p.E817, by permission of Oxford University Press

1.5.3 Individual Anatomical/Genetic factors

Although various hypotheses attempted to explain SANS, the reason not all crewmembers are affected when all presumably experience the fluid shifts on exposure to microgravity remains. This is also relevant as these ophthalmic changes have been shown to not affect all crewmembers of a shared mission despite being exposed to a similar environment.

This led to the study of more individual-specific factors. A study conducted in 2012 wanted to see if vision changes after spaceflight were related to alterations in folate- and vitamin B-12-dependent one-carbon metabolism (Zwart et al., 2012).

Within the cells of our bodies lie nutrient-derived molecular interactions. These molecules are converted to energy through metabolic pathways and enzymes. It's been demonstrated that in-flight astronauts have increased levels of the amino-acid homocysteine that express errors in amino acid-carbon atom chains. More specifically, it is within a very important pathway (i.e. the one-carbon metabolism pathway) that the moving of carbon atoms and their attachment to amino acids occur (NASA, 2016). This process thereby forms new amino acids constantly, however, with the passage of time, any disruptions that have occurred in this chain are revealed through homocysteine. In fact, the first indicator that paved the way for scientists to look into the one-carbon metabolism pathway as a possible SANS cause was the increase in homocysteine levels found in the blood of astronauts with SANS (NASA, 2016). As two different forms of genetic alterations in the enzymes of this pathway were discovered, they could be related to the reason SANS occurs only in some astronauts (NASA, 2016).

The results showed that the affected crewmembers' folate- and vitamin B-12-dependent 1-carbon transfer metabolism was affected before and during flight. It seems this pathway may somehow interact with microgravity to cause these pathophysiologic changes (NASA, 2016). Perhaps the observed increase in homocysteine in microgravity would induce an increase in vascular permeability (i.e. as it has been shown to have an effect on endothelial structure; Bhatia, Gupta, & Sharma, 2014) then leading to "hypersensitivity" to high cabin CO_2 as well as other environmental stressors including cephalad fluid shifts. This plausible mechanism would explain this correlation between SANS and the 1-carbon metabolism pathway. After all, crewmembers that have developed SANS were found to have been exposed to a higher level of CO_2 in their cabins relative to those unaffected, overall (Zwart et al., 2012). This could also suggest a hypoxic contribution to the etiology.

Also put forward more recently is the possibility of men having an equivalent to **Polycystic ovary syndrome** (**PCOS**) and its possible contribution to SANS. PCOS in women shows similarities in characteristics to astronauts with SANS (Lunau, 2016; NASA, 2016). Presenting mostly in obese women, PCOS is often associated with a thickened RNFL, increased ICP (i.e. intracranial hypertension) and an increase in homocysteine (Zwart et al., 2015). Interestingly, PCOS was also found to associate with variations in the one-carbon metabolic pathway; possibly rendering many PCOS changes quite similar to those occurring in men with SANS (Zwart et al., 2015). Since the condition does revolve around a surplus of testosterone-like hormones in the body, its occurrence in men is conceivable (Lunau, 2016; Mohammad & Seghinsara, 2017).

In summary, long-term exposure to microgravity could enhance the effect of these genetic factors (i.e. relative to on Earth), rendering some individuals more susceptible to a wide set of ocular diseases than others. Results seen suggest that ocular issues in missions are associated with a difference in the folate– and vitamin B-12−dependent 1-carbon transfer pathway (NASA, 2016) and possibly PCOS.

1.5.4 Secondary Contributors

Secondary contributors are thought to be partially responsible for the syndrome. The main “confounding” factors include resistive exercise, high sodium intake, high cabin CO_2 levels compared to Earth(≥ 10x), and potentially, radiation (Marshall-bowman et al., 2013).

Briefly, resistive exercise is thought to impact fluid flow in microgravity. More specifically, this essential activity for bone loss, cardiovascular and musculoskeletal deconditioning prevention during spaceflight is thought to increase both IOP and ICP (Stenger et al., 2017). This is achieved by increases in mean arterial pressure (MAP), which can lead to cerebral, retinal, foveal and subarachnoid hemorrhages. Through hypertension, increases in sodium intake are also thought to contribute to SANS in a similar way. Moreover, a recent study

found IOP to increase during resistive exercise (with a higher increase in IOP under hypercapnic conditions) while an older one in which the Valsalva manoeuvre was performed (i.e. a method of slowing heart rate by exhaling through the mouth into a closed airway; Srivastav, Jamil, & Zeltser, 2005) simultaneously with resistive exercise found IOP to increase to 28 ± 9.3 mmHg, as mentioned by Mekjavic and colleagues (Mekjavic et al., 2020). Of course, this older theory would require ICP increases to be higher than those of IOP to create the hypothesized TLPD changes. Overall, it seems many studies assume increased IOP somehow contributes to SANS when in fact, its increase should be desirable to maintain TLPD.

As for CO_2 levels, the 15-20% increase found on the ISS is thought to exacerbate the effects of microgravity-induced fluid shifts. While it has been shown that CO_2 does not affect MAP itself in multiple studies (Laurie et al., 2017; Mekjavic et al., 2020), the vasodilation effect of CO_2 is largely responsible for cerebral blood flow increases (thus increasing ICP) when blood pressure is controlled for (Battisti-Charbonney, Fisher, & Duffin, 2011) and might contribute to optic disc edema. While this has been observed in some studies, others found CO_2 to have no such effect (Laurie et al., 2017). Studies in HDT have also found CO_2 to increase IOP more than increases induced by HDT alone (Laurie et al., 2017).

Last of the main confounding factors is radiation. Although not much is known about its mechanism, it is well known that radiation causes DNA mutation and tissue degeneration (Wojcik, Kini, Al Othman, Galdamez, & Lee, 2020). Terrestrially, radiation has also shown to elicit cotton wool spots through ischemia (Rose et al., 2018; Wojcik et al., 2020). As Aleci (2020) mentions in his review paper, as long as astronauts are present in low Earth orbit, they are protected by a magnetic field from solar particles events and galactic cosmic radiations (Aleci, 2020). However, long-duration spaceflight to destinations further away render astronauts susceptible to changes, especially ocular ones (Demontis et al., 2017), as the eye lacks the protection of skin like the rest of the body as well as a skull like the brain (Demontis et al., 2017).

There have also been studies that associated microgravity-induced ocular changes to heavier pre-flight body weight (Buckey, Phillips, Anderson, Chepko, & Archambault-leger, 2018) and others that suggest that it's more likely to occur in men (relative to women) with poorer cardiovascular health (Zhang & Hargens, 2017). Males typically have higher resting blood pressure (Alhawari et al., 2018) and lower IOP (Jeelani, Taklikar, Taklikar, Itagi, & Bennal, 2014) than in females. That being said, only a small percentage of astronauts have been women (Lunau, 2016) and space-induced ocular changes are not limited to men, despite popular belief (Brunstetter, 2018a). Indeed, within the small sample of women who have been on missions (i.e. 11 women in Expeditions 1-53) there were a few long-duration female astronauts with ocular changes (Brunstetter, 2018a). Amongst these changes were some extent of optic disc edema, an increase in choroidal thickness, globe flattening and refractive error shifts (Brunstetter, 2018a). These changes were, however, not within the set criteria upon which the basis of SANS is diagnosed (i.e. the disc edema was not extensive enough to meet the definition of SANS), rendering SANS a male-confined syndrome up to this day (Brunstetter, 2018a). The small sample size of women on expeditions leads to uncertainty on whether SANS is truly confined to males.

A recent finding was put forth claiming that the ONH cup volume may be associated with SANS diagnosis (with smaller changes in volume at risk of being missed). As SANS is more prevalent in long-term spaceflight, researchers have compared its prevalence in novice astronauts to the more experienced astronauts but found it to be about the same (Brunstetter, 2018a). While SANS is likely the result of a cumulative effect in microgravity, this might suggest that its development is dependent on the duration spent in space per mission rather than the number of missions overall. Finally, age could be a predisposing factor to the susceptibility of astronauts to SANS; since astronauts are usually above the age of 40. For example, hyperopic-shifts occur with age on Earth in "normal" 1-G (Irving, Machan, Lam, Hrynchak, & Lillakas, 2019; Marshall-bowman et al., 2013). This could be accelerated with reduced gravity.

In short, because of the scarcity of in-flight data and the difficulty obtaining it, the specific cause of SANS remains obscure. The exact contributions of each of these hypotheses and their underlying mechanisms need further clarification and investigation.

1.6 Terrestrial Diseases with similarities to SANS

1.6.1 Idiopathic Intracranial Hypertension

Idiopathic intracranial hypertension (IIH) is the terrestrial condition most similar to SANS (Brunstetter, 2018b; Lee et al., 2018). It is characterized by raised intracranial pressure (ICP) in the absence of an identifiable cause such as space occupying lesions (Jensen, Radojicic, & Yri, 2016). This disease leads to elevated subarachnoid pressure, which is thought to be directly transmitted from the intracranial to the intraorbital compartment through the perioptic subarachnoid space (SAS). This leads to optic nerve sheath distension and axoplasmic flow stasis resulting in axonal swelling and disc edema (Hayreh, 2016; Hingwala, Kesavadas, Thomas, Kapilamoorthy, & Sarma, 2013; Mader et al., 2011). Furthermore, elevated intrasheath pressure (i.e. of the subarachnoid space) is thought to apply an anterior force that indents the posterior sclera, resulting in posterior globe flattening, folding of the choroid and axial length shortening; explaining the hyperopic shift (Mader et al., 2011). Idiopathic intracranial hypertension is, however, not without its differences to SANS.

IIH has the common symptom of chronic significant headaches (experienced in >90% of patients) amongst other complaints, none of which have been reported by any astronaut with SANS (Brunstetter, 2018a; Lee et al., 2018; Mader et al., 2011). This is very relevant as it is the case even with exposure to higher levels of CO_2. The small increases in ICP (taken post-flight and expected to occur in-flight) are disproportionate to the significant signs of SANS (i.e. disc edema, flattening of the posterior pole, choroidal folds, and ON sheath distention; Mader et al., 2011). Moreover, the optic disc edema is usually bilateral and equal in extent when high ICP is transmitted to the ON sheath (i.e. as seen in IIH), unlike in SANS (Mader et al., 2020). Although almost all astronauts returning from long-duration missions were found to have some extent of disc edema, it seemed to usually be more prominent in one eye than the other (Mader et al.,

2020). Taken together, these findings are inconsistent with increased ICP as the etiology of SANS. The information in table 1 below concludes that SANS does not exactly mimic IIH and further demonstrates why so many researchers don't believe an increased ICP to be the sole etiology behind this astronaut-burdening syndrome.

1.6.2 Hypotony Maculopathy

Raised ICP is not the only cause of disc edema. Hypotony maculopathy (HM) is well documented to cause disc edema (i.e. papilledema), posterior globe flattening, choroidal folds and hyperopic shifts all very similar to observed changes in SANS (Costa & Arcieri, 2007). HM occurs when IOP goes below 6.5 mmHg (Thomas, Vajaranant, & Aref, 2015) resulting in over perfusion of the eye as well as IOP/ICP mismatch. It can be seen after penetrative ocular injuries or post-glaucomatous surgeries, both presenting with low IOP and the mentioned fundus signs (Costa & Arcieri, 2007).

Although hypotony maculopathy shares many of the signs seen in SANS, such a decrease in IOP has not been documented during spaceflight. After its initial spike, IOP in space usually returns slowly to baseline measurements in a compensatory fashion. A very low IOP is therefore not believed to cause SANS.

1.6.3 Malignant Hypertension

Malignant hypertension is associated with extremely high MAP and has detrimental effects on the eye (presumably through overperfusion) and other organs of the body (Steinegger, Bergin, & Guex-Crosier, 2015). Ocular abnormalities include retinal hemorrhages, exudation, macular edema, cotton wool spots (i.e. nerve fiber layer infarcts from local ischemia; Hammond, Wells, Marcus, & Prisant, 2007) and optic disc edema (Steinegger et al., 2015). In this case, ischemia leads to axoplasmic flow stasis and thus, edema. Exhibiting a flame shape along the nerve fiber layer pathway, intraretinal hemorrhages also occur when the blood-

retinal barrier is compromised (Hammond et al., 2007). That being said, due to the minimal branching of choroidal vessels and their inability to autoregulate MAP as well as the retinal blood vessels, acute increases in blood pressure usually affect the choroidal vessels (i.e. ischemia) supplying the retina more than the retina itself (Hammond et al., 2007). Table 1 summarizes the similarities and differences between SANS, IIH, HM and malignant hypertension. Green boxes indicate similarities of the diseases to SANS and red boxes the differences.

