Université de Montréal

L'effet hypotenseur de l'exercice sur la PIO :

Une interaction de la condition physique et l'efficacité parasympathique ?

(The hypotensive effect of exercise on IOP : An interaction of physical fitness and parasympathetic efficacy)

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Cette thèse intitulée :

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RÉSUMÉ

Suite à une centaine de publications sur la réduction de la PIO post-exercice, il est connu que parmi un grand nombre de programme d'exercices de différentes durées et intensités, les effets hypotenseurs de l'exercice sur la PIO sont atténués chez les sujets en bonne condition physique. Le mécanisme proposé est l'augmentation potentielle de l'efficacité du système parasympathique avec l'activité physique. Le principal objectif de cette thèse est d'identifier les facteurs contribuants à la réduction de la PIO post-exercice et d'élucider les différents mécanismes possibles.

L'étude 1, une méta-analyse, a été menée afin de quantifier les contributions relatives de l'intensité et de la durée de l'effet de l'exercice sur la PIO et la mesure dans laquelle ces variables affectent les sujets sédentaires et normalement actifs. La tendance ressortant des résultats est que la diminution de la PIO suite à de l'exercice aérobie est plus élevée chez les sujets sédentaires que les sujets en bonne condition physique. (ES = -4.198 mm Hg et -2.340 mm Hg, respectivement). L'absence d'un contrôle des liquides ingérés avant l'activité physique est à souligné dans cette étude.

L'hyperosmolarité (un effet secondaire de la déshydratation) est l'un des mécanismes proposés influant l'effet hypotenseur de l'exercice. L'étude 2 comparait la réduction de la PIO dans deux conditions, soit hypohydraté et hyperhydraté, avant, pendant et après un effort de 90 minutes sur un ergocycle. Après une diminution initiale pour les deux conditions, la PIO revient aux valeurs de départ pour la condition hypohydratée malgré une perte de poids significative et elle augmente pour la condition hyperhydratée (résultat du protocole d'hydratation).

Étant donné le niveau élevé de participants en bonne condition physique dans l'étude 2, la troisième étude a été conçue afin de etude la relation entre la PIO et la condition physique. À l'aide d'analyses corrélationnelles il a été possible d'observer la relation entre le test de vo2max et la moyenne des mesures de PIO prises sur un intervalle de huit semaines. Une relation significative n'existait que pour les participants se situant dans la portion supérieure du continuum de la condition physique.

C**onclusion:** Les résultats de la présente étude suggèrent que l'effet hypotenseur de l'exercice sur la PIO est probablement une réponse homéostatique à la dérégulation de l'humeur aqueuse causée par l'initiation de l'exercice et le protocole d'ingestion de fluides pré-exercice.

Mots-clés : la pression intraoculaire, exercice, condition physique, ingestion de liquide, intensité, déshydration, homéostasie, sédentaire, Glaucoma, activité physique

Abstract

After over 100 papers on post exercise reductions in IOP it is known that under a vast number of exercise protocols, of differing intensities and durations, the hypotensive effects of exercise on IOP are attenuated in the physically fit. A proposed mechanism is the parasympathetic nervous system that potentially increases in efficacy with physical training. The general objective of this thesis was to further tease apart those factors that contribute to post exercise reductions in IOP and to elucidate possible mechanisms.

Study 1, a meta-analysis, was conducted to quantify the relative contributions of intensity and duration to the effect of exercise on IOP and the degree to which these variables affect sedentary and normally active populations. A pattern of results emerged such that those persons who are Sedentary experience a greater drop in IOP after aerobic exercise than those who are physically fit (ES = -4.198 mm Hg and -2.340 mm Hg, respectively). A lack of pre-exercise control over covariates such as fluid ingestion was also observed.

Hyperosmolarity (a side effect of dehydration) is one of the proposed mechanisms driving the hypotensive effect of exercise. Study 2 compared reductions in IOP in both a hypo-hydrated (water restricted) and hyper-hydrated condition before, during and after an ergocycle ride of 90 minutes. After an initial decrease in both conditions, IOP returned to baseline in the Hypo-hydrated condition despite a significant loss of bodyweight and increased in the Hyper-hydrated condition as a result of the hydration protocol.

Given the high level of physical fitness among our participants in Study 2, Study 3 was designed to further elucidate the relationship between physical conditioning and IOP. Using correlational analyses we observed the relationship between a test of VO_2max and an average of IOP measurements made over the course of eight weeks. A significant relationship existed only for those participants in the upper range of the fitness continuum.

Conclusion. The results of the current study suggest that the hypotensive effect of exercise on IOP is likely a homeostatic response to dysregulation of the aqueous humor caused by the initiation of exercise and pre-exercise fluid intake protocols.

Key Words: intraocular pressure, exercise, physical fitness, fluid intake, intensity, dehydration, homeostasis, sedentary, Glaucoma, physical activity

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List of Abbreviations

ACSM	*American College of Sports Medicine*
BP	*Blood pressure*
BMI	*Body mass index*
BPM	*Beats per minute*
CCT	*Central corneal thickness*
CME	*Continuous moderate exercise*
DCT	*Dynamic contour tonometry*
ES	*Effect Size*
GAT	*Goldmann Applanation Tonometry*
HIT	*High Intensity Training*
HR	*Heart rate*
HRmax	*Maximal heart rate*
IOP	*Intraocular pressure*
IT	*Impression tonometry*
METS	*Metabolic equivalent*
MHR	*Maximum heart rate*
mm Hg	*Millimetres of mercury*
NCT	*Non-contact tonometry*
OD	*Right eye*
OS	*Left eye*

OU	*Both eyes*
PAR-Q	*Physical Activity Readiness Questionnaire*
POAG	*Primary Open Angle Glaucoma*
Q-AAAP	*Questionnaire sur l'aptitude à l'activité physique*
RB	*Rebound tonometer*
VO_2max	*Maximal aerobic capacity*

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Chapter 1

General History of the Relationship Between Exercise and IOP

It is well known that exercise helps to control weight, improves musculoskeletal health and reduces the risk of Type 2 Diabetes, hypertension, cardiovascular diseases and numerous other pathologies (Sesso, Paffenbarger, & Lee, 2000; Vuori, 2004; Wannamethee, Shaper, & Alberti, 2000; World Health Organization [WHO], 2010). It also exhibits a hypotensive effect on intraocular pressure (IOP), which is the ratio between production and outflow of the aqueous humour (Reviews: Gale, Wells, & Wilson, 2009; Risner at al., 2009). Early links between exercise and IOP appeared simultaneously in fields such as aerospace medicine (Cooper et al., 1965) and exercise science (Janiszewska, 1963. In: Risner et al., 2009). Currently, there are well over 100 experimental papers on exercise and IOP, as well as case studies and reviews (e.g., Gale et al., 2009; Risner et al., 2009). Much of this research is produced with the intent of exploring the usefulness of the hypotensive effect of exercise on IOP in the management and prevention of certain eye diseases. However, despite decades of research on this topic there is little standardization with regard to exercise protocols and participant stratification across fitness, age and clinical categories. These elements are necessary to ascertain whether the magnitude of decreases in IOP produced by aerobic exercise are reliable, predictable and controllable, and ultimately clinically viable as a complimentary therapy or even a reliable biomarker of eye health. Neither is there a consensus on the mechanism driving the effect of exercise on IOP possibly because the fluctuating value is part of a simple homeostatic response to aerobic exercise and offers no further benefit outside of the holistic benefit of exercise itself.

Exercise lowers IOP to different degrees after both aerobic and isometric exercise protocols of varying duration and intensity, although some types of resistance exercises can also produce an increase in IOP. In some studies a significant reduction occurs less than 5 minutes after beginning the exercise protocol (Buckingham & Young, 1986; Dane, Koçer, Demirel, Ucok & Tan, 2006a; Orgül & Flammer, 1994; Qureshi, 1995a,b). After the cessation

of exercise, IOP returns to baseline, usually within 60 minutes (Risner et al., 2009). Although the magnitude of reductions in IOP differ across studies, in general, the pattern of these findings hold true for healthy, normally active adults of all ages (Era, Parsimony, Kallinen, & Suominen, 1993; Gale et al., 2009; Marcus, Krupin, Podos, & Becker, 1970; Qureshi, Xi, Huang, & Wu, 1996b; Risner et al., 2009), sedentary subjects (Dane et al., 2006a,b; Qureshi, 1995a,b; Qureshi, 1996a; Qureshi et al., 1996b), physically conditioned people (Dane et al., 2006a,b; Harris, Malinovsky, & Martin, 1994; Passo, Goldberg, Elliot, & Van Buskirk, 1987, 1991; Qureshi et al., 1996b; Qureshi, 1996a; Qureshi, Wu, Xi, Yang, & Huang, 1997a; Qureshi, 1997b) and those with elevated IOP (Passo et al., 1991; Qureshi, 1995b; Shapiro, Wolf, Ferber, & Merin, 1983).

Another pattern that characterizes the hypotensive effect of exercise on IOP is emerging from the disparate results across studies. The results of some studies show that participants with greater physical conditioning exhibit lower baseline IOP values than sedentary and elderly participants. Further, there is an attenuated effect on IOP after acute exercise in those who are physically fit (Dane et al., 2006a,b; Harris et al., 1994; Passo et al., 1987; 1991; Qureshi, 1996a) but there is also evidence to the contrary (Dane et al., 2006a; Era et al., 1993). In the exploration of mechanisms driving the hypotensive effect of exercise the stratification of participants is especially important. A physically conditioned body will react differently to various intensities of exercise than will a sedentary one and many mechanisms proposed throughout the literature on exercise and IOP are involved in thermal and fluid regulation and are themselves conditioned by exercise (deVries & Housh, 1994a-e, Harris et al., 1994).

The general objective of this thesis was to further tease apart those factors that contribute to post exercise reductions in IOP and to elucidate possible mechanisms. To first establish the magnitude of the hypotensive effect of aerobic exercise and make a possible step toward quantifying a pattern of dose-response, the first study will compare the relative contributions of duration, intensity and physical fitness to post exercise reductions in IOP.

The literature search pertaining to the relationship between aerobic exercise and IOP contains many suggestions as to the mechanism driving the relationship between exercise and IOP and it is often suggested that ocular hyperosmolarity such as might occur during systemic dehydration plays a role (Hunt, Feigl, & Stewart, 2012; Passo et al., 1987; Sollanek et al., 2012; Qureshi, 1996a; Williams, 2009). However, there are studies that produced results to the contrary (Harris et al., 1994; Martin, Harris, Hammel, & Malinovsky, 1999). It is possible that systemic dehydration could contribute post exercise reductions in IOP provided the duration of the exercise protocol is long enough. However, there is often an initial drop in IOP that could not possibly be related to dehydration (Buckingham & Young, 1986; Orgül & Flammer, 1994; Qureshi, 1995a; Dane et al., 2006a).

Given this potential relationship between IOP and dehydration, and based on the findings of Study 1, Study 2 will explore the notion that dehydration could ultimately cause hyperosmolarity that correlates with a decrease in IOP. To that end we will observe participants exercising in both a state of Hypo-hydration (water restricted) and Hyper-hydration.

Finally, given the high fitness level of the participants both across the literature and within our own studies, Study 3 will explore the relationship between baseline IOP and increased physical conditioning. $V0_2max$, one test of maximal aerobic capacity, will be used to examine a possible correlation such that the higher a person's $V0_2max$ the lower the baseline intraocular pressure.

The sheer number of variables attached to every aspect of the relationship between exercise and IOP demands that the current exploration begin with an overview of the variations that occur during measurement as well as those factors unrelated to exercise specifically but which contribute to the overall fluctuation of IOP. These fluctuations in IOP are often of the same magnitude as those produced by aerobic exercise and will therefore affect study results in terms of response magnitude.

Chapter 2

Intraocular Pressure

2.1 The Eye and IOP

Post aerobic exercise reductions in IOP are produced time and again under many circumstances. To fully understand the nature of these reductions it is necessary to first understand the cycle of the production and outflow of the aqueous humour, a clear fluid that circulates the orb of the eye and is responsible for hydration, nutrition of the avascular cornea and lens, and the removal of metabolic waste products.