Table 1 *Summary of Observations in SANS Compared to Idiopathic Intracranial Hypertension, Hypotony Maculopathy and Malignant Hypertension*

Observations	**SANS**	**IIH**	**HM**	**Mal. Hypert.**
Optic disc edema	Present	Present	Present	Present
Blur of vision	N>D	N>D	N>D	Present
Cotton wool spots	Present	None	Present	Present
Posterior globe flattening	Present	Present	Present	None
Retinal hemorrhage	Present	Present	None	Present
Hyperopic shift	[+0.25, +1.75 D]	Present	Present	None
Thicker RNFL and choroid	Present	Present	Choroidal	None
Headache	None (mild)	Present	None	Present
Age	Adults above 35	Young	All ages (but associated with young)	Elderly
Physique	Normal-athletic	Overweight	ND	Overweight

Retinal: Choroidal folds	Retinal<Choroidal	Retinal>Choroidal	Chorioretinal	None
Affected Gender	Male only thus far	F>M	M>F	F>M
IOP	Increase then moderates	ND	<6.5 mmHg	Increased
ON distention	Present	Present	None	None
Optic nerve (ON) tortuosity	Present	Present	None	None
Ocular dominance	OD>OS	Usually bilateral	monocular>binocular	Bilateral
ICP increase	ND	ICP increased	None	Present
Association found with weight	Present	Present	ND	Present
6th nerve palsy	None	Present + Diplopia	None	None
Scotoma	Present	Present	Present	Present

ND – non-determined/ specified

N – near

D – distance

OD – right eye

OS – left eye

An interesting observation arises when looking at hypotony maculopathy (HM) and malignant hypertension. In HM, IOP is lowered and therefore the difference between it and MAP augments. As for malignant hypertension, MAP is increased, and while this is also accompanied by an increase in IOP, the discrepancy between them is still enhanced. The difference between MAP_{eye} and IOP is called ocular perfusion pressure (OPP; Kanadani et al., 2016). As an increase in MAP determines MAP at the ocular level (MAP_{eye}), both cases lead to an over perfusion of the eye. In both diseases, an observed optic disc edema accompanies this likely increased OPP. This is relevant to SANS as a relationship between it and OPP is possible. Although research is currently investigating this relationship, no conclusions can be drawn as it is a relatively new hypothesis.

1.7 Monitoring and Management

Since the discovery of SANS, it has become clear to researchers that more specific data is needed to better understand the disease and mitigate it. One immediate solution to obtain such data is in the making by Web Vision Technologies. It involves two devices that NASA can use onboard the ISS for monitoring disease progression. As it is a self-imaging retinal camera, the first would allow ophthalmologists on Earth to monitor the retina of astronauts for progressions in SANS. The other one allows for visual field testing along with many other visual tests through a “goggle-based headset” (Web Vision Technologies, 2018). Both devices might be very useful in monitoring the progression of the syndrome as time passes in space.

Another device that could potentially be used on the ISS is the ultrasound-guided lumbar puncture (USGLP) that is controlled from a distance. Since ICP has never been invasively measured onboard the ISS, Lerner and his colleagues aimed to create a “new ultrasound approach for definitive placement of an LP needle” that can be used with minimal training in microgravity (Lerner, Chima, Patel, & Parmet, 2019). However, its accuracy in relation to lumbar punctures might be a limitation.

While these devices are promising for future monitoring, SANS is currently managed by other means until an etiology can be confirmed, and treatment can be provided. Furthermore, while IOP/ICP mismatch can't be confirmed until both ICP and IOP are measured simultaneously inflight, one must remember that even if such a mismatch was confirmed, there's a good chance the ICP increase isn't large enough, the same as was found in the study that measured ICP invasively in parabolic flight (Lawley et al., 2017) to cause SANS on its own. Thus, while research attempts to find the etiology behind SANS by further investigating hypotheses, management has been through many methods including "Space Anticipation Glasses", plus lenses offered to astronauts age of 40 years and over onboard the ISS in anticipation of possible hyperopic shifts (Larkin, 2018). In addition to those, low-sodium diets have been implemented for a while now along with astronaut education (Smith, Rice, Dlouhy, & Zwart, 2013).

Since microgravity is believed to be the main etiology, its reversal through artificial gravity in space might seem like the ideal solution. Researchers have considered devices like Chibi lower-body negative pressure to reverse headward fluid shifts with the placement of a vacuum on the lower extremities, as well as thigh cuffs (Brunstetter et al., 2018). Thigh cuffs have shown efficacy in mitigating headward fluid shifts by being tied to each leg and pumping at 60 mmHg to compress the femoral vein. Finally, artificial gravity in which gravitational force is simulated by rotation was also considered (Brunstetter et al., 2018). These solutions are, however, currently inapplicable as some are expensive, big, and movement restricting while others would negatively impact the vestibular system and health of the crew (Brunstetter et al., 2018). Additionally, parameters like constant shuttle rotation would definitely lead to crew discomfort (Brunstetter et al., 2018). In short, these limitations render these devices impractical for continuous use.

1.8 Summary

The spaceflight-associated neuro-ocular syndrome is still idiopathic and one of the top barriers preventing NASA from their planned long-duration missions. As each of the analogs presently available have their limitations and since even the closest terrestrial disease to SANS seems to have a different pathophysiology, means of creating artificial gravity should be

studied further. Obtaining as many measurements as possible during missions should contribute to better understanding correlations of the syndrome's progression to time and ocular structures affected.

Furthermore, sending a greater percentage of female astronauts on missions should also contribute to understanding SANS. This would be especially beneficial if SANS really is confined to men. As for earthly-conducted experiments with analogs, there is a crucial need for a more representative sample through the inclusion of older participants in more studies. Moreover, although IOP during spaceflight is not as low as in HM and MAP not as high as in malignant hypertension (remains relatively unchanged or decreases slightly), the similarities between SANS, HM and malignant hypertension suggest a possible link between OPP and SANS. As high IOP leads to decreased perfusion and disc excavation in glaucoma, by a similar mechanism in the opposite direction one might expect a lowered or unchanged IOP relative to slightly changing ICP or MAP_{eye} to result in disc edema. Since little research has been conducted thus far on the role played by OPP in SANS, more studies are needed to explore this hypothesis further. One should also remember that a single etiology might not be the case for SANS. The various signs found in astronauts (that were decidedly named SANS for ease) might each have their own independent mechanism of action. Therefore, although convenient to try and group all signs under one umbrella, one should refrain from doing so without substantiating evidence. To conclude, as prolonged missions to Mars and other deep-space destinations are actively planned, it is increasingly important to understand the pathophysiology of the spaceflight-associated neuro-ocular syndrome.

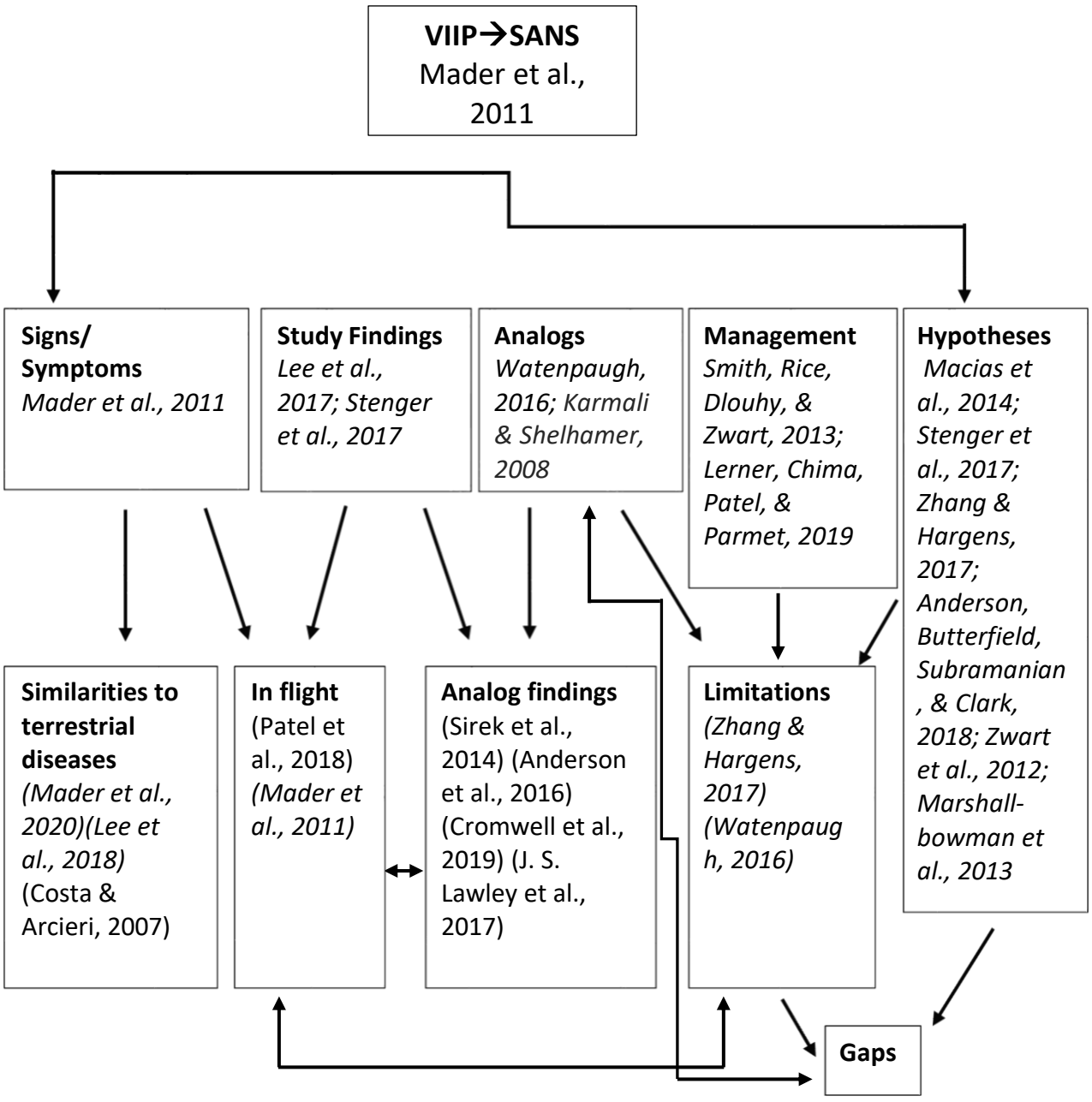

Figure 3 *A literature map on SANS.* The map illustrates the main topics most papers on SANS touch on as well as a summary of a few relevant citations under each. Although all subheadings correlate with each other in some way, the obvious ones are mapped with arrows.

Chapter 2: Ocular Perfusion Pressure

2.1 Ocular Perfusion Pressure

In the previous chapter, the main hypotheses behind the pathophysiology of SANS were briefly explained. However, there is one other possible theory that is currently gaining attention and momentum: Increased ocular perfusion pressure (OPP). Ocular perfusion pressure can be defined as the difference in pressure between the arterial and venous systems of the eye needed to maintain proper blood flow (Kim et al., 2020; Vera, Jiménez, Redondo, & García-Ramos, 2020). Inadequate blood flow to any tissue in the body impacts the blood perfusion in that area (Wang, Cull, & Fortune, 2015). Therefore, when OPP is increased, maintaining proper ocular blood flow through autoregulatory mechanisms is crucial for proper visual performance in spaceflight.

Having a lower residing pressure than arteries, veins are the more vulnerable vessels in the cardiovascular system. In order for them not to collapse, their pressure must exceed that of their surroundings: ocular venous pressure therefore should always slightly exceed IOP to maintain adequate blood flow (Van Keer, Barbosa Breda, Abegão Pinto, Stalmans, & Vandewalle, 2016). Since retinal venous pressure is considered to be approximately equal to IOP (Flammer & Konieczka, 2015; Hayreh, 2001), OPP is calculated as the difference between the mean arterial pressure of the ophthalmic artery or central retinal artery (Kostic et al., 2020; Stodtmeister et al., 2013) at the level of the eye (MAP_{eye}) and IOP (i.e. OPP= MAP_{eye}-IOP). Most studies derive MAP_{eye} from mean arterial pressure (MAP or MAP_{heart}) with the use of different

coefficients. For instance, MAP while seated is often assumed to equal 2/3 of MAP_{heart} (Kostic et al., 2020).

In cases where low ocular perfusion occurs, tissue function is compromised and leads to optic nerve pathology (i.e. in the case of abnormal perfusion pressure in the optic nerve; Wang et al., 2015). Since glaucoma generally presents itself with high IOP and/or low MAP_{eye} (Kim et al., 2020) it is associated with an overall lowering in OPP. Ischemia, visual field defects and optic disc excavation are all observed with this lowering (Leske, 2009). In contrast, based on the observations in SANS and comparison with diseases/conditions that produced disc edema there is reason to believe OPP increases could be at least partially responsible for the disc edema in SANS as opposed to the disc excavation seen in glaucoma with decreased OPP.

Malignant hypertension and hypotony maculopathy are earthly diseases in which a high OPP can be expected due to a significant increase in MAP and decrease in IOP, respectively. Optic disc edema, blurred vision and cotton wool spots are observed in both diseases while most of the other signs of SANS are distributed between them (Table 1). Relative to Earth, an increase in OPP during microgravity through either an increase in MAP or a decrease in venous drainage might cause an imbalance that could precede SANS. As this is a relatively new hypothesis, the exact mechanism of action from high OPP to SANS is unknown and one can only speculate. For instance, it is possible that this high ocular blood pressure (relative to IOP) would not only lead to a disc edema but might also damage ocular capillaries (Chua et al., 2019). In turn, this would lead to retinal hemorrhages, ischemia, choroidal edema, vision blur and possibly a scotoma. As for cotton wool spots, they are good indicators of RNFL disease. Often resulting from arterial occlusion, cotton wool spots indicate local ischemia and disruption in axoplasmic flow (as in the case of advanced retinal hypertension; Sharma & Brown, 2006). Reduced axoplasmic flow has also been shown to cause disc edema in monkeys (Hayreh, 2016). Although the expected elevation in MAP_{eye} might not be enough to compare a “chronic” SANS to advanced hypertensive retinopathy, there are similarities to be drawn between the two albeit not in this paper. As for the posterior globe flattening and hyperopic shifts found in SANS,

hypotheses thus far have deemed the IOP/ICP mismatch responsible. Moreover, since OPP = MAP_{eye} – venous pressure, understanding the effect of environmental stressors (i.e. upright vs HDT postures) on MAP_{heart} (from which MAPeye is determined) and IOP is crucial to better understanding OPP in microgravity.

2.1.1 Effects of positional changes on OPP IOP and MAP_{heart}

In the literature, different body position tilts have been used, and each obtained different findings. For instance, studies using tilts ranging between 6° and 90° HDT have shown varying changes in OPP, IOP and MAP (Lam, Wu, Wong, & Ho, 2013; Lawley et al., 2017; Lee et al., 2020; Marshall-Goebel et al., 2016). Study baseline measurements taken also varied between sitting, standing and supine. As this variation in baseline position exists, specifying which is being used is necessary. For OPP studies, both IOP and MAP must be taken into account. A recent study conducted on OPP in different HDT angles (ranging from 15° to 90° head-up tilt and -15° to -90° HDT) found MAP_{eye} to increase more than IOP (Lee et al., 2020). In just two minutes in each of these positions, this resulted in an overall increased OPP as subjects were tilted head-up to the fully head-down tilt of -90°. The short duration spent in each position probably wouldn't reflect what happens to OPP long-term on the ISS. For instance, IOP values spike within the first few hours/days of spaceflight (i.e. as was found in this study). However, they then return to pre-flight values which may or may not have been observed by staying in these tilts for longer. HDT is not a perfect analog to spaceflight, and a few days in a tilted bed will likely not reproduce the results of an equal number of days in space. Nevertheless, these findings could provide valuable data for at least the first few days in microgravity.

An older study looking at 2 minutes and 90 minutes in 7° HDT has provided "less acute" data (Kergoat & Lovasik, 2005). With a baseline and recovery position of +30° from the vertical, blood pressure increased by 16 mmHg at the end of the 90 minutes while IOP increased 3 mmHg in both durations. Furthermore, both MAP and OPP increased with time spent in the tilt

and both returned to baseline values after 2 minutes of recovery. As for IOP, it decreased below baseline during recovery. In short, IOP changes seemed to plateau at some point after 2 minutes in the tilt resulting in an overall OPP increase of 13.3 mmHg at the end of the 90 minutes. Therefore, OPP seems to increase in very short durations of HDT and in longer-lasting ones. These findings on MAP, IOP and OPP seem to be in agreement with even older studies (Kergoat & Lovasik, 1990; Linder, Trick, & Wolf, 1988).

Moreover, many studies looked at IOP separately (10 mmHg < normal IOP < 22 mmHg; Wang, Xu, Wei, & Jonas, 2018) and found it to vary in different positions. A study compared supine measurements to various tilts (i.e. 3.5 hours in each of 6°,12° and 18° HDT) in a randomized order. IOP (measured with a rebound tonometer after 3.5h) increased from the 15.7 mmHg supine baseline by about 2 mmHg with 12° HDT and about 3.5 mmHg from supine to 18° HDT (Marshall-Goebel, Mulder, et al., 2017). However, it seemed that IOP showed an increase related to both time and condition. In a second part of this study, IOP was measured in the 16 participants after having spent 30 minutes in the baseline supine position and 5 minutes in each of the following positions at random: +12°, 0°, -6°, -12°, -18°, -24° with and without lower body negative pressure (LBNP; Marshall-Goebel et al., 2017). A washout period of 10 minutes was achieved by returning back to supine before each following condition. Results found IOP to have increased approximately 1-4 mmHg with the steeper tilts accompanied by the higher increases. In summary, both parts of the study found IOP to increase as the tilts steepened overall (Marshall-Goebel, Mulder, et al., 2017). Furthermore, a study looking to compare tonometers in the sitting and supine positions found IOP to also increase for most participants in supine. Although IOP did decrease in some individuals, most either experienced no change or an increase up to 6 mmHg from sitting values after 15 minutes in each (Lam et al., 2013).

When it comes to blood pressure (70 mmHg < normal MAP < 90 mmHg; Delong & Sharma, 2019; Traum & Somers, 2007), sitting MAP has been shown to have values below that of supine measurements and higher than standing ones (Eşer, Khorshid, Yapucu Güneş, &

Demir, 2007). This has been demonstrated in a study looking at MAP after about a minute in different postures. They found systolic blood pressure (SBP) to be lowest when standing and highest in supine when comparing sitting, standing and supine MAP with each other, in that order (Eşer et al., 2007). Diastolic blood pressure (DBP), on the other hand, statistically did not change significantly. These findings are in agreement with other studies also having found SBP and DBP to increase in supine relative to these positions (Van Der Steen et al., 2000). However, in a study utilizing a 10° HDT for 30 minute in normotensive participants, no statistically significant changes were detected in blood pressure from the supine baseline measurements (London et al., 1983). This shows a probable need for a baseline position closer to upright in order to better appreciate BP changes, especially in microgravity-related studies. Moreover, a study conducted on glaucoma suspects and controls while sitting and during 10° HDT found MAP to surprisingly decrease during the tilt in the controls (Porciatti et al., 2017). This is in agreement with Lawley's findings when participants' MAP decreased from sitting to supine (Lawley et al., 2017).

Another study compared supine measurements to various tilts (i.e. 4.5 hours in each of 6°,12° and 18° HDT) in a randomized order. Conducted on nine males, MAP had a statistically significant increase from baseline in all tilts (Marshall-Goebel et al., 2016) with its largest difference at 6° HDT. Although a minimum of 5 days was left in between conditions as a washout period, statistically significant in-between tilt changes for MAP were not observed in the nine participants suggesting a possible ceiling effect. In Marshall-Goebel's study looking at IOP, MAP was also measured for the 16 participants after 3.5 hours spent in each tilt (Marshall-Goebel, Mulder, et al., 2017). Results found MAP to increase at 18° HDT. In short, MAP has been shown to increase, decrease and even remain unchanged in HDT (London et al., 1983; Siamwala, Macias, Lee, & Hargens, 2017).

2.2 Summary

Most of the abovementioned studies used the supine condition as a reference point. Since there do seem to be temporal effects and the upright posture (sitting and standing) is the most assumed position during the day, it is important to know the physiological impact of the upright position vs that of HDT: our analog for microgravity. Based on the mentioned studies comparing changes between the supine and upright positions, one can expect OPP and IOP to increase in HDT relative to the sitting position. However, the extent of observed effects in bed rest experiments and duration needed to achieve them vary between studies. Of course, baseline position, equipment choice and degree of HDT positions are also to be considered. Nevertheless, as SANS seems to have a higher prevalence in longer-duration spaceflight, a cumulative effect of chronic elevations in OPP is a plausible etiology. The following table summarizes findings of a few studies regarding OPP, IOP and MAP. Among other findings, it shows that IOP increases in larger increments when undergoing more severe tilts rather than depending on duration spent in said tilt.

***Table 2**. Literature findings on positional change*

Variable/ Conditions	*Baseline*	*Baseline Value (mmHg)*	*Duration in Baseline*	*HDT°*	*Duration in HDT/ 2nd Position*	*HDT Value (mmHg)*	*Δ Value mmHg (Position-Baseline)*
OPP **(Lee et al., 2020)**	Supine	≅ 65	5 min	45° 90°	2 min	≅ 70 ≅ 82	5 15
(Kergoat & Lovasik, 2005)	30° from vertical	61.4	<5 min	7°	2 min 90 min	69.7 74.7	8.3 13.3

IOP **(Kergoat & Lovasik, 2005)**	30° from vertical	13.7	< 5 min	7° 7°	2 min 90 min	16.7 16.6	3 3
(Lee et al., 2020)	Supine	≅ 20	5 min	45° 90°	2 min	≅ 30 ≅ 40	10 20
(Cromwell et al., 2019)	ND	12.9	ND	6°	70 days	ND	≅1-1.5
(Taibbi et al., 2016)	ND	13.78	13 days	6°	14 days 70 days	15.2 15.57	1.42 1.79
(Eklund et al., 2016)	Supine 2nd Supine	17.2 16	15min 7 min	Sitting 9°	7 min 7 min	14.5 17.5	-2.7 1.5
(Marshall-Goebel, Mulder, et al., 2017)	(Part 1) Supine (Part 2) Supine	15.7 15.3 14.7	ND<5min 30 min	12° 18° 12° 18° 24°	3.5 hrs 3.5 hrs 5 min 5 min 5 min	17.9 18.7 15.7 16.5 18.4	2.2 3.4 1 1.8 3.7
(Laurie et al., 2017)	Sit	15	1 hr	6°	1 hr	15.7	0.7
MAP_{heart} **(Eşer et al., 2007)**	Sit Stand	78 77	1 min 1 min	Stand 0°	1 min 1 min	77 81	-1 NC 4
(Marshall-Goebel et al., 2016)	Supine	73.17 75.3 70.95	4.5 hrs 4.5 hrs 4.5 hrs	6° 12° 18°	4.5 hrs 4.5 hrs 4.5 hrs	87.92 84.72 82.13	14.75 9.42 11.18

(Marshall-Goebel, Mulder, et al., 2017)	Supine	73.2 75.3 71	3 hrs 3 hrs 3 hrs	6° 12° 18°	3.5 hrs 3.5 hrs 3.5 hrs	82 81.8 84.3	8.8 6.5 13.3
(Kergoat & Lovasik, 2005)	30° from vertical	75.4	< 5 min	7°	2 min 90 min	86.4 91.4	11 16
(Lawley et al., 2017)	*Supine Upright	≅ 85 ≅ 98	ND 5 min	0° 0°	ND 5 min	≅ 85 ≅ 85	-1.85 NC -13
(Lee et al., 2020)	Supine	≅ 80	5 min	45° 90°	2 min	≅ 102 ≅ 120	≅ 22 ≅40
(O'Leary et al., 2007)	Supine	85	≈35 min	60 HUT	5 min	85.3	NC

* - parabolic flight

NC – not significant change from baseline

ND – non-determined/ specified

HUT – Head-up tilt

2.3 Rationale and Objectives

The etiology of SANS is still unknown. As most hypotheses rely on an ICP increase to precede posterior globe flattening at the very least, reliable in-flight ICP measurements are of urgency during missions. Furthermore, as ICP changes found in parabolic flight suggest increased ICP is not the main cause (Lawley et al., 2017), this thesis is dedicated to investigating OPP as a potential contributor to SANS. Although there currently isn't much literature on the direct effect of high OPP on the eye, the hypothesis of this study revolves around the possible

effects of posture on OPP, which would be expected to be different than the effect of reduced OPP seen in glaucoma. Additionally, the expected high MAP in both hypotony maculopathy and malignant hypertension (diseases with shared signs to SANS) further contributed to our hypothesis of increased OPP. IOP has been found to be higher in females over 40 than males in some studies (Jeelani et al., 2014) while MAP was found to be lower below 65 (Alhawari et al., 2018; London et al., 1983; Reckelhoff, 2001). These would both contribute to a lower OPP and could explain why SANS remains a male-confined syndrome. It therefore seems that SANS might be the result of an interaction between three pressures: OPP, IOP and ICP. The objectives of this thesis are:

1. To determine the effect of supine, 12° and 30° HDT on OPP relative to the baseline sitting position in healthy adults

2. To determine the effect of supine, 12° and 30° HDT on IOP relative to the baseline upright position in healthy adults

3. To study the effect of sex on OPP and IOP

2.4 Hypotheses

Based on previous literature, we had three hypotheses we were interested in looking into:

Hypothesis #1

H_0: OPP_{Sit} will not be affected by body position

H_1: OPP will increase with tilt angle

Hypothesis #2

H_0: IOP_{Sit} will not be affected by body position

H_1: IOP will increase with tilt angle

Hypothesis # 3

H_0: OPP and IOP will not vary with sex

H_1: OPP and IOP will vary with sex

Chapter 3

3.1 Methods and Data Analysis

3.1.1 Ethics Approval

This study has received ethics clearance from the University of Waterloo. Participants' consent was obtained after they were first informed of the study procedures.

3.1.2 Participants

Due to the COVID-19 pandemic, a total of 11 participants out of the original intended 16 were recruited from the University of Waterloo campus as well as from a database/participant pool. Recruitment was completed via posters, social media and email. Participants were given a questionnaire to determine eligibility. The following is a table depicting the inclusion and exclusion criteria of this study.

Table 3 *Participant inclusion and exclusion criteria*

Inclusion Criteria	• 18-55 years of age • Healthy
Exclusion Criteria	• No participants with a history of arterial disease, venous disease, blood clotting disorders, stroke, myocardial infarction, heart failure, heart valve disease, autonomic failure, rheumatic fever; kidney disease; liver disease; chronic inflammatory disease; diabetes mellitus; neurological disorders; severe skin sensitivities • No ocular disease or disorder; glaucoma, ocular hypertension, steroidal medication, a history of ocular trauma, chronic smokers, corneal scarring,

	pregnancy, any active ocular infection, thyroid disease, and hypersensitivity or allergy to any anesthetic. • Allergy to latex and individuals diagnosed with positional vertigo were also excluded.

3.1.3 Instrumentation and Procedures

A slit lamp pre-assessment to ensure corneal health in both eyes was performed. After this was completed (without the use of fluorescein), eligible participants were fitted with the required equipment (Patterson, 2020).Those include:

- The Transcranial Doppler ultrasound (TCD) through the Waki^{e} 1TC (Kashif, Verghese, Novak, Czosnyka, & Heldt, 2014) for middle cerebral artery (MCA) blood velocity measurements (as a means of predicting ICP noninvasively; although not validated).
- The Finapres Nova system for continuous blood pressure measurements through a finger cuff (calibrating itself through the arm cuff). It functions so that MAP at the finger is recalculated at the brachial artery/heart level. Since IOP measurements took about 3-5 minutes to obtain, MAP measures were averaged over the period of time it took to obtain these IOP values each time.