2.2 Production and Evacuation of the Aqueous Fluid

The aqueous fluid is formed by secretion of the epithelium of the ciliary processes, the folded layers of the vascular area of the eye known as the choroid. First sodium, chloride and bicarbonate ions are transported into spaces in the epithelial cells. This results in osmosis of water from blood capillaries lying below the same epithelial spaces. This solution washes from the posterior chambers of the eye, passes around the equator of the lens, and flows through the pupil into the anterior chamber of the eye (Guyton & Hall, 2006a, Quigley, 2011).

The aqueous fluid leaves the eye via drainage canals between the cornea and the outer edges of the iris and then through the trabecular meshwork into a circular channel in the eye (Canal of Schlemm) that collects the aqueous humor and finally delivers it into the bloodstream where it is absorbed. This process of production and removal generates IOP. When IOP is approximately 15 mm Hg it means that the amount of fluid leaving the eye is averaging 2.5 microlitres per minute thus approximating the production inflow (Guyton & Hall, 2006a; Quigley, 2011). As such IOP is a relatively simple homeostatic function. It can be expressed as:

$$IOP = F / C + EPV,$$

Where F = aqueous fluid formation rate, C = outflow rate, EPV = episcleral venous pressure [of the movement away from the eye] (Guyton & Hall, 2006a; Quigley, 2011).

This regulatory control of IOP is well documented and the range of normal IOP levels are generally thought to range from 10 to 21 millimetres mercury (mm Hg). Clinically high IOP is often differentiated by repeated readings over 21.0 to 24.0 mm Hg (Bengtsson & Heijl, 2005; Quigley, 2011; Wilson, 1997). The transient reductions in IOP after exercise are usually between 1.4 and 5 mm Hg. These fluctuations are in a small range ultimately affected by many variables in addition to those produced by exercise. For example, there is an abundance of literature that examines the disruption of this homeostatic control of IOP after fluid ingestion (Diestelhorst & Krieglstein, 1994). As previously mentioned, exercise protocols are not standardized across the literature and pre-exercise fluid ingestion is one factor that could be greatly affecting study results (See section 3.13). This relationship between IOP and fluid ingestion is examined further in Study 2.

2.3 Types of Measurement Tools

Given the small range of values of post exercise reductions in IOP it is important that the measurement of IOP be as precise as possible. There are however, a great many factors involved in obtaining IOP measurements. IOP is most often measured with a process known as applanation or indentation tonometry, whereby the resistance to pressure used to applanate (flatten) or indent a small area of the cornea is quantified. The problem with most forms of applanation tonometry is that the repeated pressure of the instrument itself during the course of a study interferes with the regulation of IOP possibly by increasing the outflow of the aqueous humour (Molina, Milla, Bitrian, Larena, & Martíneza, 2010; Whitacre & Stein, 1993).

The resulting IOP values are further compromised by the thickness of the cornea. Central corneal thickness affects most applanation measurement tools by varying resistance to the tonometer probe. A thick cornea gives rise to a greater probability of an IOP being overestimated and a thinner cornea causes underestimation all of which can affect the results of studies on exercise and IOP. (Lee, Khaw, Ficker, & Shah, 2002).

The following non-exhaustive list outlines some of the differences and difficulties with the tools used to measure IOP across the literature to date.

2.3.1 The Goldmann Applanation Tonometer (GAT). The GAT is considered the gold standard in applanation tonometry (Kaufmann, Bachmann, & Thiel, 2004; Molina et al., 2010; Tonnu et al., 2005; Whitacre & Stein, 1993). The GAT uses a disinfected prism mounted on the tonometer head, which is placed against the cornea. Local anesthetic drops are administered as the probe sits on the eye for number of seconds. The GAT has an inter-observer variability of 0.4 mm Hg and an intra-observer reliability of 1.7 mm Hg, 95% Limit of agreement [± 2.6 mm Hg] (Kotecha, White, Shewry, & Garway-Heath, 2005). It is the GAT to which other methods of measurement are compared.

2.3.2 Rebound tonometry (RB). The rebound tonometer uses a very lightweight probe to make momentary contact with the cornea. The higher the IOP, the faster the probe decelerates and the shorter the contact time. The measurement is barely noticed by the patient and anesthesia is not required (Kim, Jeoung, Park, Yang, & Kim, 2013). At lower GAT values the rebound tonometer can overestimate IOP but it still shows a good correlation with GAT ($r = 0.6995$, $p < 0.001$) (Kim et al., 2013). The rebound tonometer will be described in detail in the Method section of Study 2.

2.3.3 Dynamic contour tonometry (DCT). DCT uses the principle of contour matching instead of applanation. The tip contains a hollow the same shape as the cornea with a miniature pressure sensor in its centre. In contrast to applanation tonometry it is designed to avoid deforming the cornea during measurement and is therefore less influenced by corneal thickness. However, because the shape of the tip is designed for the shape of a normal cornea it is more influenced by corneal curvature. In one comparative study the group with the lowest baseline IOP produced the greatest differences between GAT and DCT (3.55+/-3.1), the intermediate baseline group showed a negative relationship (-1.86+/-2.60), and the highest group more negative still (-3.88+/-3.3; P<0.0001) (Francis et al., 2007).

2.3.4 Pneumatonometer. A pneumatonometer utilizes a pneumatic (a piston floating on an air bearing) sensor. Filtered air is pumped into the piston and travels through a small (5-mm diameter) perforated membrane at one end, which is placed against the cornea. The balance between the flow of air from the machine and the resistance to flow from the cornea affect the movement of the piston and this movement is used to calculate the intra-ocular pressure. The pneumatonometer has a mean difference of 0.72 ± 2.82 mm Hg from the GAT (Molina et al., 2010).

2.3.5 Impression tonometry (IT). IT measures the depth of corneal indentation made by a small plunger carrying a known weight. The higher the intraocular pressure, the harder it is to push against and indent the cornea. The movement of the plunger is measured using a calibrated scale. The Schiøtz tonometer, which has a mean difference from GAT of +0.24 (*SD* = 3.18) mm Hg, is the most common device to use this principle, however it is not widely used in current research (Jain, Saini, & Gupta, 2000).

2.3.6. Non Contact Tonometry (NCT). Currently the emphasis is on creating a measurement instrument that does not interfere with the circulation of IOP around the eye. This means developing instruments that have limited, or no contact with the eye such as non-contact tonometry, which uses a rapid air pulse to applanate the cornea. Intraocular pressure is estimated by detecting the force of the air jet at the instance of applanation. Historically, non-contact tonometers were not considered to be an accurate way to measure IOP in the lab. However, modern non-contact tonometers correlate well with the GAT (mean difference from GAT ≈ 1.5 mm Hg, 95% Limit of agreement ≈ ± 3.0; Ogbuehi, 2006).

Chapter 3

Fluctuations in Intraocular Pressure (IOP)

3.1 Normal Fluctuations of Intraocular Pressure (IOP)

Complicating the process of obtaining accurate IOP measurements, there is a circadian fluctuation of IOP and there are a number of variables that can affect that natural rhythm (Liu & Weinreb, 2011; Liu, Zhang, Kripke, & Weinreb, 2003a; Sit, 2014). It is well known that fluctuations of IOP are ongoing throughout the day (Hamilton et al., 2007; Liu & Weinreb, 2011). They are influenced by any number of variables that are difficult to control for in any one study and greatly affect the possibility of accurate comparisons of the hypotensive effect of exercise across studies. Therefore the protocols governing IOP measurements during research need to control for these factors. Relevant to the current discussion are those factors that would necessarily affect an examination of the hypotensive effect of exercise on IOP and mechanisms related to either increased physical fitness or dehydration.

3.1.1 Diurnal variation of IOP. IOP fluctuates significantly over the course of a 24-hour period (Liu & Weinreb, 2011; Liu et al., 2003a; Liu, Bouligny, Kripke, & Weinreb, 2003b; Sit, 2014). In the general population, IOP ranges between 10 and 21 mm Hg with a mean of about 15 or 16 mm Hg, plus or minus 2.75 mmHg to 3.5 mm Hg during a 24-hour cycle (Liu & Weinreb, 2011; Quigley, 2011). It is observed that IOP quickly increases by about 3mm Hg to 4mm Hg in normal eyes when a person assumes a supine posture (lying down) regardless of the time of day. After the initial increase IOP settles at an elevated plateau, possibly because of a redistribution of body fluid in the supine position which results in a decrease in aqueous humour production (Liu et al, 2003a; Liu et al., 2003b). However, although aqueous humour production decreases at night, IOP increases nocturnally, regardless of posture (Brubaker, 1991; Liu et al., 2003b; Mosaed, Liu, & Weinreb, 2005). When a person wakes IOP is initially elevated before decreasing back to the current baseline IOP. Because the fluctuations caused by nocturnal and diurnal variation are so great, fluctuations of IOP can be greater than the post exercise reductions in IOP produced in many studies. For this reason

most studies on exercise and IOP are constrained to the daylight hours, usually at the same time each day and all measurements are taken in an upright position (Brubaker, 1991; Gale et al., 2009; Risner et al., 2009; Liu & Weinreb, 2011). However, it is also important to control for the activities of the participants in the hours leading up to the actual experiment, especially close to the participant's normal waking hour.

3.1.2 Seasonal variation of IOP. It also common, in the exploration of exercise and IOP, to find that studies are confined to one of the four seasons because there is literature to suggest that IOP is subject to seasonal as well as diurnal variation. IOP is low in the summer and high in the winter and can fluctuate as much as 0.14 to 0.39 mmHg ($p \leq 0.02$; Gardiner, Demirel, Gordon, & Kass; 2013), with a peak in January or February (Gardiner et al., 2013; Qureshi et al., 1996c). The mechanism responsible for seasonal fluctuations remains unclear. One suggestion is changes in the secretion of Melatonin from the pineal gland, which is affected by the daily total amount of light entering the eyes. Melatonin affects the anterior pituitary gland, and the resulting increase in the secretion of progesterone and estrogen could be increasing the outflow of IOP in the summer months (Gardiner et al., 2013). Regardless, given the small range produced by most experimental studies on exercise and IOP a change from winter to summer, or vice versa could easily obscure study results.

3.1.3 The impact of fluid ingestion on normal IOP. The ingestion of fluid has a direct and lasting effect on IOP. Yet, the protocols of many studies do not allow for comparison of this variable, although there are exceptions (Hunt et al., 2012; Moura, Rodrigues, Waisberg, de Almeida, & Silami-Garcia, 2002). This is important with regard to the discussion of mechanisms governing post exercise reductions in IOP. In the short term, water ingestion might interfere by elevating IOP, while hyperosmolarity, caused by dehydration, would be modulated by pre-exercise water ingestion in exercise protocols of a longer duration. Control of covariates such as pre-exercise fluid intake would greatly improve the generalization of results across studies (Sollanek et al., 2012).

A test used to diagnose pathologically elevated IOP, the water provocation test, requires that the patient rapidly drink one litre of water, then IOP is measured at 10 to 15-

minute intervals. Greater increases are thought to mean greater risk (Diestelhorst & Krieglstein, 1994). In one study that looked at water drinking and IOP in normally active people without ocular disease, one litre of water caused a 2.0 mm Hg increase in IOP at ten minutes post consumption and another increase at 70 minutes to 4.0 mm Hg. Baseline IOP was not regained for over 140 minutes (Buckingham & Young, 1986). These increases are as great as some post exercise reductions in IOP and would serve to nullify the effect of exercise if water is consumed to close to the beginning of the exercise protocol.

3.1.4.1 Caffeine and IOP. Because caffeine is a stimulant it has a slightly different pattern of effect than simple water on IOP and is important to this study with regard to the coffee habits of participants in experimental studies. Tachycardia (abnormally rapid heart rate), such as can occur after coffee consumption, and increased blood flow through the vessels increases aqueous production efficacy. The results of one study found that two cups of coffee produces a rapid increase in IOP of 3.3 mm Hg that peaks between 20 and 30 minutes. IOP returned to basal values 95 minutes later (Buckingham & Young, 1986). Another study finds the same magnitude of increase and longer recovery times (Okimi, Sportsman, Pickaerd, & Fritsche, 1991). It should be noted that a more recent study found that the effect of caffeine on IOP differs with population, those with normal IOP saw no effect, while those with pathologically elevated IOP and ocular hypertension saw a significant increase (Li, Wang, Guo, Wang, & Sun, 2011).