Other equipment used only by collaborators (Patterson, 2020) and not to be reported in this thesis include:

- Orcheo Lite B-scan ultrasound (on the left eye): taken every 5 minutes throughout the protocol excluding the sitting position
- Coded hemodynamic imaging (CHI) measurements; a non-contact camera-based system by which the jugular vein pressure is measured as a representative of ICP, every 5 minutes of the protocol for all positions excluding sitting.
- Phillips vascular ultrasound for left internal jugular vein measurements

- ECG for continuous heart rate measurements throughout the entire protocol
- A catheter in about half of the participants' forearms
- A nasal cannula to continuously measure expired CO_2

This experiment involved taking the average of 8 IOP measurements from the right eyes of 11 participants (6 male, 5 female) with the handheld Reichert Tono-Pen XL in 4 different positions on a tilting table: Upright, horizontal/supine, 12° HDT and 30° HDT. The IOP measurements were taken with the handheld Reichert Tono-Pen XL rather than with the Icare rebound tonometer for more accuracy and participant compliance through a lessened blinking reflex (due to the anesthetic's effect). The Tono-Pen XL readings obtain the average of four IOP measurements each time. Therefore, when possible, two sets of measurements were taken per position to obtain the average of 8 measurements in total. The Tono-pen XL is also validated for use in HDT positions whereas the validity of the rebound tonometers hasn't been given consideration. Most models require specific head positions. The limitation in number of times the anesthetic may be administered during the protocol limited the number of time points at which measurements were taken. Therefore, the experiment design did not permit for recovery measurements of IOP. Experiments were conducted one participant at a time and no pillows were used as to not attenuate cephalic fluid shifts. In order to prevent participants from sliding off the bed when tilted, participants were strapped across their feet to the tilting table in the supine and HDT portions of the experiment. Participants' corneas were re-examined using fluorescein strips and the slit lamp's cobalt blue filter at the end of the experiment. This was to scan for any corneal abrasions/ scratches caused during the experimental procedure.

All measurements during experiments (excluding IOP) were transferred through the Powerlab/16sp (AD Instruments) and collected/recorded into the Lab Chart computer program. This enabled extraction of averaged MAP_{heart} data over the period of time IOP was obtained. To determine OPP, one needs to know MAP at the eye (MAP_{eye}). MAP_{eye} can be corrected for the orthostatic gradient between the heart and the eye level by the following equation:

MAP_{eye} = MAP_{heart} + vertical distance (in cm) multiplied by a hydrostatic gradient conversion factor (0.78 mmHg/cm blood)

The conversion factor is a function of the unit's conversion from cmH_2O to mmHg (1mmHg = 1.36 cmH_2O) and the ratio of the densities of blood (1060 kg/m^3) and water (1000 kg/m^3). The pressure was added to the MAP because the head is below the heart in HDT. If it were above the heart (as is the case when sitting upright), the pressure would have been subtracted.

Thus, the angle isn't relevant when sitting. The vertical distance (h) is the same as the distance between the heart and the eye (x). So, MAP_{eye} = MAP_{heart} – vertical distance (in cm) * 0.78 when sitting. The vertical distance is calculated as follows:

$h = x \cdot \cos(a)$

where x = measured distance between heart and eyes (with a measuring tape)

a = angle

Since cos(angle) = adjacent/hypotenuse = h/x

Rearranged, $h = x \cdot \cos(a)$.

For 0° HDT, a = 90- 0= 90°

for 12° HDT, a = 90-12 = 78°

for 30° HDT, a = 90-30 = 60°

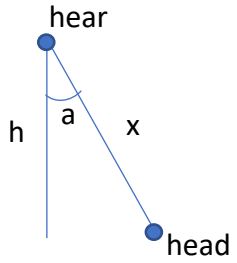

Figure 4. Variables involved in calculating mean arterial pressure of the eye during HDT

For instance, in a heart to eye distance (x) of 26 cm,

h_{12} = 26 x cos (78) = 5.4 cm

h_{30} = 26 x cos (60) = 13 cm

Therefore, h_0 (in supine) is always equal to 0.

Once MAP eye is known OPP can be calculated by subtracting the IOP from MAP_{eye}.

In our study, non-invasive ICP (nICP) using TCD was derived from continuous MAP and MCA blood flow velocity measurements averaged over a 30 heart beat estimation window using the Heldt equation (Kashif et al., 2014). The equation used was:

$$\hat{\mathrm{ICP}} = \overline{p_a(t)} - \hat{R}\overline{\hat{q}_1(t)}$$

In this equation, $p_a(t)$ is the MAP mean at the MCA level, over the 30-beat estimation window. MAP at this level was recalculated from MAP_{heart} by using the same correction factor used for OPP (i.e. $h = x \cdot \cos(\alpha)$). However, h and x here are the distance from the brachial artery to the MCA and temporal window of the skull, respectively. R represents the estimated resistance of cerebral blood vessels and is obtained through the following equation: R= MAP at MCA/ cerebral blood flow velocity. $\hat{q}1(t)$ is the mean cerebral blood flow velocity of the MCA throughout our estimation window. Data collection and analysis of nICP were provided by collaborator Courtney Patterson (Patterson, 2020).

3.1.4 Experimental Design

After five minutes of sitting upright, an anesthetic topical drop of proparacaine hydrochloride 0.5% (DROP-TAINER, Alcon Laboratories, Inc.) was instilled in each of the participant's right eyes (i.e. as a local anesthetic) and a baseline measurement of IOP was taken. Participants then laid horizontally on a table, and after at least 5-minutes of lying in that position, baseline B-Scan ultrasound, CHI, TCD and supine tonometry measurements were taken. The table was then gently tilted into a head-down tilt position of 12° (from horizontal). They remained in this position for 30 minutes, with ultrasound, CHI and TCD being taken every 5 minutes and tonometry measures being completed (after instilling another anesthetic drop in the right eye) at the end of the 30 minutes in this position. At the end of the 30 minutes, the table on which the participants were laying was further tilted to 30° (from horizontal). They remained in this position for another 30 minutes, with ultrasound, CHI and TCD being taken every 5 minutes and tonometry (after instilling a third anesthetic drop in the right eye) measures being completed

only at the end of the duration. There were about 10 minutes between TCD and IOP measurements each time and a target was provided with each use of the Tono-Pen XL. Although collaborators had the study proceed by returning participants to the supine tilt for another 30 minutes (with all abovementioned measurements continuing every 5 minutes), the protocol for our study was completed at the end of the 30° HDT.

3.1.5 Data Analysis

A minimum sample size of 14 participants was estimated based on an alpha of 0.05, a 0.80 1- β and an IOP effect size of 3 mmHg (based on difference between the right and left eye that is considered significant) and standard deviation of 2.8. In this study, a mixed/split plot repeated measures ANOVA was used to analyze the data. Outcome variables were OPP, IOP, MAP_{heart}, MAP_{eye}, nICP (derived from TCD measurements) and translaminar pressure difference (TLPD). Linear regressions were conducted to determine OPP interactions with ICP. The two independent variables were bed tilt (within-subject variable) and sex (between-subject variable). The main relationship determined was that between HDT and OPP. Further analysis was conducted to determine the effect of sex on all dependent variables.

Chapter 4 Results

Six males and five females were recruited. One female dropped out from feeling nauseous at the last condition and was excluded from the study for data analysis purposes. This leaves the total of six males and four females discussed here on out. Participants' ages ranged between 19-41 years (*M*=25.7 ± 6.8)

Table 4 Participant Characteristics

Participant Characteristics	Male (n=6)	Female (n=4)	Mean of Male +Female
• Weight (kg)	71.3 ± 8.2	55.3 ± 4.9	63.3 ± 10.7
• Height (cm)	169.8 ± 7.8	157 ± 6.8	163.4 ± 10.2
• Age	27.5 ± 8.5	23 ± 1.4	25.7 ± 6.8

4.1 OPP as a Function of Tilt and Sex

As shown in figure 5, OPP averages increases with tilt angle for both sexes. From sitting to 30° HDT, OPP increased about 29 mmHg in males and 35 mmHg in females with the male to female ratio being 6:4. Using SPSS to conduct a mixed ANOVA, there was a statistically significant main effect of tilt, $F(3,24)= 37.71$, $P< 0.001$, with both OPP_{Sit} ($M= 55.26$), OPP_{Supine} ($M= 77.05$), OPP_{12} ($M=75.97$) and OPP_{30} ($M= 86.70$) all being significantly different from each

other statistically, with the exception of OPP_{supine} with OPP_{12} and OPP_{12} with OPP_{30}. However, there was not a statistically significant main effect of sex, $F(1,8)= 1.47$, $P= 0.978$ nor a statistically significant interaction between sex and tilt, $F(3,24)= 1.17$, $P = 0.342$. With this exhibited pattern comes the ability to reject the first null hypothesis stating that OPP_{Sit} will not be significantly lower than following tilts statistically. However, we could not reject the third null hypothesis stating that sex will not significantly impact OPP statistically.

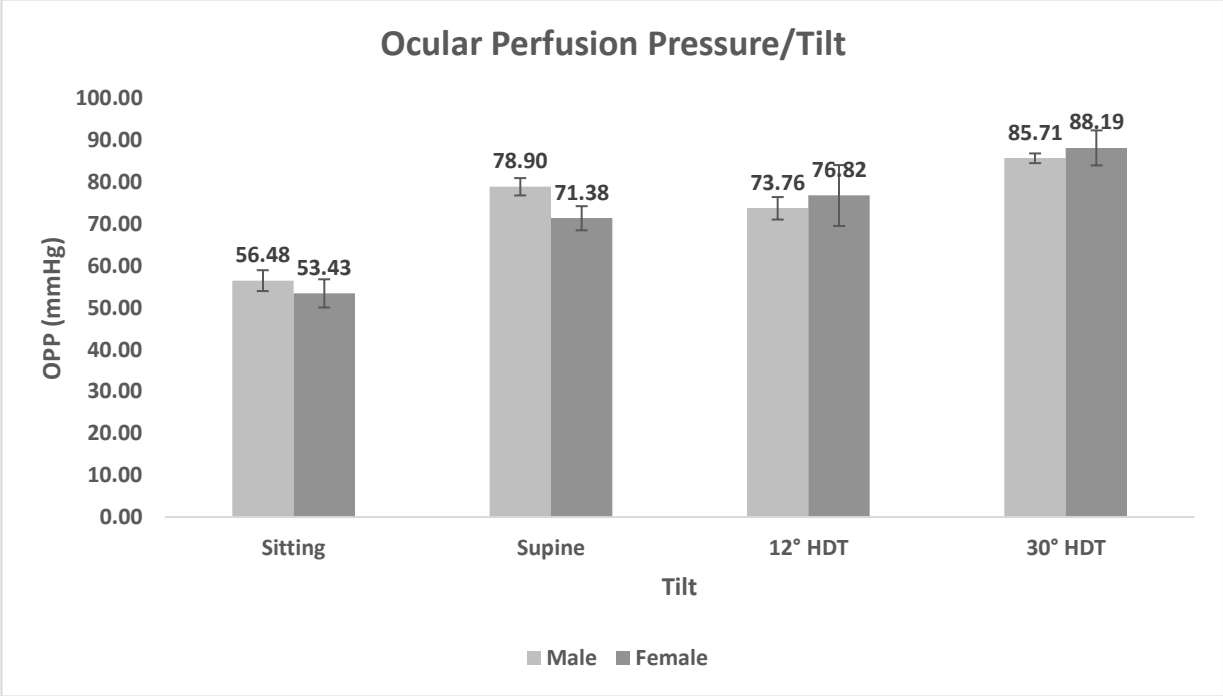

Figure 5 The impact of tilt and sex on OPP showing averages of both sexes and their standard error of the mean.

Figure 5.1 demonstrates the data of individual participants across tilts with shades of blue representing males and shades of pink representing females. A visible increase (along with a participant's outlier in 12° HDT) is also illustrated. This graph makes it apparent that all participants (with the exception of OPP 1) exhibited the same pattern with their OPP lowest when seated and highest in the 30° HDT.

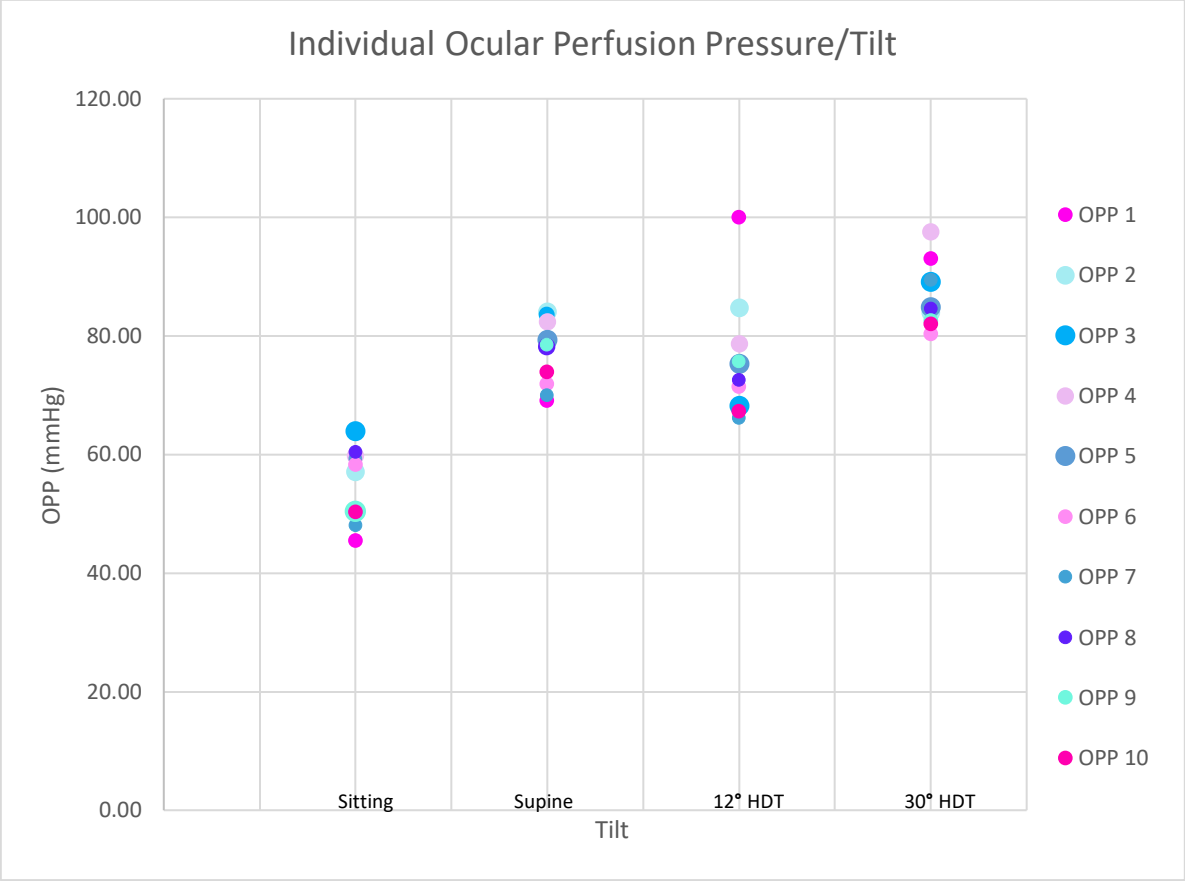

Figure 5.1: Individual ocular perfusion pressures per tilt and color coded by sex for all ten participants. Due to the presence of some overlapping OPP values, not all 10 points are distinctly visible for each tilt.

4.2 IOP as a Function of Tilt and Sex

As shown in figure 6, IOP increases are approximately linear for both sexes across tilts reaching its peak at the 30° HDT. Female IOP is consistently slightly higher than that of males throughout the experiment, albeit this was not statistically significant. IOP increased by 9

mmHg in males and 7 mmHg in females from the start of the experiment to its ending, with the male to female ratio being 6:4. Using SPSS to conduct a mixed ANOVA, there was a statistically significant main effect of tilt, $F(3,24)= 41.45$, $P< 0.001$, with IOP_{Sit} ($M= 14.17$), IOP_{supine} ($M= 17.13$), IOP_{12} ($M= 19.50$) and IOP_{30} ($M= 22.21$) all being significantly different from each other statistically, with the exception of IOP_{supine} and IOP_{12} relative to one another. There was not a statistically significant main effect of sex, $F(1,8)= 1.26$, $P= 0.294$ nor a statistically significant interaction between sex and tilt, $F(3,24)= 0.54$, $P = 0.657$. With these findings in mind, we could reject our second null hypothesis stating that IOP_{Sit} will not be significantly lower than following tilts statistically. However, our third null hypothesis stating that sex does not significantly impact IOP (statistically) could not be rejected.

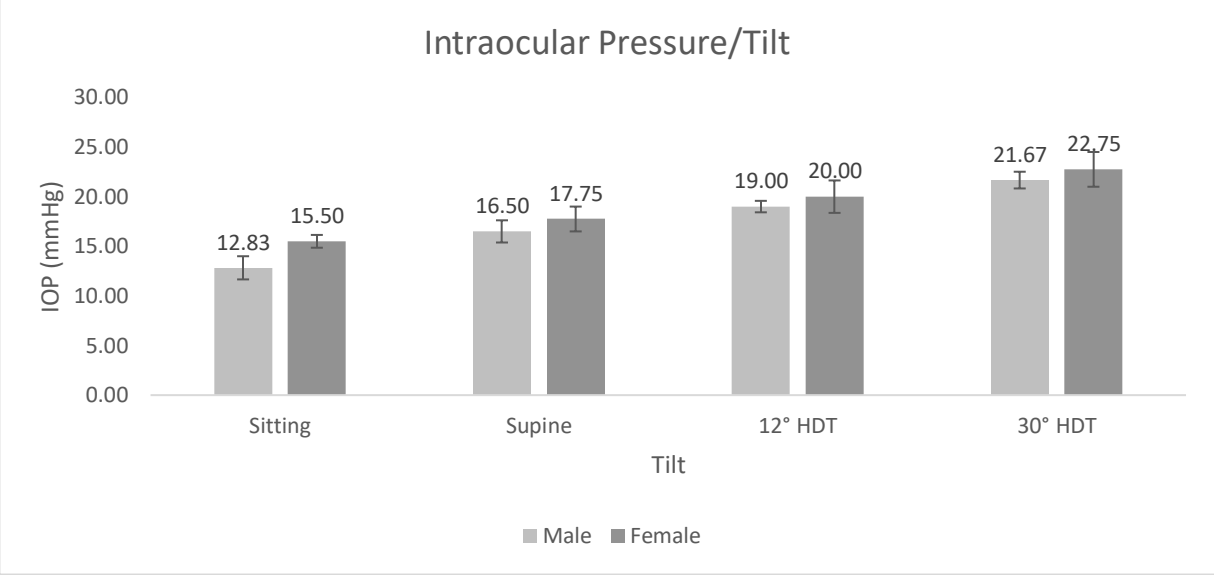

Figure 6 The impact of tilt and sex on IOP showing averages of both sexes and their standard error of the mean.

Figure 6.1 shows individual IOP data of all ten participants. With a positive correlation for most participants across tilts/positions, this pattern is in agreement with the literature on IOP in HDT.

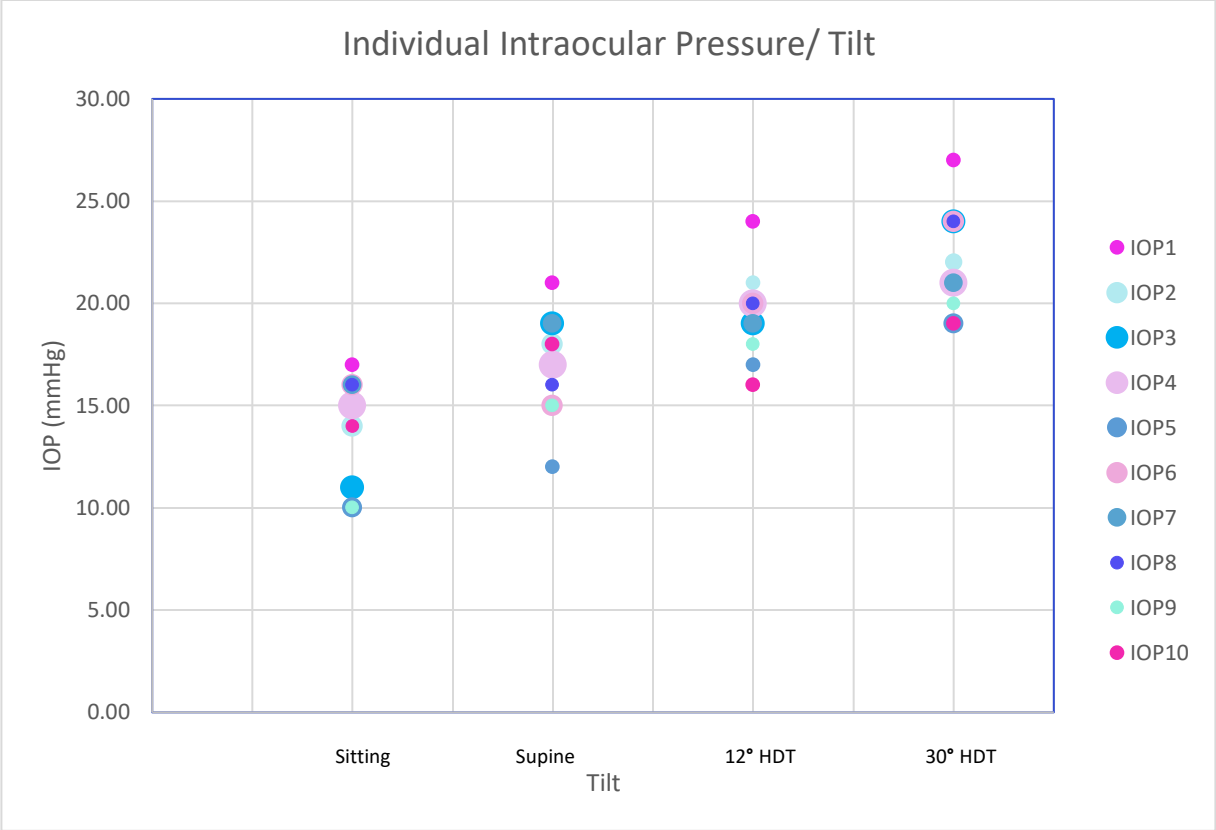

Figure 6.1 Intraocular pressure per tilt and color coded by sex for all ten participants. Due to the presence of some overlapping IOP values, not all 10 points are distinctly visible for each tilt.

4.3 MAP_{HEART} AS A FUNCTION OF TILT AND SEX

Figure 7 demonstrates the average MAP_{heart} of males and females across tilts with a 6:4 male to female ratio. No statistically significant differences were found in MAP_{heart} across all conditions. It is worth noting that males tend to have a higher resting MAP_{heart} than females (Alhawari et al., 2018; Reckelhoff, 2001), as reaffirmed in the graph below (although this is not statistically significant). Using SPSS to conduct a mixed ANOVA, there was not a statistically significant main effect of tilt, $F(3,24)= 1.11$, $P= 0.366$, with $MAPheart_{Sit}$ ($M= 94.89$), $MAPheart_{supine}$ ($M= 93.60$), $MAPheart_{12}$ ($M= 90.65$) and $MAPheart_{30}$ ($M= 96.35$) all being not significantly different from each other statistically.

Additionally, there wasn't a statistically significant main effect of sex, $F(1,8)= 0.23$, $P= 0.644$ nor a statistically significant interaction between sex and tilt, $F(3,24)= 1.26$, $P = 0.31$. Figure 7.1 shows MAP_{heart} data points for each participant individually including the outlier at the 12° HDT.

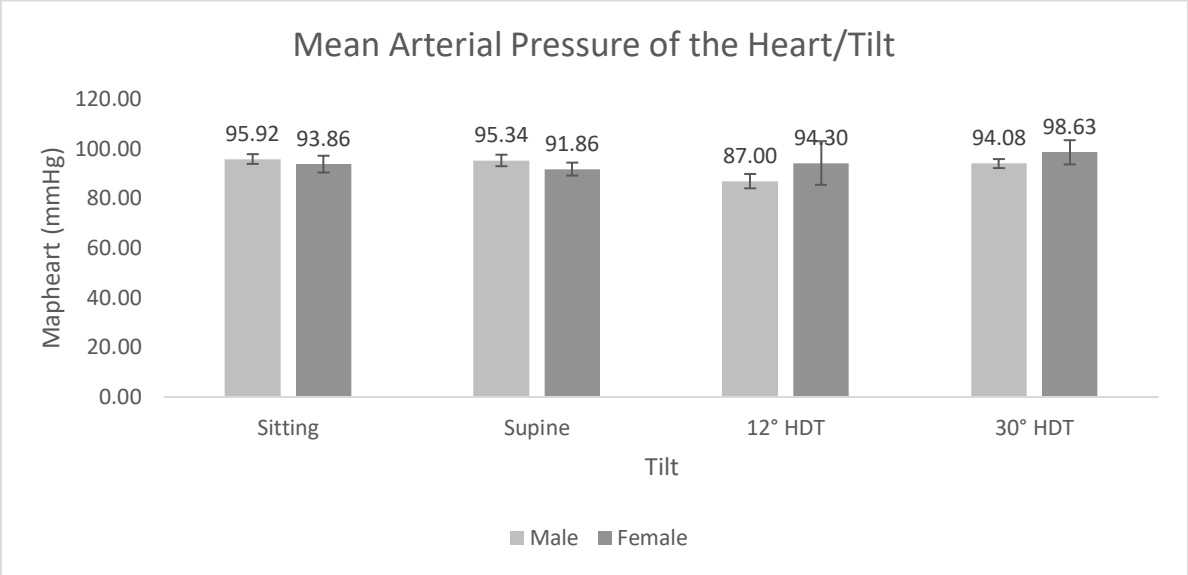

Figure 7 The impact of tilt and sex on MAP_{heart} showing averages of both sexes and their standard error of the mean.