3.2 Other Factors in the Fluctuation of IOP

3.2.1 Age. Although hemodynamics do not often correlate with changes in IOP after exercise (Harris et al., 1994; Karabatkis et al., 2004, Kiuchi et al., 1994; Passo et al., 1987; 1991), there could be a relationship between IOP and age mediated by the dual effects of systolic blood pressure and aging (Klein & Klein, 1981; Klein, Klein, & Knudston, 1995; Leske and Podger, 1983; McLeod, West, & Quigley et al., 1990; Qureshi, 1995c; Schulzer & Drance, 1987). However, Schulzer and Drance (1987) suggest that systolic blood pressure does not necessarily rise with age before IOP begins to increase. Qureshi (1995c) observed that IOP was significantly negatively correlated with systolic blood pressure in 8036

participants. A progressive analysis revealed that the increase is non-significant until 40 years of age but highly significant ($P < 0.001$) from 41 to 60 years of age. Interestingly there is a nominal decrease during the ages of 61 to 70 and another, greater, increase in participants 70 years and older. Overall the researchers found an average increase in IOP of 0.28 mmHg per decade (Qureshi, 1995c).

Obviously, as in most research of the human body, factors of aging potentially influence any study of post exercise reductions in IOP. As we age some diseases of the eye (see the following section for an example) become increasingly prevalent, therefore the majority of studies on exercise and IOP use participants under the age of 40.

3.2.2 Pathologically elevated IOP. Glaucoma is a group of eye diseases characterized by a progressive loss of retinal ganglion cells. It is often diagnosed because of repeated higher than normal IOP measurements (Quigley, 2011). Currently Glaucoma is described as a neurodegenerative disease with many unknown factors. However, increased IOP is still the most easily recognizable and treatable symptom of Glaucoma (Bengtsson & Heijl, 2005; Quigley, 2011). Primary Open Angle Glaucoma (POAG) is the most common subtype of Glaucoma and it occurs when the aqueous humour cannot drain properly or at all. Pressure builds within the eye damaging the sensitive nerve fibres that run from the retina to the optic nerve. Eventually visual information is lost before it reaches the cortex (Quigley, 2011). The pattern of visual field loss for those with Glaucoma is not vastly different than that of normal aging of the eyes. For that reason, coupled with the fact that elevated IOP is not painful unless the drainage canals are fully blocked, Glaucoma is often not detected until there has already been irreversible visual field loss (Gordon & Kass, 1999; Jay & Murdoch, 1993; Quigley, 2011). This is a problem when screening participants for inclusion in this type of research. Traditionally, participants with elevated IOP are not included unless the study is specifically targeting a clinical population, although that does not necessarily mean the participant has Glaucoma, especially in the absence of other factors.

The majority of studies on post-exercise reductions in IOP, which compared a clinical population to normally active or physically fit individuals, find that there is a greater reduction

in post-exercise IOP for those with Glaucoma (Passo et al., 1991; Qureshi, 1995b). It is for this reason that research on exercise and IOP is often elaborated with the aim of complimentary therapy. Although clinical populations are not represented in the studies included in this thesis, it is important to understand that this is one of the motivations driving this body of literature.

Space does not permit a thorough examination of all factors that could potentially affect IOP during exercise. Therefore, the current discussion focused on those factors that appeared most often within the literature on the hypotensive effects of aerobic exercise on IOP and which are most relevant to the studies contained herein. However, there are many more factors at play such as second hand effects on IOP through systemic diseases affecting the cardiovascular system, Type 11 diabetes, and conditions that affect the normal contraction of intraocular and extraocular muscles (Bengtsson & Heijl, 2005; Gale et al., 2009; Portmann et al., 2011; Quigley, 2011).

Chapter 4

Exercise And IOP

4.1 The Pattern of the Hypotensive Effects of Exercise on IOP

As previously mentioned there are decades of research on the hypotensive effects of exercise on IOP. For the most part the general protocol of most experimental studies proceeds in the following manner. First, there is a pre-exercise measurement of IOP and of the vitals of the participants. After which, the participant engages in an exercise intervention of some kind, usually 90 or less minutes, the intensity of which is determined by a test of maximal (or sub maximal) capacity. IOP might or might not be measured during exercise. Finally, post exercise measurements of IOP are conducted, continuing up to 2 or 3 hours after exercise in some studies (Reviews: Gale et al., 2009 and Risner et al., 2009). It is there that the similarities between studies end. There are large variations in types of exercise, durations and intensities of exercise, fluid protocols, group descriptions, and the list goes on. For that reason the relationship between exercise and IOP, while it certainly does exist, is difficult to fully characterize.

4.1.1 Aerobic Exercise and IOP. Aerobic or dynamic exercise is generally defined as moderate intensity (≈60%) exercise that is within the cardio respiratory system's capacity to replenish oxygen in the working muscles (Guyton & Hall, 2006b). The majority of research on the hypotensive effects of IOP centre on the acute effects produced after one bout of moderate aerobic exercise. On average research shows reductions in IOP from pre-exercise values on the order of 1.4 to 8.0 mm Hg in sedentary and normally active populations. (Reviews: Gale et al., 2009 and Risner et al., 2009).

When it comes to reductions in IOP however, all aerobic exercise is not equal. For example, Qureshi (1995b) showed that IOP decreased 2.43 mm Hg (±0.30) after walking, 3.85

mm Hg (±0.55) after jogging, and 4.0 mm Hg (±0.37) after running. The effects were magnified in a clinical population with elevated IOP but the pattern remained the same (Qureshi, 1995a). This discrepancy between reductions is constant in those studies that compared exercise intensity (Harris et al., 1994; Kiuchi et al., 1994; Qureshi et al., 1996b). It is suggested by these authors that exercise intensity is the limiting factor in the magnitude of reduction in IOP that can be expected post exercise.

4.1.2 Effects of intensity and duration on post aerobic exercise reductions in IOP. Across the literature there is a general consensus that relative intensity rather than duration is correlated to post exercise reductions in IOP (Harris et al., 1994; Kiuchi et al., 1994; Qureshi, 1995a,b; Qureshi et al., 1996b). The interaction between duration and intensity with regard to the hypotensive effect of exercise is less clear. Field running for 15 minutes produced reductions in IOP of 4.3 mmHg in normally active people (Kiuchi et al., 1994) and running up and down seven flights of stairs, which takes only 2 minutes but is a higher intensity exercise also produced a reduction of 4.3 mmHg (Buckingham & Young, 1986). Finally, Ashkenazi, Melamed and Blumenthal (1992) also found a decrease of 4.1 mm Hg after a 24-hour march.

An interesting study from Conte et al. (2014), found that 30 minutes of high intensity interval training (HIT), which included 2 minutes of walking at 50% of heart rate reserve alternated with 1 minute of jogging at 80% heart rate reserve, and 30 minutes of continuous moderate exercise (CME), jogging at 60% of heart rate reserve, exerted an equally hypotensive effect on IOP. It appears that intensity is indeed a factor in the post exercise reductions in IOP but there is a potential interaction between duration and intensity that bears further examination.

4.1.3 Isometric exercise and IOP. Static exercise, such as gripping a bar or holding a lunge, involves predominantly isometric activity (the muscle and joint angles do not change during contraction) and the active muscles usually require the anaerobic metabolism. Some research finds nominal decreases after isometric exercise, although the magnitude is considerably less than after aerobic exercise (Avunduk, Yilmaz, Sahin, Kapicioglu, &

Dayanir, 1999; Marcus, Edelhauser, Maksud, & Wiley, 1974; Ozmerdivenli, Simsek, Bulut, Karacabey, & Saygin, 2006; Rüfer et al. 2014).

Isometric exercise can lead to hyperventilation and hypocapnia (decreased carbon dioxide levels), which is thought to correlate with reductions in IOP (Imms & Mehta, 1989; Kielar, Teraslinna, Rowe, & Jackson, 1977; Marcus et al. 1974). The results of one study showed a reduction in IOP of 2.7 mm Hg after isometric exercise (Harris, Malinovsky, Cantor, Henderson, & Martin, 1992). However, when participants maintained a normal breathing pattern rather than hyperventilating, thus maintaining carbon dioxide levels, no reduction in IOP was observed (Harris et al., 1992).

Even when discussing only isometric exercise, the type of exercise is still a factor. Chromiak, Abadie, Braswell, Koh and Chilek (2003) found the return to baseline IOP was slower after lower-body resistance training than upper-body resistance training (Chromiak, Abadie, Braswell, Koh, & Chilek, 2003). This same group also found that IOP was reduced following chest press and leg press exercises, provided the intensity of the exercise amounted to 70% of a repetition's maximum force (Chromiak et al., 2003).

4.1.4 Aerobic versus isometric exercise. A couple of studies attempted to compare directly the disparate effects of isometric and aerobic exercise on IOP. Ozmerdivenli et al., (2006) found that aerobic exercise produced a 27% change from baseline IOP as compared to a 17% change caused by isometric exercise in a study using matched duration rather than matched intensity (Ozmerdivenli et al. 2006). Conversely. Kielar et al. (1975) compared aerobic and isometric exercise of a matched intensity and found no significant difference in the reductions in IOP.

Rüfer et al., (2014) compared aerobic exercise on a cycle ergometer to isometric exercise on a leg curl machine for the lower limbs and on a butterfly machine for the upper body. The researchers found a reduction in IOP of 2 mm Hg after cycling and did not find any reductions in IOP after upper or lower body resistance. The researchers suggested that the nominal increase (<1 mmHg) after upper body exercise might be related to an involuntary

Valsalva maneuver (a forced exhalation against closed lips) (Rüfer et al., 2014).

4.1.5 Weightlifting and the Valsalva maneuver. During a sustained isometric muscular contraction or extreme effort participants sometimes perform what is known as a Valsalva Manoeuvre, which is a forceful exhalation against a closed airway. When this happens during an isometric contraction, such as during weightlifting, IOP typically increases (Dickerman et al., 1999; Kiss et al., 2001; Vieira, Oliveira, de Andrade, Bottaro, & Ritch 2006). When the contraction is relaxed IOP gradually returns to baseline (Marcus et al., 1974; Movaffaghy, Chamot, Petrig, & Riva, 1998; Vieira et al., 2006).

With respect to weightlifting specifically it was found that the increase in IOP occurs whether the breath is held or not, but the magnitude of that increase changes. Vieira, Oliveira, de Andrade, Bottaro and Ritch (2006) found that IOP increased 4.3 mm Hg (±4.2) when participants held their breath and only 2.2 mmHg (±3.0) when breathing was normal (Vieira et al., 2006). Brody, Erb, Veit, and Rau (1999) further showed that a Valsalva maneuver increases IOP whether one is exercising or not.

4.2 The Impact of Long-Term Physical Conditioning on Baseline IOP

There is evidence that physical conditioning (Harris et al., 1994; Passo et al., 1987,1991; Qureshi, 1996a; Williams, 2009) and physical labour in the workplace (Qureshi et al., 1997a), induce adaptations of the sympathetic nervous system that contribute to an overall reduction in baseline IOP. Study 3 explores this notion further but in general a greater reduction in IOP after exercise is observed in sedentary populations, some of who exhibit a higher baseline IOP, as compared to those who are physically active, however, this is not often quantified (Harris et al., 1994; Passo et al., 1987, 1991; Qureshi, 1996a). As of the writing of this thesis there are very few controlled studies on the long-term effects of exercise on IOP and the relationship between levels of IOP and level of physical fitness are far from clear.

In one field study, Qureshi, Wu, Xi, Yang and Huang (1997a) divided 150 male volunteers from a steel factory into two groups. The subjects of Group 1 were sedentary

workers, whereas the job descriptions of Group 2 included regular heavy exertion. Physical fitness was evaluated by the measurement of maximal oxygen uptake (VO_2max). IOP was significantly lower in those whose job description included moderate or severe exertion. The VO_2max difference between Groups 1 and 2 was found to be 5.1 ± 1.1 ml/kg/min (p <0.001) and the difference in baseline IOP was 1.9 ± 0.7 mmHg (p <0.001).

Passo, Goldberg, Elliot and Van Buskirk (1987) found that baseline IOP was reduced by 1.3 mmHg (p <0.02) after long-term exercise conditioning of three months and it returned to pre-conditioning levels after three weeks. Qureshi (1996a) replicated this pattern of results in a study of 32 sedentary age-matched males, categorized equally into control and exercise groups. After three months, baseline IOP values decreased by 0.31 mm Hg (+/- 0.11, p < 0.05) and 1.37 mm Hg (+/- 0.15, p < 0.001) in control and exercise groups, respectively (Qureshi et al., 1996b). The combined evidence suggests those who are physically fit could potentially maintain a baseline IOP that is lower than those who are sedentary (Harris et al., 1994; Passo et al., 1987, 1991; Qureshi, 1996a).