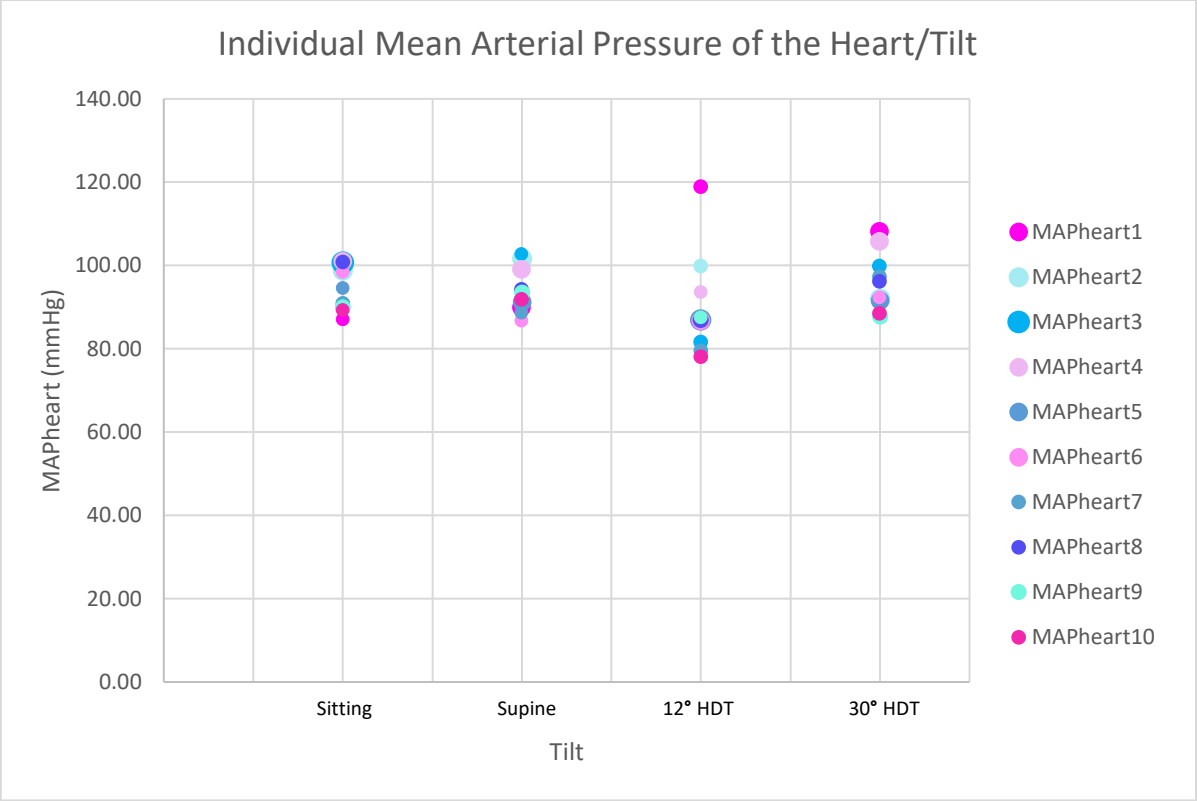

Figure 7.1 Individual mean arterial pressure of the heart per tilt and color coded by sex for all ten participants. Due to the presence of some overlapping MAP_{heart} values, not all 10 points are distinctly visible for each tilt.

4.4 MAP_{EYE} AS A FUNCTION OF TILT AND SEX

Figure 8 shows male and female MAP_{eye} averages. Overall, MAP_{eye} increases across tilts. From sitting to 30° HDT, MAP_{eye} increased 38 mmHg in males and 42 mmHg in females, with a 6:4 male to female ratio. Using SPSS to conduct a mixed ANOVA, there was a statistically significant main effect of tilt, $F(3,24)= 50.94$, $P< 0.001$, with $MAPeye_{Sit}$ ($M= 69.24$), $MAPeye_{supine}$ ($M= 93.95$), $MAPeye_{12}$ ($M= 95.30$) and $MAPeye_{30}$ ($M= 108.83$) all being significantly different from one another statistically with the exception of $MAPeye_{supine}$ with $MAPeye_{12}$. However, there was not a statistically significant main effect of sex, $F(1,8)=$

0.266 , *P*= 0.620 nor a statistically significant interaction between sex and tilt, *F*(3,24)= 0.96, *P* = 0.427. Figure 8.1 shows individual MAP_{eye} data points for each participant.

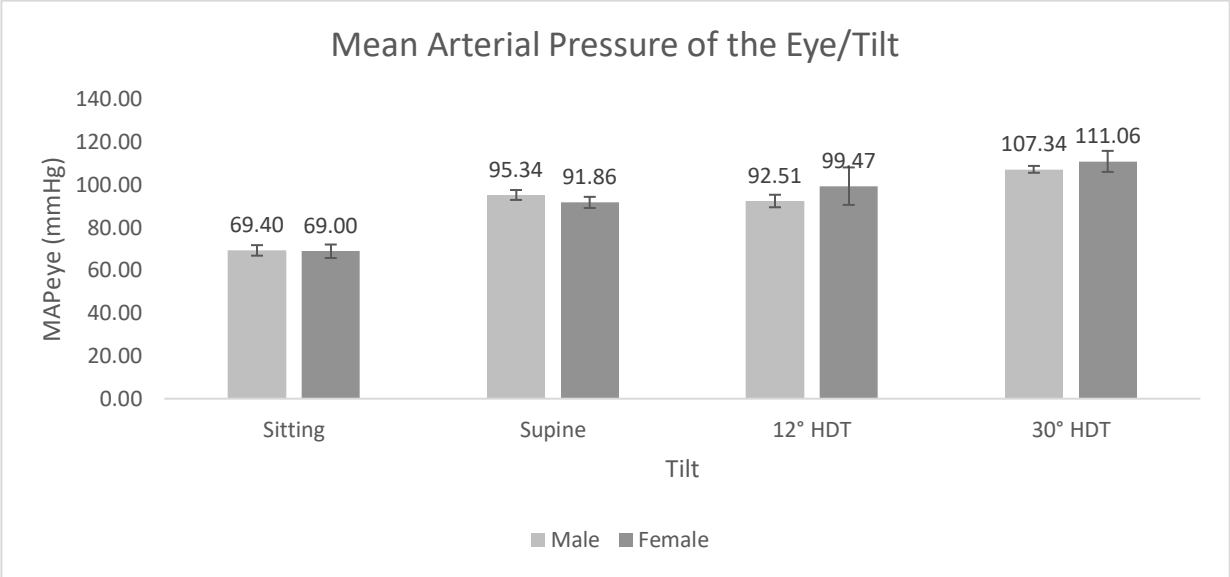

Figure 8 The impact of tilt and sex on MAP_{eye} showing averages of both sexes and their standard error of the mean.

In figure 8.1 on MAP_{eye}, a participant's outlier is seen in 12° HDT. Values were considered outliers when outside of quartile range.

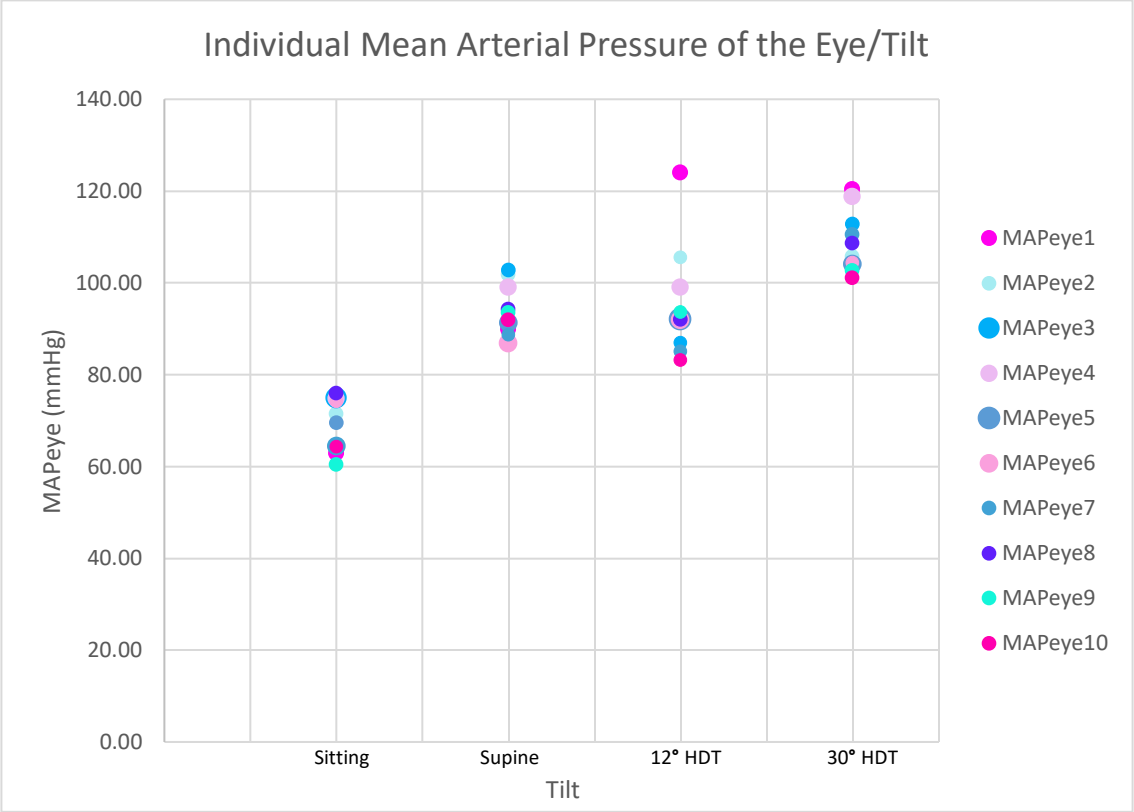

Figure 8.1 Individual mean arterial pressure of the eye per tilt and color coded by sex for all ten participants. Due to the presence of some overlapping MAP_{eye} values, not all 10 points are distinctly visible for each tilt.

4.5 ICP as a Function of Tilt and Sex

Figure 9 demonstrates the effect sex on ICP from the supine position to 30° HDT. ICP values of participants were measured and provided by collaborators (Patterson, 2020). While

male ICP consistently increases reaching its peak at the last tilt, females exhibit a sharp U-shaped trend with their ICP also being highest at the last tilt. Albeit not statistically significant, it is also apparent that females are affected by these posture changes more dramatically than males, with a 5:4 male to female ratio. Using SPSS to conduct a mixed ANOVA, there was a statistically significant main effect of tilt, *F(2,14)*= 8.41 , *P*= 0.004 , with ICP_{12} (*M*= 15.93) and ICP_{30} (*M*= 30.27) significantly differing from one another statistically. However, ICP_{Supine} (*M*= 18.20) was not significantly different from either ICP_{12} or ICP_{30} statistically. Additionally, there was not a statistically significant main effect of sex, *F*(1,7)= 0.99 , *P*= 0.353 but a statistically significant interaction between sex and tilt was present, *F*(2,14)= 5.03, *P* = 0.023.

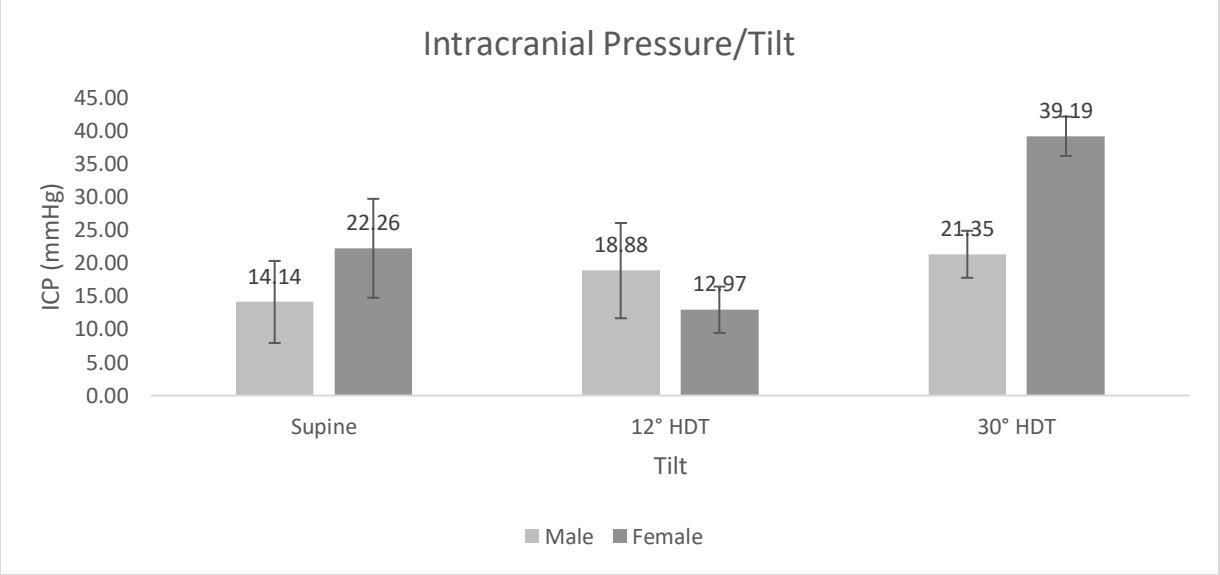

Figure 9.1 The impact of tilt and sex on ICP showing averages of both sexes and their standard error of the mean.

Figure 9.1 shows that data of males and females combined are quite variable. Overall, ICP_{supine} and ICP_{12} plateau before increasing at the last tilt. Moreover, figure 9.1 shows that although ICP in the last tilt was higher than in supine, the 12° HDT was not also higher than our supine baseline.