Conversely, Sargent et al. (1981) found that although the physically conditioned participants in their study had a lower baseline IOP as compared to those who were sedentary, both groups experienced a significant and comparable decrease in IOP over 6 months of conditioning. The researchers concluded that there is no correlation between physical fitness and baseline IOP. They performed a multiple regression analysis for each individual group and for combined groups and found that changes in IOP were not dependent upon changes in physical fitness. However, IOP is generally higher in the winter. Because the study was 6 months in duration and covered fall to winter it is possible that the seasonal drop in the summer months obscured the results between the groups (Gardiner et al., 2013; Qureshi et al., 1996c).

4.3 Long-Term Physical Conditioning and Acute Post Aerobic Exercise Reductions in IOP

There is research to suggest that long-term physical conditioning affects acute post-

aerobic-exercise reductions as well as baseline IOP, such that those who are physically fit experience a blunted effect of exercise on IOP. In the aforementioned study, Passo et al. (1987) found that before 3 months of training, acute exercise decreased IOP in Sedentary participants by 41% from baseline. After three months of exercise conditioning, three days per week, acute exercise reduced IOP by 12% from baseline, a reduction that persisted for an average of three weeks in some participants (Passo et al., 1987).

Qureshi and colleagues replicated the decrease in baseline IOP after exercise in a number of studies (1995b, 1996b, 1997a, 1997b). In one study the acute decreases following the first exercise test were 4.18 mmHg (±0.41) and 4.38 mmHg (±0.47) in control and experimental groups, respectively. After 3 months these values were 4.12 (±0.45) and 2.69 (±0.28) mmHg and the mean recovery time, post exercise, was reduced by 43.03% (Qureshi et al., 1996b).

The opinion on the effect of physical fitness on reductions in IOP is not unanimous however. A study by Dane et al. (2002a) showed that highly conditioned athletes produced a significant increase in IOP before decreasing to baseline. In the sedentary group IOP immediately decreased and remained decreased at 30 minutes and up to 2 hours post exercise (Dane et al., 2002a,b). Ozmerdivenli et al. (2006) found IOP was significantly decreased compared with pre-exercise values when measured after both aerobic and anaerobic exercise in both athletes and sedentarians. However, they also found that the magnitude of the decrease was not significantly different between the two groups (Ozmerdivenli et al., 2006).

4.4 Potentially Damaging Increases in IOP With Exercise

It is important to note that in some clinical populations the effect of vigorous exercise on IOP is a negative one and participant selection criteria should be designed accordingly. Although this thesis does not deal with clinical populations, this section serves to illustrate the transient nature of the relationship between exercise and IOP.

4.4.1 Severe Glaucoma and vigorous exercise. The majority of studies suggest that exercise not only lowers IOP in those with Glaucoma, but that it does so to a greater degree than in normal populations. However, there is some evidence to show that vigorous aerobic exercise might be damaging to those with severe Glaucoma. The results of three case studies in young adults show a transient visual field decrease in patients with Glaucoma after vigorous aerobic exercise (Uhthoff's Syndrome). Although the researchers were unable to infer the mechanism of the transient vision loss, processes related to demyelination of the optic nerve and disruption of the optic blood flow were discussed (Haynes, Johnson, & Alward, 1992; Shah, Whittaker, Wells, & Khaw, 2001).

4.4.2 Yoga. There is also some controversy regarding the effect of regularly practiced headstands, such as during yoga classes. One notable study looked at the effects of the headstand on IOP in 75 long-term yoga practitioners. They found that despite a two-fold increase in IOP during the headstand, across age groups, there was no increased incidence of ocular hypertension, and no correlation between risk factors contributing to Glaucoma and the magnitude of the increase in IOP (Baskaran et al., 2006). However, other studies find that repeated and prolonged headstands can potentially cause deficits in the visual field (Bertschinger, Mendrinos, & Dosso, 2007; Gallardo, Aggarwal, Cavanagh, & Whitson, 2006; Jonas, 2007).

Although the aforementioned anomalies exist, overall, the literature on the hypotensive effect of exercise on IOP is of a positive nature, or at least part of a normally functioning ocular system. There is no doubt that exercise has an effect on IOP. Whether the effect is hypotensive or hypertensive, IOP fluctuates with all exercise, to some degree, in the majority of populations. The enormous variety of pre-exercise control and exercise protocols across the literature make the results of these studies difficult to synthesize. Further, a possible relationship between physical fitness and IOP could have significant implications regarding the mechanism or mechanisms driving the hypotensive effect of exercise on IOP.

Chapter 5

Mechanisms

There is no consensus on what mechanisms contribute to the reduction of IOP after acute aerobic exercise. Over the decades changes in colloid osmotic pressure (one factor in capillary fluid exchange), increases in plasma osmolarity, ocular blood flow, increased blood lactate, and decreases in blood PH were all posited as possible mechanisms that initiate a reduction in IOP (Harris et al., 1992; Harris et al., 1994; Hunt et al., 2012; Karabatakis et al., 2004; Kiuchi et al., 1994; Martin et al., 1999). However, Ashkenazi et al. (1992) found no correlation between the magnitude of reduction in IOP and blood lactate level, pH, serum proteins or haematological parameters after a 24-hour march that produced reductions in IOP of 4.1 mm Hg (Ashkenazi et al, 1992).

Although all of the aforementioned mechanisms are present in both anaerobic and aerobic exercise, increased osmolarity (hyperosmolarity) is found only during aerobic exercise. Hyper-osmolarity, such as occurs during systemic dehydration, has received renewed interest in recent literature as a possible modulator of exercise induced reductions in IOP in exercise protocols of longer durations (Hunt et al., 2012; Moura et al., 2002; Sollanek et al., 2012).

5.1 Factors Related to Dehydration and IOP

When people sweat over time processes such as an increase in plasma osmolarity, which results in low sodium, potassium and chlorine (electrolytes) and colloid osmotic pressure (pressure exerted by proteins in blood plasma) occurs. This is because the sweating that occurs during moderate to heavy exercise results in shift of fluid from the plasma to the interstitial fluid (Guyton & Hall, 2006b, c, d). To maintain normal osmotic pressure water diffuses in the direction necessary through cell membrane. This raises the concentration of non-diffusible substances of interstitial fluid, resulting in water transfer across cell membranes of various tissue cells from intra to extracellular components therefore the tissues also become

dehydrated. Thus a higher proportion of electrolytes (sodium, potassium and chlorine) are secreted through sweat (deVries & Housh, 1994a, b, d; Guyton & Hall, 2006c, d). This homeostatic process has the potential to cause osmotic changes in the retinal and uveal vasculature. It is suggested that it could that ultimately could reduce the volume and formation of intraocular fluids, thereby reducing IOP (Guyton & Hall, 2006b, Martin et al., 1999).

As humans acclimatize to progressive heat through training they sweat more profusely which increases the plasma volume and diminishes the loss of electrolytes, thereby maintaining plasma osmolarity (deVries & Housh, 1994a, b, d; Guyton & Hall, 2006d). Via this mechanism, dehydration is delayed and possibly the deregulation of IOP as well (Martin et al., 1999). Other indices of hydration such as hematocrit and plasma protein concentration are not shown to exert effect on IOP (Feitl & Krupin, 1996). Because the sweating mechanism is known to improve with physical conditioning, it is an important variable in any study of IOP as a possible marker of hydration.

There are many other proposed mechanisms that are not as widely studied in the current literature on exercise and IOP but were posited as contenders in the past. In all cases the proposed mechanisms are a part of systems that increase in efficacy with long-term physical conditioning and they bear mentioning because of their relationship to the fitness level of the participants.

5.2 Other Proposed Mechanisms

5.2.1. Lactic Acid. The discrepant results across studies with regard to the role of lactic acid in post exercise reductions of IOP might be explained by differences in how our energy system works under different conditions. When exercise is so vigorous (>75% VO_2max) so as not to allow sufficient oxygen exchange, the metabolic cycle is abbreviated resulting in lactate production (deVries & Housh, 1994b; Guyton & Hall, 2006b). Therefore, a long moderate run and a short sprint will use different energy systems and might lower IOP through different mechanisms (Harris et al., 1994).

It is also argued that the relationship between IOP and increased lactate is seen only in anaerobic exercise (Kielar et al., 1975). In people who are extremely physically fit lactate production is slower to occur as such they can perform at high intensities longer than those who are sedentary before build up occurs (deVries & Housh, 1994b; Farrell, Wilmore, Coyle, Billing & Costill, 1979; Harris et al., 1994). Although the exact punitive effects of increased lactic acid on IOP are unknown, a correlation between reductions in IOP and increased lactate production would suggest a relationship to absolute rather than relative intensity markers contrary to much of the literature on post exercise reductions in IOP.

5.2.2 Vascular factors. There are many other factors that potentially contribute to normal fluctuations in IOP that have to do with the hemodynamics of the body and eyes. With regard to exercise their influence is widely debated. The majority of studies on exercise and IOP report no relationship with IOP and blood lactate, blood PH, diastolic blood pressure, heart rate or ocular perfusion pressure or blood flow (Harris et al., 1992; Karabatakis et al., 2004; Kiuchi et al., 1994; Krejci, Gordon, Moran, Sargent, & Magun, 1981; Passo et al., 1987; Qureshi, 1996a). The studies contained within the current thesis did not pursue the vascular influences on IOP during exercise therefore they are not discussed in detail here.

5.2.3 Adrenaline. Another possible mechanism driving the hypotensive effect of exercise on IOP is hormonal regulation by an increased release of adrenaline (Güngör et al., 2002; Qureshi et al., 1997a; Qureshi, 1997b). There is the suggestion that the extra adrenaline increases outflow through the trabecular meshwork and reduces aqueous humour formation (Wang, Hayashi, Yablonski, & Toris, 2002). In clinical practice, patients often begin treatment with β-adrenergic antagonist eye drops to lower IOP (Quigley, 2011). However, there is a steeper increase in metabolic demand when sedentary people begin exercising causing the adrenaline to be released in a different time pattern than that of very fit participants.

To further complicate the characterization of the relationship between exercise and IOP, the results of some studies show an initial drop in IOP that could not possibly be related to dehydration (Buckingham & Young, 1986; Dane et al., 2006a; Orgül & Flammer, 1994; Qureshi, 1995a,b) and would likely be driven by a different mechanism.

5.3 Initial Reduction in IOP in the Moments After Beginning Exercise

The progression of reductions in IOP during exercise is not clearly linear. Often, when exercise first begins IOP drops significantly within the first 5 minutes, after which IOP usually fluctuates to varying degrees, most often decreasing further as exercise continues (Buckingham & Young, 1986; Dane et al., 2006a; Orgül & Flammer, 1994; Qureshi, 1995a,b; Qureshi et al., 1996b).

Orgül and Flammer (1994) took a closer look at this pattern and found that even 8 to 10 seconds of deep knee bending produces nominal post-exercise reductions of 1.9 +/- 0.3 mmHg in 17 young men, compared with 0.8 +/- 0.2 mmHg for the 15 men who did nothing before the second IOP measurement. If hyperosmolarity is indeed a factor in the mechanisms that govern post exercise IOP it could not occur in the first 5 minutes of exercise. Orgül and Flammer (1994) found a correlation between the relative decrease in IOP and increase in heart rate, a correlation not often found after longer durations (Harris et al., 1992; Karabatakis et al., 2004; Kiuchi et al., 1994; Krejci et al., 1981; Passo et al., 1987; Qureshi, 1996a; Qureshi et al., 1996b). Possibly, mechanisms related to acute homeostatic balance are at play for shorter duration exercise protocols or when exercise is initiated.

There is no doubt that exercise exerts an effect on IOP. The effect can be nominal or robust, and occurs under a vast number of combinations of intensity and duration of exercise. The hypotensive effect of IOP seems to present in participants differently dependent on their level of physical conditioning. It is possible that exactly for that reason, the mechanism, or mechanisms remain unknown. It is also possible that different mechanisms are at play for the initiation of exercise and for exercise protocols of longer durations.

5.4 Objective of Thesis

The general objective of this thesis was to further elucidate the pattern of results emerging from the vast literature on the effect of exercise on IOP and begin to clarify a possible direction for the standardization of exercise protocols in this area of study. A further aim of the current thesis is to elucidate the mechanisms at play during post aerobic exercise reductions in IOP, specifically those that relate to the parasympathetic nervous system.

5.5 Objectives by Study

In the first study of this thesis, a meta-analysis will be conducted to quantify the relative contributions of intensity and duration to the effect of exercise on IOP and the degree to which these variables affect sedentary and normally active populations (Section 6.4, Study 1). It is posited that the effect will be greater for those that are deemed to be physically fit than for those who are sedentary.

In the second study, we will observe participants riding an ergocycle for 90 minutes to further explore relationship between dehydration and post exercise reductions in IOP (Section 6.5, Study 2). We propose that after an initial decrease, further reductions in IOP will correlate with loss of body weight when fluids are restricted and that there will be little movement in IOP when fluids are held constant.

Finally, Study 3 will attempt to clarify the relationship between physical fitness and baseline IOP by correlating four discrete baseline measures conducted over an eight-week period, and a single test of VO_2max on an ergocycle (Section 6.6, Study 3). We suggest a linear relationship between baseline IOP and $V0_2$max such that the higher a person's $V0_2$max the lower the baseline intraocular pressure.

5.6 Conclusion

The hypotensive effect of exercise is widely studied and much debated. Study protocols and the magnitude of results are inconsistent across the literature, regardless, there are patterns emerging from these results that bear examination. One pattern shows that

reductions in IOP are blunted for those who are physically fit compared to those who are sedentary or who have elevated IOP. The attenuated effect of exercise in a conditioned person is possibly related to an increased efficacy of the parasympathetic system. A better understanding of the way exercise impacts the IOP of people of differing fitness levels and how the duration and intensity of the various exercise protocols factor into that relationship, is necessary to elucidate our understanding of the mechanisms that drive the hypotensive effects of exercise on IOP.

Chapter 6

Experimental Studies: Research Questions and Hypothesis

6.1 Study 1. A meta-analysis on post exercise change in IOP via acute aerobic exercise

Objectives. The meta-analysis was designed to analyse the data from a group of studies that investigated the relationship between acute aerobic exercise and IOP, in order to obtain a quantitative estimate of the overall effect of this intervention. Specifically, our objective was to quantify the relative contributions of intensity and duration to the effect of exercise on IOP and the degree to which these variables affect sedentary and normally active populations.

Hypotheses.

H1) We propose that the hypotensive effect of exercise on IOP will be robust and will differ between populations that are sedentary and those that are physically fit.

6.2 Study 2. Post exercise change in IOP and Dehydration

Objectives. To observe a possible correlation between progressive reductions in IOP during exercise and systemic dehydration participants will perform a 90-minute ride on an ergocycle. In the hyper-hydrated condition water will be available during the ride. In the hypo-hydrated condition water will be restricted. Both weight and IOP will be measured before, during and after the exercise protocol.

Hypotheses.

H1) Using change in body weight as a measure of hydration, we propose that IOP will correlate with loss of body weight when fluids are restricted and that there will be little movement in IOP when fluids are held constant.

H2) It is possible that we will also replicate initial reductions in IOP when the exercise begins that are unrelated to dehydration and more likely related to changes in level of activity.

6.3 Study 3. The Correlation Between Baseline IOP and Physical Fitness

Objectives. To clarify the relationship between maintained physical conditioning and baseline IOP the current study will perform four discrete baseline measures conducted over an eight-week period, and a single test of VO_2max on an ergocycle. In this way we hope to analyze the correlation between baseline IOP and a person's level of physical conditioning.

Hypothesis.

H1) There will be a negative correlation between baseline IOP and $V0_2$max such that the higher a person's $V0_2$max the lower the baseline intraocular pressure.

H2) At the higher end of $V0_2$max values, it is further proposed that baseline IOP will be stable from week to week.

6.4 Article 1

Reductions in intraocular pressure after acute aerobic exercise: a meta-analysis

A meta-analysis on post exercise change in IOP via acute aerobic exercise: Looking toward prevention of POAG.

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ABSTRACT

Purpose. Aerobic exercise is known to reduce elevated intraocular pressure (IOP), a primary risk factor for a disease of the eye known as Primary Open Angle Glaucoma (POAG). Given the disparate nature of experimental protocols across the literature an analysis of studies, on the effect of acute aerobic exercise on IOP, is necessary to verify the influence of participant characteristics, exercise intensity and duration.

Method. The electronic databases PubMed, Web of Science and Embase were searched producing 35 empirical studies for review. Ten studies producing 14 independent groups were chosen as per the criteria of the analysis.

Results. Random-effects models were used to produce subgroup analyses and meta-regressions were used to verify the impact of group allocation, intensity and duration on the inter-study variability of the effect size. The outcome variable of post exercise change in IOP produced a significant effect of exercise, almost two-fold greater for sedentary populations than for normally active populations (ES = -4.198 [CI -5.151, -3.245], ES =-2.340 [CI -3.305, - 1.375], respectively). Intensity and duration do not contribute to the overall effect size nor do they explain the difference between sedentary and normally active populations.

Conclusions. There is a robust effect of exercise on IOP for sedentary participants. However, the heterogeneity across study parameters such as exercise protocol, IOP measurement and participant selection prohibited the inclusion of studies in this analysis that may have influenced the results. The current analysis makes clear the need for standardization of protocol across this field of research.

Introduction

Primary Open Angle Glaucoma (POAG) is a disease of the eye that progresses asymptomatically for many years, until visual deficits and irreversible damage to the retina have already occurred (Quigley & Broman, 2006; Quigley, 2011). POAG is the second leading cause of blindness worldwide and will affect 80 million people by the year 2020 (Quigley & Broman, 2006). Complementary lifestyle changes alongside clinical treatment of POAG are becoming increasingly important as prevalence of the disease increases coupled with decreasing access to eye health care for low-income, elderly populations (Winters, 2008). Of the many implicated risk factors including age, heredity and corneal thickness, elevated intraocular pressure (IOP) remains the only controllable risk factor for POAG (Bengtsson & Heijl, 2005; Chauhan et al., 2008; Quigley. 2011). Exercise is a significant factor in the prevention and management of many chronic and age-related diseases and the literature on the relationship between exercise and IOP spans over five decades (Gale, Wells, & Wilson, 2009; Risner et al., 2009). Although studies vary widely with regard to population descriptions and exercise protocol, the majority show a transient reduction in IOP after acute aerobic exercise (Gale et al., 2009; Risner et al., 2009).

Normal IOP levels are generally thought to range from 10 to 21 millimeters mercury (mm Hg) and clinically high IOP is often differentiated by repeated readings over 21.0 to 24.0 mm Hg (Gordon & Kass, 1999; Quigley, 2011) (see Wilson [1997] for a discussion on this topic). The majority of studies on the effect of aerobic exercise on IOP find reductions from pre-exercise values on the order of 1.4 to 8.0 mm Hg in sedentary and normally active populations (Risner et al., 2009; Gale et al., 2009; Hamilton & Feeney, 2012; Karabatakis et al., 2004).

Acute aerobic exercise produces transient reductions in IOP across intensity levels that range from very light, such as a brisk walk, to vigorous running on a treadmill, to volitional exhaustion on treadmills or cycle ergometers (Risner et al., 2009). There is evidence that it is exercise intensity alone and not exercise duration that is the key factor involved in the magnitude of the reduction in IOP (Harris, Malinovsky, & Martin, 1994; Kiuchi et al., 1994;

Qureshi, 1995a,b; Qureshi, Xi, Huang, & Wu, 1996b).

A qualitative comparison of results across studies suggests the relationship between the intensity of aerobic exercise and IOP is not entirely clear. Field running for 15 minutes and walking for 13.5 minutes in normally active participants (Kiuchi et al., 1994; Hamilton-Maxwell & Feeney, 2012, respectively) produce reductions in IOP of 4.3 and 1.4 mm Hg, respectively. There is a nominal difference in duration between the two conditions but running is a higher intensity exercise than walking and produces a greater reduction in IOP (Ainsworth et al., 2003; Ainsworth et al., 2011). However, an even higher intensity exercise, running up and down seven flights of stairs, also produces a reduction of 4.3 mm Hg (Buckingham & Young, 1986). If intensity is a major factor in the reduction of IOP there may be a ceiling effect, a level beyond which intensity no longer impacts the magnitude of reduction in IOP.

Another factor affecting post exercise IOP is the current fitness profile of a participant. A greater reduction is observed in sedentary populations when compared to those who are physically active (Risner et al., 2009; Harris et al., 1994; Dane et al., 2006a). Harris et al. (1994), compared two groups of participants divided posteriori into sedentary and active groups by the concentration of lactate (lactic acid which has diffused out of the muscle) in the bloodstream after a vigorous 10-minute session on a cycle ergometer. The point at which lactate increases faster than the body can flush it from the muscle is known as the Lactate Threshold. The lower the threshold is, the more sedentary the individual (Gibbons et al., 1996; McArdle, Katch, & Katch, 2006). When the results were stratified, the sedentary group experienced an almost two-fold reduction in IOP as compared to the active group (-4.7 versus -2.7 mm Hg, respectively, Harris et al., 1994).

Objectives

The current meta-analysis was designed to obtain a quantitative estimate of the overall effect of acute aerobic exercise on IOP as well as the relative contributions of exercise intensity and duration, and the degree to which these variables affect sedentary and normally active populations. For those populations most at risk for the development of POAG it is

important to examine the potential of aerobic exercise as a factor in the management of continued eye health.

Materials and Methods

Search Strategy

An open search was performed on the electronic databases PubMed from 1977, Web of Science from 1979 (including Medline from 1950) and Embase from 1974, through to March 2, 2012.

The Cochrane List of Registered Trials and the archived abstracts from the annual meetings of the Association for Research in Vision and Ophthalmology and the Vision Sciences Society, from 2001 to the present, were also searched for unpublished studies. The references of relevant studies were hand searched. The keywords used in a pilot search of PubMed for related literature were physical activity or exercise* AND intraocular pressure OR ocular blood flow OR ocular tension OR glaucoma. For the final search the MeSH (PubMed), EMTREE (Embase) and free text keywords "exercise*" and "intraocular pressure" were used.

Identification of studies. The search yielded 658 papers as follows: PubMed (n = 188), Web of Science/Medline (n = 230) and Embase (n = 240) including 355 duplicates. Of the remaining studies, 268 of the studies were excluded by abstract (Figure 1.1). There were 35 potentially relevant sources from which two were excluded because the results pertaining to a specific set of participants were used in a previous publication. Nineteen studies were excluded because of missing statistical information that could not be obtained from the authors contacted (n = 8). Ten studies were included in this meta-analysis producing fourteen independent groups (Table 1.1).

An independent reviewer (Dave Ellemberg, PhD) was consulted for all questions regarding inclusion of a potentially relevant study.

Inclusion Criteria

The following inclusion criteria were imposed:
1) Studies must include post exercise Δ IOP measured after the first acute bout of aerobic exercise on a given test day, and associated *SD* or *SE*, or raw participant data.
2) Participants should be sedentary, normally active or athletic (excluding professional athletes) displaying no pre-existing ocular pathologies or IOP over 18 mm Hg.
3) To reduce the likelihood of age related pathologies that may affect the eye, all participants should be no more than 55 years of age (Klein & Klein, 1981; Schulzer & Drance, 1987).
4) Exercise should be aerobic in nature and the intensity must be quantifiable using physiological target measures such as a percentage of VO_2max or sub maximal heart rate (MHR).
5) The duration of exercise should be no less than 2 minutes ensuring at least partial recruitment of the aerobic system and no more than 60 minutes within daylight hours to constrain the effect of diurnal variation (Liu, Zhang, Kripke, & Weinreb, 2003; Hamilton, Pye, Aggarwala, Evian, Khosla, & Perera, 2007).

Assessment of Risk and Bias

Of potential studies to be included in this analysis only Harris et al. (1994) and Passo, Goldberg, Elliot and Van Buskirk (1987) are included in the Cochrane Register of Controlled Trials (Higgins & Altman, 2011). In both cases, only a subset of the conditions could be included. Therefore the evaluation tool for assessing risk of bias was not employed.

An independent reviewer (Dave Ellemberg, PhD) was consulted for all questions regarding inclusion of a potentially relevant study.

Data Extraction

The following information was extracted from each study: post exercise Δ IOP measured in mm Hg and associated variance, participant characteristics, type and duration of exercise, physiological and absolute measures of exercise intensity, IOP measurement methodology and tools, latency of the post exercise measure, authors, date and country of

publication and any information pertaining to the control of covariates.