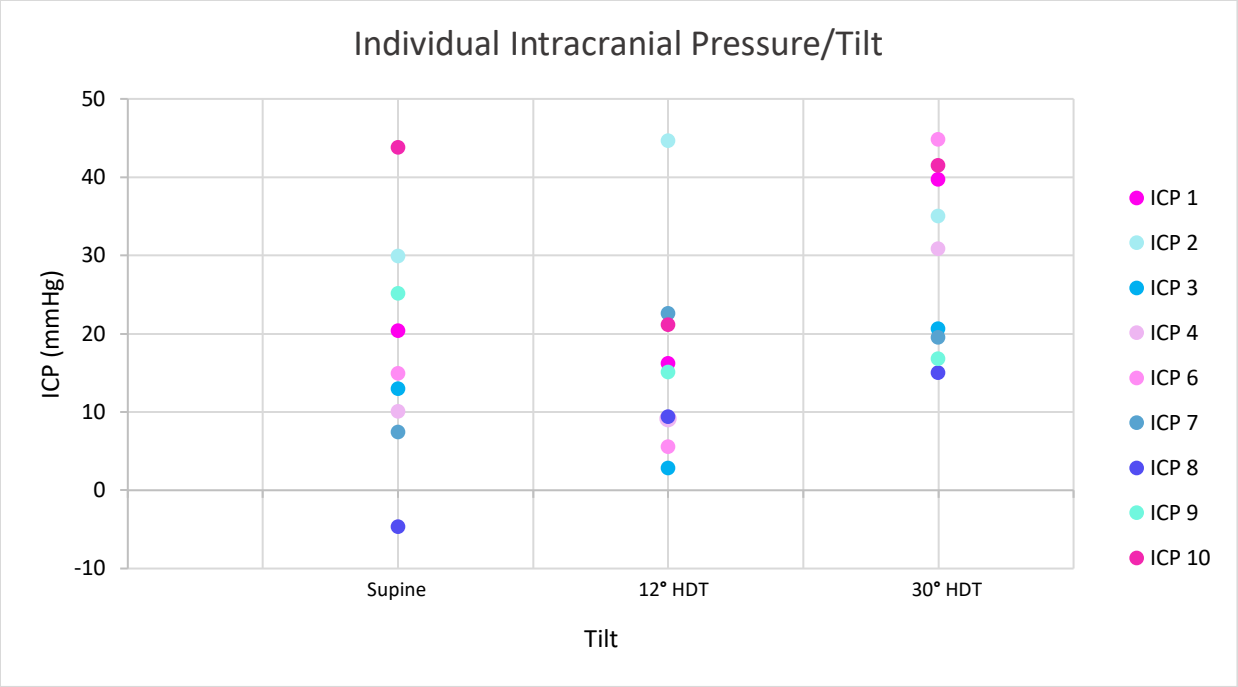

Figure 9.1 Individual intracranial pressures per tilt and color coded by sex for all nine participants. Due to the presence of some overlapping ICP values, not all 9 points are distinctly visible for each tilt.

4.6 Summary

As seen in the results above, our first and second null hypotheses were successfully rejected while the third was not. For comparison, figure 10 illustrates the trends (male and female combined) for the three pressures of interest in this study. Possible TLPD changes (i.e. TLPD=IOP-ICP/thickness of lamina cribrosa; Price, Harris, & Mathew, 2019) across three bed tilts can also be determined from this graph. While we did not measure the thickness of the lamina cribrosa, it is expected to remain constant across conditions rendering any changes in IOP and ICP responsible for TLPD variations. Starting out relatively equal, IOP then surpasses ICP at the end of 12° HDT by 4 mmHg. At the end of the more extreme 30° HDT, the TLPD at the lamina cribrosa is possibly compromised as ICP surpasses IOP by 7 mmHg. Using SPSS to conduct a mixed ANOVA on TLPD, there was a statistically significant main effect of tilt, $F(2,14)= 6.08$, $P=$

0.013 , with $TLPD_{12}$ (*M*= 3.41) and $TLPD_{30}$ (*M*= -6.83) significantly differing from one another statistically. However, $TLPD_{Supine}$ (*M*= -0.19) was not significantly different from either $TLPD_{12}$ or $TLPD_{30}$ statistically. Additionally, there was not a statistically significant main effect of sex, *F*(1,7)= 0.78 , *P*= 0.405 but a statistically significant interaction between sex and tilt was present, *F*(2,14)= 6.39, *P* = 0.011. Lastly, reflecting pressure at the ophthalmic artery, OPP might have a minimal non-obvious interaction with ICP as seen in figure 11.

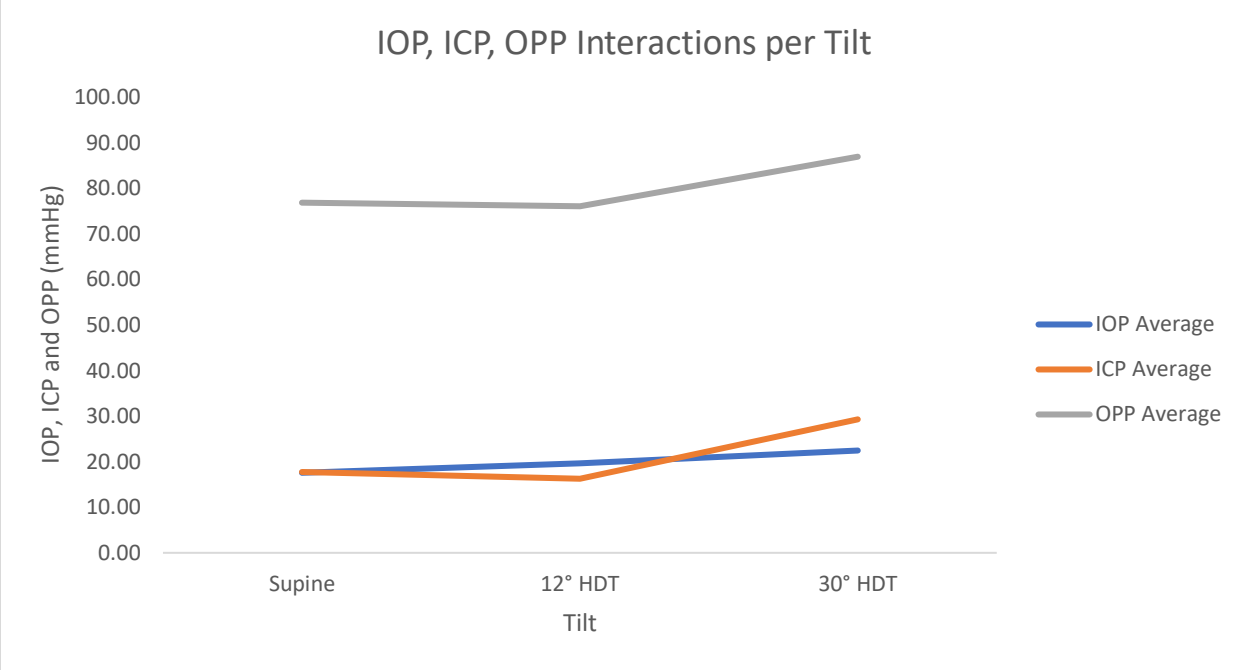

Figure 10 Relationship between intracranial pressure, ocular perfusion pressure and intraocular pressure across tilts. Data of the same nine participants in ICP are demonstrated for OPP and IOP.

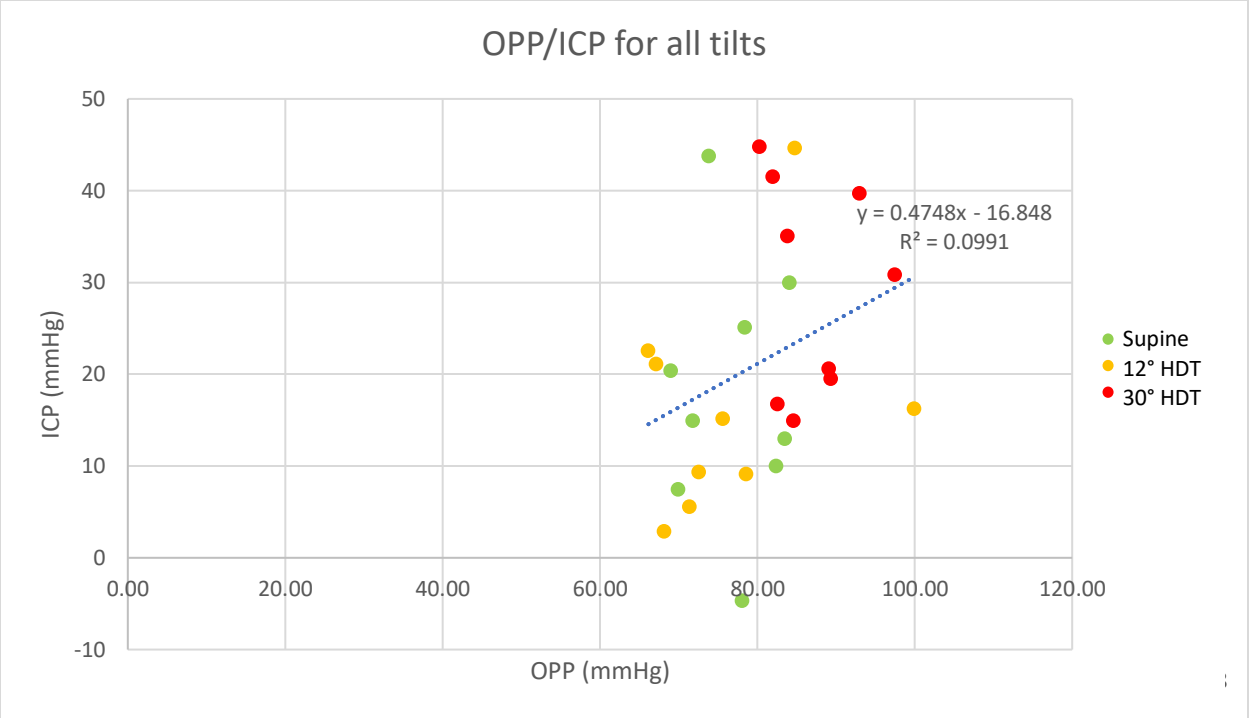

Figure 11 A linear regression for OPP and ICP in three tilts. Data of the same nine participants in ICP are demonstrated for OPP.

Chapter 5 Discussion

5.1 Objective 1: The Effect of HDT on OPP

This study's main objective was to determine the effect of our HDT microgravity analogs on OPP in healthy adults. In hopes of better understanding SANS, OPP was investigated in the most assumed position during the day and compared to its values during various tilts: supine, 12° and 30° HDT, respectively.

Relative to baseline, overall our results showed OPP to increase linearly with increased tilt, similar to what was hypothesized. This increase in OPP was the result of MAP_{eye} increasing more than IOP and across conditions. An increase in MAP_{eye} was present despite MAP_{heart} not changing significantly across any of the positions statistically. Furthermore, the results suggest that MAP_{eye} is the main influencer of OPP due to the large values of blood pressure, and thus the increments in which it changes, relative to IOP. The contribution of MAP_{eye} to OPP is also seen in outliers as the outlier in MAP_{eye} was carried onto OPP data. Although no statistically significant tilt-sex interactions were present upon analysis, figure 5 shows OPP to be higher in males in the first two tilts and higher in females in the last two.

Our OPP increases are consistent with previous findings in the literature albeit more pronounced (Hélène Kergoat & Lovasik, 2005). More specifically, from baseline, OPP increased by 21.8 mmHg in supine, 20.7 mmHg in 12° HDT, and 30.8 mmHg in 30° HDT. While it is unknown which of these tilts is most representative of spaceflight occurrences, these OPP increases might be enough to compromise local autoregulation especially over an extended duration.

On Earth, when autoregulation is intact, ocular tissues are expected to maintain their blood flow in response to OPP changes so long as OPP remains within 30 to 70 mmHg (Schmidl, Garhofer, & Schmetterer, 2011). Values of OPP above or below that range result in a compromised autoregulation in which blood flow is no longer maintained. An example of successful autoregulation is observed in OPP increases accompanying the supine posture. In a healthy scenario, retinal arterial vasoconstriction occurs to maintain normal blood flow despite the increase (Alzughaibi, 2015). However, OPP in our study surpassed 70 mmHg in the supine posture. Should these values be maintained throughout our 8 hours of sleep (i.e. assuming pillows don't attenuate OPP values and OPP increases are maintained throughout the night), this demonstrates our eyes' capacity to autoregulate values above 70 mmHg for 8 hours a day. It is conceivable that values much higher than 70 mmHg (as those observed in our more extreme 30° HDT) won't be tolerable for as long. Autoregulation is also thought to be compromised with an IOP value higher than 27-30 mmHg or a 30-40% increase in MAP_{heart} (Alzughaibi, 2015), none of which occurred in our study. However, MAP_{eye} did experience a 36-57% increase across tilts and OPP surpassed the 30-70 mmHg range in which autoregulation is presumably intact. As for the optic disc, it has been shown to have a large autoregulatory capacity in the presence of OPP changes.

A study looking at autoregulation during isometric exercises found the optic disc's blood flow to not change until OPP increased by 34% from baseline (Schmidl et al., 2011). Autoregulation was also still intact in these healthy subjects when OPP was lowered through an increase in IOP that reached 40-45 mmHg (Schmidl et al., 2011). As our OPP values surpassed a 34% increase in all positions following baseline, this suggests a compromised autoregulation at the optic disc (assuming HDT yields similar results as exercise) and might contribute to the characteristic disc edema in SANS when maintained for long durations of spaceflight. It is even possible that the 30-70 mmHg range reduces when these OPP increases persist in long-term spaceflight. All that being said, it's important to remember that OPP derived in studies might not be equal to its true value at the optic nerve (Yun et al., 2020).