Outcome Variables

The primary outcome variable to be examined in this analysis was post exercise Δ IOP. The relative contribution of exercise intensity and duration to the relationship between exercise and IOP, and their differential effects on each population, were also evaluated. To standardize the energy cost of the exercises across studies, physiological markers of intensity were converted to a metabolic equivalent of task (MET; see Table 1.2). For studies using a submaximal percentage of $VO2_{max}$ as the target training range the standard formula for conversion from $VO2_{max}$ to a MET value was applied (%$VO2_{max}$ [ml•kg•min]/ 3.5) (ACSM, 2010, p. 162; Dane et al., 2006a; Passo, Goldberg, Elliot and Van Buskirk, 1987). Four studies required a conversion of the given sub MHR to a percentage of $VO2_{max}$ for which we used a linear regression (% MHR = 0.646 × [%$VO2_{max}$ x 100] + 37.182) (Dane et al., 2006a; Karabatakis et al., 2004; Kiuchi et al., 1994; Read & Collins, 2011; Swain, Abernathy, Smith, Lee, & Bunn, 1994). Where necessary MET values were weighted for sex using $VO2_{max}$ normative tables for females and males between 20 and 29 years of age in the 50^{th} percentile (Dane et al., 2006a; Hoffman, 2006; Karabatakis et al., 2004; Read & Collins, 2011). For the remaining four studies MET values were assigned using the 1993 and 2011 Compendia of Physical Activities (Ainsworth et al., 1993; Ainsworth et al., 2011; Hamilton-Maxwell & Feeney, 2012; Harris et al., 1994; Buckingham & Young 1986; Qureshi et al., 1996b).

Statistical analyses

Assuming that all studies were not functionally equivalent, random-effects models were used to produce subgroup analyses and a forest plot. Meta-regressions were used to verify the impact of group allocation, intensity and duration on the inter-study variability of the effect size (ES). Analyses were done with Stata version 12.1 using a significance level of 5%.

Results

Search Results

Participant characteristics. The combined studies produced 231 participants of which 67 were female and 130 were male (Table 1.1). The gender of 34 participants was not specified (Harris et al., 1994; Buckingham & Young, 1986). The normally active group includes all participants described as trained, athletic or otherwise normally active (n = 124).

Study characteristics. Four studies produced two independent groups each (Table 1.1). The preconditioning results from both the experimental and control group in the long-term study by Qureshi (1996a) are included as two sedentary groups. In the study by Karabatakis et al. (2004) the results from a single group including "Untrained" and "Athletic" participants were divided into a sedentary group (Group U, n = 4) and a normally active group (Group A, n = 25). The two groups in the "fixed" intensity condition from Harris et al. (1994) and both the sedentary and the Athletic group from the Dane et al. (2006a) were included in this analysis. The preconditioning results from all ten participants included in Passo et al. (1987) are included in this analysis as a single sedentary group.

Two of the studies included in this analysis tested different intensity conditions in a within subjects design (Table 1.2). Qureshi et al. (1996b) had sedentary participants ride a cycle ergometer at six combinations of intensity and duration over six days. We included only the 15-minute, 60% MHR condition in the current analysis. Kiuchi et al. (1994) had normally active participants run at five combinations of intensity and duration. The 15-minute, 70% MHR condition was included in this analysis. In both cases, the condition chosen represented a duration and intensity not represented by the other included studies.

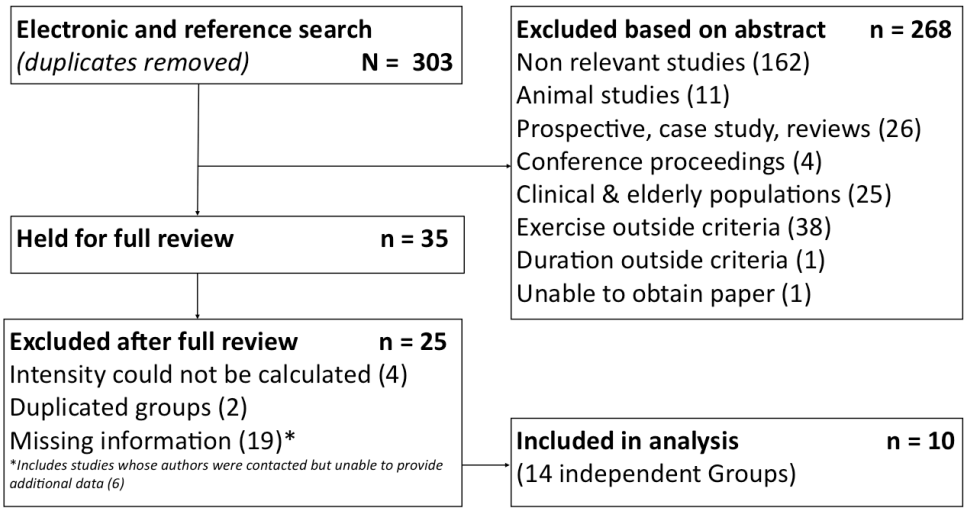

Figure 1.1. *Literature Search and Exclusions*

Table 1.1

General characteristics of participants

First Author and Country	Year	N	Participant Description* (Female/Male)	Age range	IOP at Baseline
Dane Turkey	2006	25 24	Sedentary (without any activity) Gr 1 (11/14) Athletes (Runners from university) Gr 2 (11/13)	17 - 22 17 - 22	15.0 SD 3.0 15.2 SD 3.3
Harris USA	1994	11 17	Sedentary Gr 3 Athletic (Competitive Cyclists) Gr 2 Both groups mixed gender	Young Adults	16.4 SD .8 16.3 SD .5
Passo USA	1987	10	Sedentary (3/7)	36.6 - 37.4	14.3 SE .7
Qureshi China	1996b	25	Healthy Sedentary (no activity 3 mths) Males	21 - 26	13.9 SE .5
†Karabatakis Greece	2004	4 25	Physically Untrained Gr U (2/2) Athletic Gr A (9/16)	13- 18	≈ 13.5
Qureshi China	1996a	16 16	Sedentary (no activity 6 mths) Gr 1 Gr 2 Both groups Male	 21-30 21-30	 15.1 SE .6 15.2 SE .7
Buckingham UK	1986	6	University Students Mixed Gender	18-21	No baseline IOP given
Hamilton-Maxwell Wales	2011	25	Healthy Students (23/2)	19.5 - 22.1	16. SD 2.6
Read Australia	2011	20	Young Adults (8/12)	21 - 29	16.5±2.2‡
Kiuchi Japan	1994	7	Healthy Males (exercise 2 hrs./wk. for 6 mths)	20 - 24	13.8 SE .5

* Participant descriptions are verbatim from the respective studies.
† The 29 participants in the study by Karabatakis et al. (2004) are divided into two groups, Gr A comprises 25 participants categorized as Athletic and Gr U comprises the four Untrained participants.
‡No variance was provided.

Table 1.2

Study descriptions

Activity	Exercise Intensity (METs)	Exercise Duration (minutes)	IOP Measurement Device	Eye*	Time of Post Exercise Measure	Post Exercise Δ IOP
Jog Treadmill	7.8	5	Pneumo-tonometer	OD	End of exercise	-1.72 SE .56(Gr1) +0.33 SE .40(Gr2)
Cycle Ergometer -	6.8	10	GAT†	OS	End of exercise	-4.70 SE .40 (Gr 3) -2.70 SE .40 (Gr 2)
Cycle Ergometer	9.2	12.1±.3	GAT	ND	5 minutes post exercise	-5.90 SE .60
Cycle Ergometer	4.1	15	GAT	OU	5 minutes post exercise	-3.50 SE .70
Jog Treadmill	5.8	20	Applanation Tonometry	OU	End of exercise	-5.75 SE 1.44 (Gr U) -2.92 SE 1.89 (Gr A)
Cycle Ergometer	4.8	60	GAT	OU	End of exercise	-4.18 SE .41 (Gr1) -4.38 SE .47 (Gr2)
7 Flight Stair Run	15	2	Noncontact Tonometer	OU	3 minutes post exercise	-4.34 SE .63
Brisk Walking	3.5	13.4±1.4	Topcon CT 80 Noncontact Tonometer	OD	End of exercise	-1.4 SE .22
Cycle Ergometer	5.8	10	Dynamic Contour Tonometer	OD	End of exercise	-1.71 SE .28
Field Running	6.2	15	GAT	OU	5 minutes post exercise	-4.30 SE.70

*Eye of Measure: OD = data from right eye only; OS = data from left eye only, OU = data averaged for both eyes
†GAT: Goldmann Applanation Tonometry
‡Only the pre-conditioning results from the studies by Passo et al. (1987) and Qureshi (1996a) were included in the analysis.
§These studies use repeated measures.

Statistical Results

The current meta-analysis reveals that there is a significant effect of exercise on post exercise IOP, unstandardized effect size (ES) = -3.263, 95% CI [-4.158, -2.368], $p < 0.001$ (Figure 1.2). When the ES is stratified by group allocation, both the sedentary group (ES = -4.198, 95% CI [-5.151, -3.245]) and the normally active group (*ES* =-2.340, 95% CI [-3.305, -1.375]) are significantly different than 0 (p <0.000; Figure 1.2, Table 1.3). Group allocation (sedentary vs. normally active) contributes significantly to the overall ES (B = -1.886, SE -0.818, p = 0.043) and explains 27.60% ($R2_{adj}$) of the between-study variability (Table 1.4).

The residual between-study variability is estimated by tau^2 (T^2) in the same metric as the Δ IOP (mm Hg). Group allocation produced a T^2 of 2.009 (Table 1.4). The I-squared (I^2) value of 89% should be interpreted as the proportion of residual variability actually attributed to between-study heterogeneity (T^2) while the remaining 11% of the between study variability assumes within-study sampling error (Higgins, Thompson, Deeks, & Altman, 2003).

To quantify the contribution of intensity (METs), duration (minutes) and quantity (METs*minutes) of exercise to the overall ES, a separate regression was performed for each, as there were not enough studies to include all variables in a single meta-regression. There was no significant contribution to the overall ES for any of these factors: B = .105, SE = .177, p = 0.562; B = -.031, SE = .026, p = 0.252 and B = -.009, SE = .005, p = 0.130, respectively (Table 1.4). To analyze whether group differences can be explained by the response of each group to intensity or duration of exercise we controlled for the variables one at time and added group allocation in a sequential multiple meta-regression. In all cases, group allocation remains significant while intensity and duration of exercise remain non-significant (Table 1.4).

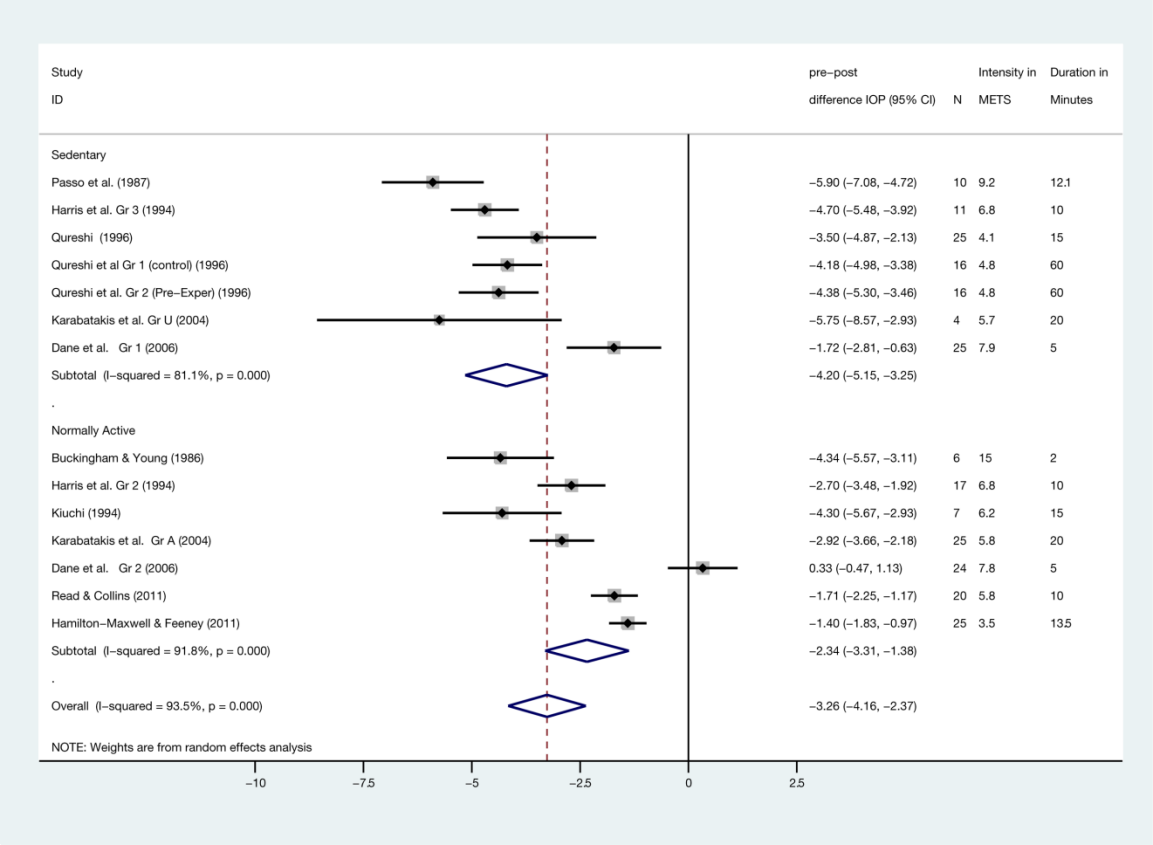

Figure 1.2. Post exercise Δ IOP with a random effect model plotted for 14 independent groups. The Δ IOP is plotted along the x-axis and the 95% confidence interval is noted for each study. The dotted line indicates the unstandardized ES of post exercise Δ IOP.