5.2 Objective 2: The Effect of HDT on IOP

5.2.1 IOP in HDT

Our second objective was to determine the effect of our HDT microgravity analogs on IOP in healthy adults. Relative to baseline, overall our results showed IOP to increase with increased tilt, similar to what was hypothesized. The pattern of increasing IOP across tilts suggest that IOP would probably require longer than an hour to plateau or decrease.

5.2.1.1 IOP/ICP mismatch

As IOP also interacts with ICP to potentially contribute to SANS via the lamina cribrosa, ICP was measured (Patterson, 2020) in the last three conditions using supine as its baseline. As mentioned in chapter 1, IOP is usually slightly higher than ICP thereby maintaining a positive pressure gradient at the lamina cribrosa. Should ICP surpass IOP values, the translaminar pressure difference would decrease and cause fundus pathologies. While it is only in the 30° HDT that ICP reached "abnormal" values, our presumably healthy females surprisingly started out with hypertensive values (i.e. $\geq$ 20 mmHg; Rangel-Castillo, Gopinath, & Robertson, 2008) in the baseline position as well, possibly contributing to the slight IOP/ICP mismatch (figure 10) in supine. These high ICP values might have also led to the non-statistically significant difference between baseline ICP and tilts as well as baseline TLPD (TLPD= IOP-ICP/ lamina cribrosa thickness) and tilts. This non-statistically significant difference in ICP between baseline and 30° HDT was however due to an almost statistically significant *P* value of 0.057 which might have been statistically significant with a larger sample size. It is also likely that TLPD would have decreased to a statistically significant extent in 30° HDT should baseline have been an upright position. While many studies in HDT have found ICP to increase from baseline to likely decrease TLPD, the resulting ICP values were not pathologically elevated. In our study, however, both a compromised TLPD and large ICP increases were present at the last tilt. Either way, it has been suggested that even a small increase in ICP or lack of decrease with upright posture could remodel the eye in astronauts when chronic (Lawley et al., 2017). There are also individual

anatomical differences in lamina cribrosa stiffness that could explain the differences in susceptibility between astronauts during missions. A thicker lamina cribrosa reduces the stress caused by changes in the translaminar pressure gradient by spreading it over a greater distance (Lee et al., 2015).

To summarize, OPP, ICP or some combination of both could lead to many of the signs of SANS including retinal hemorrhages, cotton wool spots and disc edema. Posterior globe flattening, choroidal folds and hyperopic shifts could be explained by a possible IOP/ICP mismatch such as that observed at our last tilt. As IOP/ICP differences in the literature were 2.8 mmHg on average (Siaudvytyte et al., 2015), the 10.24 decrease in TLPD observed between 12° HDT and 30° HDT might contribute to SANS by compromising TLPD (assuming lamina cribrosa thickness is unchanged throughout conditions). In short, with IOP values likely returning to baseline in long-term spaceflight, increases in ICP and OPP (caused by MAP_{eye} increases in some astronauts) might largely contribute to SANS along with the previously mentioned secondary factors. While the similar pattern exhibited by OPP and ICP in figure 10 is likely due to their common extraction from blood pressure, the possibility that OPP and ICP mostly act independently is supported by our low coefficient seen in figure 11. Of course, these findings are acute and true ICP values in space are not known.

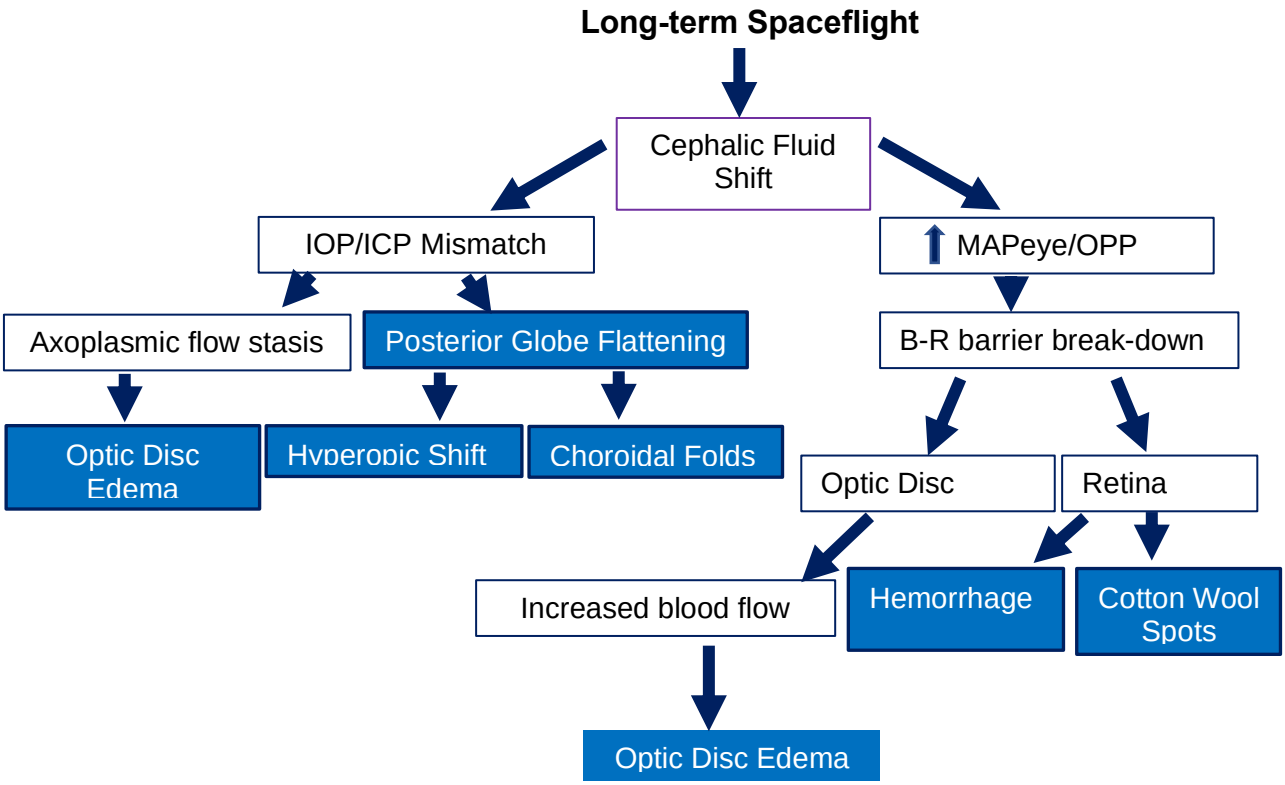

Figure 12 The role of OPP and IOP/ICP mismatch in the mechanism of SANS

5.3 Objective 3: The effect of Sex on OPP and IOP

The third objective of this thesis was to study the effect of sex on OPP and IOP. Results of our experiment showed sex to not have a statistically significant main effect on either. This was also true for all other outcome variables, including ICP, MAP_{heart} and MAP_{eye}. Given that sex differences have been observed in MAP_{heart} (Alhawari et al., 2018) and glaucoma is more prevalent in females (Vajaranant, Nayak, Wilensky, & Joslin, 2010), we expect that this non-statistically significant difference is due to the small sample size of each sex relative to the effect size and variability. This reasoning behind non-statistically significant sex effects is further supported as ICP in females seemed to be affected by posture changes more dramatically than in males as observed in figure 9. Moreover, the lesser degree of SANS signs found in female astronauts could be the result of individual factors discussed in the first chapter and/or the

lower resting blood pressure and higher IOP females tend to have relative to males (Siamwala et al., 2017). This lesser MAP and higher IOP would mean a lower OPP than males should this inter-sex difference be present in low-gravity conditions also. We suggest OPP increases might reach a threshold in microgravity after which autoregulation is compromised. With a lower OPP at baseline in females, this threshold would be more readily reached by male astronauts thus explaining their greater extent of signs. Albeit not occurring in a statistically significant way in our small sample, this blood pressure and IOP difference between sexes at baseline was present with IOP consistently higher in females throughout the experiment. It is also worth noting that while sex had no statistically significant effect, it was interesting that female OPP was higher than in males in the last two tilts. Of course, more female astronauts on long-duration missions are needed in order to determine if SANS truly is more prevalent in males.

5.4 Management

Over time, the diet of astronauts has been controlled, reading glasses provided and continuous monitoring during missions implemented. The lower body negative pressure device is a solution that directly addresses cephalic fluid shifts yet is inconvenient for continuous wear. On Earth, it is clear that healthy individuals can handle 8 hours of cephalic fluid shifts and OPP changes during sleep without complications arising throughout the rest of their day. As each day in space results in approximately 16 hours more of these shifts towards the head, it is conceivable that continuous wear of the lower body negative pressure device is not necessary, and its intermittent use would suffice instead. However, OPP increases in spaceflight might not be equal to those in the supine position at night on Earth. If OPP is indeed compromised after a 34% increase from baseline as suggested (Schmidl et al., 2011), our findings propose this compromise might be the case during spaceflight. Therefore, there is need for more studies on OPP changes during HDT looking at the ocular system's capacity to accommodate increases in OPP with and without lower body negative pressure.

Chapter 6 Limitations and Future Directions

To my knowledge, our study is one of the few looking at the impact of head-down tilt on OPP. Instead of using the equation that roughly estimates OPP during various conditions (i.e. OPP_{Sit}= 2/3 MAP-IOP), we determined MAP_{eye} more accurately by using the distance between each participants heart and eye. We took the average of 8 IOP measurements instead of the usual 4 given by the Tono-Pen XL. As SANS is male confined thus far, our study's inclusiveness of both males and females attempted to better understand the effect simulated microgravity has on both sexes. Furthermore, our employed tilts have been shown to reflect cardiovascular, ocular and intracranial changes occurring in microgravity well. However, our study also had limitations.

Although all of our participants were healthy, most were under the age of 30. Therefore, there is a limitation in the comparisons that could be drawn between them and astronauts. Our sample size was also reduced from 16 to 11 participants due to the COVID-19 pandemic and further to 10 participants (i.e. for some analysis) due to one participant's drop out at the last tilt. This smaller sample size also resulted in an inequality between the number of males and females in the study.

Another limitation is in the possible overestimation of blood pressure as it is recalculated from the finger cuff to the brachial artery (Patterson, 2020). This overestimation is also true for MAP at the MCA level (Rasulo et al., 2017) and presumably would be at the eye also. An overestimated MAP would then lead to an overestimated OPP. As for nICP, it is believed to be underestimated with TCD measurements (Koskinen et al., 2017). Furthermore, as ICP measures were not gold standard, compromised accuracy is seen in one of our participants with a negative value in the supine position likely stemming from a value closer to zero. The relatively short duration spent in each position makes it harder to draw inferences that are comparable

to longer duration spaceflight. Our study's design did not allow for IOP measurements on both eyes, which could have provided insight into binocular differences seen in SANS nor does it have recovery from tilt measures. IOP measurements might have been inaccurate due to the following reasons:

1. Some participants had a persistent blinking reflex even after instilling anesthetic drops. The high and increasing IOP values might be subject to overestimation as a result of participants' straining and blinking. In turn, this might underestimate true OPP values.

2. We were not able to obtain all eight IOP measurements from all participants which likely renders IOP averages (and therefore OPP values) inexact/more variable.

3. Circadian variations in IOP are generally about 5 to 8 mm Hg from morning to mid-day and afternoon (Weinreb et al., 2015). Our participants were not brought in at the same time every day with some having measurements taken in the morning and others finishing around 5:00 PM.

4. Corneal thickness was not taken into account when measuring IOP and has been shown to over- and underestimate IOP in the past (Wang, Melles, & Lin, 2014). While a thicker cornea from repetitive anesthetic administration would overestimate IOP and underestimate OPP, statistically significant changes in thickness throughout the experiment are unlikely. The absolute baseline value may be affected by corneal thickness, but the effect of tilt should not.

5. The process of obtaining multiple IOP measurements with an applanation tonometer could have prompted an increase in aqueous humor drainage through the trabecular meshwork. This would lead to attenuated IOP values and therefore an overestimated OPP.

Future directions: Age-wise, a more representative sample to astronauts is recommended in future studies along with a larger sample size, and a longer duration (i.e. approximately two weeks) spent in head-down tilt. This would be especially beneficial for OPP as not enough studies have explored the impact of HDT on its values and would help reaffirm or contradict our findings. Moreover, participants should undergo the study at the same time each day to avoid diurnal effects on data. Finally, future studies should further explore OPP changes during HDT with and without lower body negative pressure to examine the ocular system's tolerance for increased OPP before being compromised at the retina, choroid and optic disc. This would further allow a better understanding of the true time needed in the lower body negative pressure devices to maintain proper ocular blood flow despite increases in OPP.

Chapter 7 Conclusion

One of the top barriers for deep space exploration is SANS. This disease is thought to result from cephalad fluid shifts and remains confined to male astronauts. However, its precise etiology remains unclear. Although some terrestrial diseases share signs with SANS, none are exactly the same. Therefore, we've investigated OPP during HDT to determine whether or not changes occur. We found statistically significant increases in OPP that potentially compromise autoregulation; however, sex had no statistically significant effect. Should microgravity also yield similar changes to 30° HDT, our study found IOP and ICP increases to result in a decreased TLPD (i.e. TLPD= IOP-ICP). While we propose these OPP increases might occur in conjunction with a decreased TLPD in SANS, our findings are those of acute HDT and might not reflect long-term spaceflight changes. In short, further investigation is needed to determine long-term effects of HDT on OPP as well as the minimum duration that lower body negative pressure (LBNP) devices would be required to protect the eyes. By better understanding the ocular system's capacity to autoregulate OPP changes in HDT conditions, we can further explore solutions to the syndrome.

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