Table 1.3

Tests of heterogeneity

	Heterogeneity Stat (Q)	*df*	I^2	T^2
Sedentary	31.79***	6	81.1%	1.2515
Normally active	73.03***	6	91.8%	1.4973
Overall	201.39***	13	93.5%	2.5986

Note. *** p < .0001
I^2 (%) = residual variation attributed to the heterogeneity between studies
T^2 = restricted maximum likelihood approach estimate of between study variance.

Table 1.4

The contribution of group allocation, exercise intensity, duration and quantity to the overall effect size

Variable	Coefficient (B)	*SE*	*t*	$p > \|t\|$	T^2	I^2 (%)	R^2_{adj}	95% CI	
†Group allocation	-1.8565*	.8184	-2.27	.043	2.009	88.55	27.60	-3.640	-.0733
Intensity (METs)	-0.1055	.1770	-0.60	.562	2.919	93.53	-5.22	-.4911	-.2801
Duration (minutes)	-0.0308	.0256	-1.20	.252	2.655	92.56	4.33	-.0866	-.0250
†Group and	-2.0152	.8204	-2.46	.032				-0.3821	-0.2096
Intensity	-0.1713	.1508	-1.14	.280	1.95	88.41	29.72	-0.5034	0.1607
†Group and	-1.6902	.9473	-1.78	.102				-3.7753	-0.3949
Duration (minutes)	-0.0103	.0261	-0.39	.702	2.19	89.33	21.07	-0.0678	-0.0472

Note. * $p < .05$
T^2 = restricted maximum likelihood approach estimate of between study variance.
I^2 (%) = residual variation attributed to the heterogeneity between studies
R^2_{adj} = proportion of between study variance explained by covariate (with Knapp-Hartung modification)
†Group = Normally active group held constant

Discussion

Over the last five decades a large number of empirical studies investigated the relationship between acute aerobic exercise and IOP. However, researchers often neglect to report the variance associated with the mean change in IOP after exercise, without which the results cannot be interpreted given the small sample sizes in many studies. Further, exercise intensity and duration are quantified differently across studies. The objective of the current work was to combine the results of studies that looked specifically at the effect of acute aerobic exercise on IOP, in order to obtain greater statistical power, and to verify the influence of the key factors implicated in the relationship between aerobic exercise and IOP. The results of this analysis indicate that there is a significant effect of an acute bout of aerobic exercise on post exercise IOP that is almost two-fold greater for sedentary populations than for normally active populations, (ES = -4.198 and -2.340, respectively, Figure 1.2). According to the available data, group differences cannot be explained by exercise intensity or duration (Table 1.4). However, given the heterogeneity across studies it is important to consider the limitations of this analysis, and the studies within, before the clinical implications of these results can be explored.

Limitations of This Analysis and Included Studies

The difference in methodology across studies is potentially reflected in the elevated I^2 values (> 88% across analyses, Tables 1.3 to 1.5). I^2 can be thought of as the proportion of residual variability attributed to between-study heterogeneity (denoted by tau^2, Tables 1.3 and 1.4) as opposed to within-study sampling error (Higgins et al., 2003). The methodological differences range from the determination of population and exercise parameters to the control of variables that cause IOP fluctuation beyond that which is caused by exercise.

The physical fitness of an individual participant is posited as a factor in the magnitude of reduction in IOP that can be expected with exercise (Dane et al., 2006a; Passo et al., 1987;

Qureshi, 1996a). Therefore, any ambiguity with regard to the parameters governing group allocation in the original study is compounded here and may affect the magnitude of the ES. By example, normally active participants in Dane et al. (2006a) are described only as "runners from the author's university" without qualification. However, those participants produced a +0.33 mm Hg increase in IOP after exercise, as opposed to a decrease, and were likely at a higher level of fitness than the other normally active groups in this analysis.

In accord with the idea that there is an interaction between a participant's current fitness level and the effect of exercise on IOP, the magnitude of reduction in post exercise IOP is often found to be in proportion with relative rather than absolute intensity measures (Hamilton-Maxwell & Feeney, 2012; Harris et al., 1994; Kiuchi et al. 1994; Qureshi et al., 1996b, Passo et al., 1987). However, as the parameters governing acute exercise were notably different across studies, including supporting physiological data, the intensity measures from each study were converted to MET values, an absolute measure (ACSM, 2010, pp.4-5). The conversion to MET values allowed for comparison across all studies and the ages of the participants were in a small range that would not bring too much weight to the higher end of the scale. In nine of the ten studies participants ranged between 17 and 30 years of age, with the exception of the ten participants in the Passo et al. (1987) study who were ≈ 37 years of age. For clarity, stratification by relative intensity is compared to the assigned METs (Table 1.5). Although there is not enough statistical power, in any one group, to create a subgroup analysis by relative intensity category, Table 1.5 provides a clearer picture of how the MET values derived for each study compare to approximations of relative values and the nature of the discrepancies.

Table 5

Comparison of MET values and relative intensity categories.

Ref#	*MET value determined for analysis	Classification of exercise intensity provided in study [Compendia #]	Type of Exercise	Exercise Duration (Minutes)	Post Exercise Δ IOP in mmHg
Moderate †[METs = 3 to 6; Relative Intensity = 64-76% MHR or 40-59% $V0_2R$ and HRR]					
10	3.5	1046 m at an average of 4.7 +/- .5 km/h	Walk	12-15	-1.40
15	4.1	‡60% MHR	Cycle	15	-3.50
32	4.8	50cpm@75W [02017]	Cycle	60	-4.18 -4.38
11	5.8	70% MHR	Jog	20	-5.75 -2.92
29	5.8	50-70% HRR	Cycle	10	-1.71
Vigorous †[METs = > 6 METs; Relative Intensity = 77-93% MHR or 60-84 $V0_2R$ and HRR]					
13	6.2	‡ 70% MHR	Run	15	-4.30
12	6.8	10min@90W [02012]	Cycle	10	-4.70 -2.70
19	7.84	‡ 70% MHR	Jog	5	-1.72 +.33
26	9.20	‖ VO_2max 32.2	Cycle	≈12	-5.90
18	15	20% increase in BP [02170]	Stair Run	2	-4.34

*****Discrepancies between relative intensity categories and MET values are noted.
†METs metabolic equivalent units (1 MET = 3.5 mL $\cdot kg^{-1} \cdot min^{-1}$); $V0_2R$, oxygen uptake reserve (resting V02 - VO_2max); HRR, heart rate reserve; MHR, maximal heart rate.
‡ The short duration of the exercise and VO_2max gender weighting from normative tables in this analysis may have caused discrepancies between the relative measure and MET value.
‖The average VO_2max (32.2) falls into the *Light* relative intensity category (VO_2max 20-39). However, the conversion to METs (32.2/3.5) placed this study in the *Vigorous* category by MET (>6). Passo et al. (1987) used an average VO_2max value with no apparent weighting for gender (7 men to 3 women) and a slightly older sample (≈ 37 years of age). Each participant cycled to a different exhaustion point both in terms of VO_2max and duration.

A qualitative analysis of the MET values assigned to each study reveals that when divided into two categories, moderate intensity exercise [3 to 6 METS] or vigorous [> 6 METS] (ACSM, 2010, pp. 4-5), the difference in the average reduction of IOP is less than 1.0 mm Hg. The difference is also less than 1.0 mmHg when the studies that straddle categories are all placed into the moderate category and when the anomalous study with a MET value of 15 (Buckingham & Young, 1986) is removed entirely (Table 1.5) (Kiuchi et al. 1994; Qureshi et al., 1996a; Dane et al., 2006a; Passo et al., 1987). Regardless of the method of categorization, intensity does not bear weight on the outcome as per this analysis.

The control of covariates is paramount when embarking on an examination of the relationship between exercise and reductions in IOP because of physiological factors which cause IOP fluctuations including posture, diurnal variation (Hamilton et al., 2007; Liu et al., 2003), smoking (Wimpissinger at al., 2003) and fluid intake (Li, Wang, Guo, Wang, & Sun, 2011; Moura, Rodrigues, Waisberg, de Almeida, & Silami-Garcia, 2002). To control for fluctuations in posture the exercise criteria of the included studies were constrained to walking, jogging, running or cycling. Duration was constrained to one hour in the daytime to control for diurnal to nocturnal variation in IOP which can be as high as 5.0 ± 0.3 mm Hg in a healthy population (Liu et al., 2003). However, a lack of information across studies did not allow the comparison of many other covariates. Pre- exercise fluid intake is a notable example as water, coffee and alcohol have differential transient effects on IOP (Buckingham & Young, 1986; Li et al., 2011; Moura et al., 2002).

One litre of water is known to cause a 2.0 mm Hg increase in IOP, at ten minutes post consumption that increases to 4.0 mm Hg at 70 minutes, with baseline IOP not regained for over 140 minutes (Buckingham & Young, 1986). Coffee consumption also creates a transient increase in IOP in some populations (≈ 3.0 to 4.0 mm Hg) that persists for up to 1.5 hours after consumption (Buckingham & Young, 1986; Li et al, 2011) while alcohol can lower IOP significantly for up to 65 minutes (Buckingham & Young, 1986).

The control of covariates is further complicated by the fact that post exercise

measurements of IOP are subject to substantial variation across equipment, and within and across observers. Five studies included in this analysis used Goldmann Applanation Tonometery (GAT) (see Table 1.2), the standard to which most other methods of IOP measurement are compared. The interobserver variability of GAT is 0.4 mm Hg and the 95% Limit of agreement is ± 2.6 mm Hg (Tonnu, Ho, Sharma, White, Bunce, & Garway-Heath, 2005). However, GAT overestimates IOP in eyes with thicker corneas and underestimates IOP when corneas are thinner (Whitacre, & Stein, 1993). The same is true of Non Contact Tonometry (NCT), used by two studies (Buckingham & Young, 1986; Hamilton-Maxwell & Feeney, 2012), which reads higher than GAT (mean difference from GAT ≈ 1.5 mm Hg, 95% Limit of agreement ≈ ± 3.0; Ogbuehi, 2006). The contact pneumotonometer used in Dane et al. (2006) has a mean difference of 0.72 ± 2.82 mm Hg from GAT (Molina, Milla, Bitrian, Larena, & Martíneza, 2010). Dynamic Contour Tonometry (DCT), a contour matching method used by Read and Collins (2011) has a mean difference of +1.7 mm Hg from GAT (Kaufmann, Bachmann, & Thiel, 2004). It is not only the equipment but also the number of IOP measurements that can affect the outcome of a study. Repeated measurements with contact tonometers can reduce IOP by increasing outflow of the aqueous humor from the eye (Molina et al., 2010).

The above factors contribute to substantial variations in the outcome of a given study and must be kept in mind when interpreting the results of the current analysis. Other factors that may impact IOP, such as gender and race are not addressed in this analysis. The above limitations notwithstanding, there is a robust effect of exercise on IOP that bears further examination.

Initial Observations

Intensity of exercise. Contrary to much of the literature (Harris et al., 1994; Kiuchi et al., 1994; Qureshi et al., 1996b; Kielar, Teraslinna, Rowe, & Jackson, 1975), intensity did not contribute significantly to the effect of aerobic exercise on IOP in the current analysis (Table 1.4). Neither could the difference in the magnitude of reduction in IOP between the sedentary and normally active groups be explained by their differential response to intensity (Table 1.4).

This is a surprising finding as two of the groups included in this analysis were from studies that looked specifically at the relationship between intensity of exercise and the magnitude of reduction in IOP (Kiuchi et al., 1994; Qureshi et al., 1996b). In both cases, in a within subjects design, the magnitude of reduction in IOP was roughly proportional to relative intensity. However, there is considerable research, including the aforementioned studies, that find no correlations between blood pressure or heart rate and post exercise change in IOP, as might be expected if relative intensity was a key factor (Harris et al., 1994; Kiuchi et al., 1994; Passo et al., 1987; Qureshi et al., 1996b).

It is also of interest that the highest intensity exercise in this analysis, a 2 minute stair run at 15 METs created the same reduction in a normally active population (4.34 mm Hg) as did a fifteen minute run at 6.2 METs (Buckingham & Young, 1986; Kiuchi et al., 1994, respectively). This suggests a floor effect on the magnitude of reduction that can be expected with exercise for normally active participants. This in accord with Dane et al. (2006a) who showed that the physically fit participants experienced almost no change in IOP as compared to the sedentary group. Further, in their studies on the change in IOP after long-term training, Passo et al. (1987) and Qureshi (1996b) showed that reductions in IOP were significantly less in the trained groups as compared to the controls. It is possible that the magnitude of reduction in IOP is solely dependent on where a participant lies along a physical fitness level continuum, thus having achieved a certain level of physical adaptation, regardless of the intensity of the exercise. This concept is discussed further in the Mechanisms section.

Duration and quantity of exercise. Like intensity, exercise duration and quantity did not significantly contribute to the effect of exercise on IOP. It should be noted that of the ten included studies, six used exercise durations of 10 to 15 minutes (see Table 1.2). The three sedentary groups from that subset produced an average reduction in IOP of 4.70 mm Hg (Harris et al., 1994; Passo et al., 1987; Qureshi, 1996a). The two sedentary groups that exercised for 60 minutes produced an average reduction of 4.28 mm Hg (Qureshi, 1996a). To examine whether it is the overall output of energy that dictates the magnitude of reduction in IOP rather than either intensity or duration alone, exercise intensity is expressed as quantity (METs*minutes; ACSM, 1991).

Comparing these two subsets we find that 60 minutes of cycling at 4.8 METs is more than three times the average quantity of the other three sedentary groups, yet the average reduction of IOP is slightly less. It seems that duration and intensity interact equivocally across studies.

Mechanisms. It remains unclear as to what mechanism contributes to the initial reduction of IOP after acute aerobic exercise. Changes in colloid osmotic pressure (one factor in capillary fluid exchange), increases in plasma osmolarity (electrolyte-water balance), ocular blood flow and blood lactate, and decreases in blood PH have all been suggested as possible mechanisms that initiate a reduction in IOP (Ashkenazi, Melamed, & Blumenthal, 1992; Harris, Malinovsky, Cantor, Henderson, & Martin, 1992; Harris et al., 1994; Kiuchi et al., 1994; Martin, Harris, Hammel, & Malinovsky, 1999; Moura et al., 2002; Marcus, Krupin, Podos, & Becker, 1970; Orgül & Flammer, 1994). There are two studies that attribute much of the transient post exercise decrease in IOP to factors related to dehydration and the amount of water ingested pre-exercise. The results of one study suggest the decrease in IOP is a simple return to basal values after water ingestion while the other implicates an increase in colloid osmotic pressure (Moura et al., 2002; Martin et al., 1999, respectively). However, duration did not contribute to the effect of exercise in this analysis as one might expect if increasing dehydration were to play a role in the reduction of IOP (Harris et al., 1994). Further, significant reductions in IOP were found after aerobic exercise of 5 minutes and less that are on par with reductions produced at much longer durations (Askenazi et al., 1992; Buckingham & Young, 1986; Dane et al., 2006a; Orgül & Flammer, 1994).

Some population-based studies report an association between systemic blood pressure and fluctuations in IOP (Klein & Klein, 1981). Although exercise is known to increase systolic blood pressure through sympathetic stimulation, it is less clear how that relationship relates to mechanisms involved in post exercise reductions in IOP. Five studies included in our analysis find no linear correlation between blood pressure and post exercise reductions in IOP (Harris et al., 1994; Karabatakis et al., 1994; Kiuchi et al., 1994; Passo et

al., 1987; Read & Collins, 2011).

Long-term effects of exercise. There is evidence that, over time, continued exercise (Passo et al., 1987; Read & Collins, 2011; Williams, 2009) and physical labour in the workplace (Qureshi, Wu, Xi, Yang, & Huang, 1997a) induce adaptations of the sympathetic nervous system that contribute to an overall reduction in baseline IOP. During exercise, the increase in metabolic muscle heat during exercise increases overall body temperature, which in turn activates mechanisms to cool the body. Loss of water and electrolytes via sweat during exercise cause increased plasma osmolarity, changes in colloid osmotic pressure and ultimately dehydration (Martin et al., 1999; Moura et al., 2002; Guyton & Hall, 2006b, c, d). As humans acclimatize to progressive heat they sweat more profusely which increases the plasma volume and diminishes the loss of electrolytes, thereby maintaining plasma osmolarity (Guyton & Hall, 2006b).

Two studies included in the current analysis, Qureshi (1996b) and Passo et al. (1987) found reductions in baseline IOP of .8 to 1.3 mmHg after long-term exercise conditioning. Passo et al. (1987) in particular, found that pre-training acute exercise decreased IOP in Sedentary participants by 41% from baseline. After 3 months of exercise conditioning, three days per week, acute exercise reduced IOP by 12% from baseline, a reduction that persisted for an average of three weeks in some participants (Passo et al., 1987). The combined evidence suggests an enduring effect of exercise on IOP that is in accord with the idea that those who are physically fit will maintain a baseline IOP that is lower than those who do not exercise (Dane et al., 2006a; Passo et al., 1987; Qureshi, 1996b; Qureshi et al., 1997a; Williams, 2009). It remains unclear whether exercise can slow down the progressive elevation of IOP that is part of the normal aging process (Schulzer & Drance, 1987; Qureshi, 1995b).

It is possible that an increase in plasma osmolarity of a magnitude sufficient to affect post exercise IOP would occur only after longer durations of exercise than are seen in this analysis. A study looking at the fluctuation of IOP over a 24 hour 110 km march found an inverse relationship between reduction in IOP and plasma osmolarity (Ashkenazi et al., 1992).

This finding stands in contrast to that of Harris et al. (1994) who reports no mean change in the plasma osmolarity of participants after 10 minutes of cycling. These two results suggest that mechanisms that govern reduction of IOP over long exercise durations may be different than those that affect shorter durations.

Clinical implications. The robust effect of exercise on IOP in the sedentary group in this analysis outlines the need to continue this research with elderly and clinical populations. There are inherent complications affecting these populations that dictate the need for standardization of population parameters and exercise protocol. Generally, research finds differential reductions in IOP in elderly populations, dependent on baseline IOP (Qureshi, 1995b; Era, Parssinen, Kallinen, & Suominen, 1993), and reductions of up to ≈ 12.0 mm Hg for clinical populations (Qureshi, 1995b). Complicating matters is the fact that as patients age they are far more likely to have undiagnosed POAG and co morbid age-related pathologies both of which progress slowly over years, making studies involving clinical populations hard to compare (Winters & Pihos, 2008; Schulzer & Drance, 1987; Qureshi, 1995c).

It should be noted that there is some controversy with regard to the effect of exercise on IOP in clinical populations. Studies including populations with advanced Glaucoma, or other severe subtypes such as pigmentary dispersion Glaucoma, have found increases in IOP and temporary vision loss after exercise of varied intensity (Haynes, Johnson, & Alward, 1992; Shah, Whittaker, Wells, & Khaw, 2001).

With regard to implementation of exercise as a complimentary reduction therapy, timing is of the essence. There is a protective effect when IOP is pharmacologically reduced immediately after diagnoses, as compared to later treatment. Unfortunately, only 60 to 70% of patients comply with long-term drug regimes, because of the slow progression of the disease and negative side effects of the medication (Friedman et al., 2007; Leske et al., 2003; Schwartz, & Quigley, 2008). Further, population screening outside the healthcare system is not cost effective and therefore many people are not even diagnosed until noticeable symptoms bring them to see their doctor (Schwartz & Quigley, 2008; Winters & Pihos, 2008).

The possibility that exercise could be another useful tool in an eye health regime is not a remote one. The results of the current analysis suggest that physical exercise can produce the magnitude of reduction in IOP required to have an impact clinically. The target reduction of IOP in a clinical setting is often 20 to 40% of baseline IOP (Winters & Pihos, 2008). The average baseline for the sedentary group is ≈15 mm Hg and the post exercise change in IOP is 4.198 mm Hg, a 28% reduction. This is encouraging as statistics from the Early Manifest Glaucoma Trial suggest that for every 1.0 mm Hg decrease in IOP there is a 10% reduction in the rate of disease progression (Leske et al., 2003). Conversely, for every 1.0 mm Hg increase in IOP there is a 19% increase in the progression of POAG (Chauhan et al., 2008). Exercise could also impact the rate of visual field loss, which increases exponentially with increasing IOP in those patients with POAG (Jay & Murdoch, 1993).

Future research needs to concentrate on whether that transient post exercise reduction can be stabilized with the introduction of a regular aerobic exercise program (Vermeire, Hearnshaw, Van Royen, & Denekens, 2001).

Conclusion

The current analysis brought together studies that looked specifically at a single bout of aerobic exercise and post exercise change in IOP. There is a clear effect of aerobic exercise on IOP, most importantly for the sedentary group (ES = 4.198 mm Hg) as compared to the normally active group (ES = 2.340 mm Hg). The differential effect of exercise between the two groups is not explained by exercise intensity or duration. There are a number of limitations in this study, largely related to the sheer number of variables that affect transient changes in post exercise IOP and the variation in parameters across studies. Regardless, the magnitude of the overall post exercise change in IOP, for the sedentary group especially, suggests continued exploration into the usefulness of aerobic exercise as an additional factor in the management of continued eye health.

Key Words: intensity; duration; sedentary; active; Glaucoma prevention; physical activity

REFERENCES

Ainsworth, B. E., Haskell, W. L., & Leon, A. S., Jacobs, D. R. Jr., Montoye, H. J., Sallis, J. F., & Paffenbarger, R. S. Jr. (1993). Compendium of physical activities: Classification of energy costs of human physical activities. *Medicine & Science in Sports & Exercise*, 25, 71-80.

Ainsworth, B. E., Haskell, W. L., Herrmann, S. D., Meckes, N., Bassett, D. R. Jr., Tudor-Locke, C. … Leon, A. S. (2011). Compendium of Physical Activities: a second update of codes and MET values. *Medicine & Science in Sports & Exercise*, 43(8), 1575-1581.

American College of Sports Medicine. (1991). Health Appraisal and Risk Assessment. In: Walter Thompson (Ed.), *Guidelines for Exercise Testing and Prescription*, (4th ed., pp. 93-119). Philadelphia: Lea and Febiger.

American College of Sports Medicine. (2010a). Health Appraisal and Risk Assessment. In: Walter Thompson (Ed.), *Guidelines for Exercise Testing and Prescription*, (8th ed., pp. 4-6), USA: Walters Kluwer: Lippincott Williams and Wilkin.

Ashkenazi, I., Melamed, S., & Blumenthal, M. (1992). The effect of continuous strenuous exercise on intraocular pressure. *Investigative Ophthalmology & Visual Science, 33*(10), 2874-2877.

Bengtsson, B., & Heijl, A. (2005). A long-term prospective study of risk factors for glaucomatous visual field loss in patients with ocular hypertension. *Journal of Glaucoma*, *14*(2), 135.

Buckingham, T., & Young, R. (1986). The rise and fall of intra-ocular pressure: the influence of physiological factors. *Ophthalmic and Physiological Optics*, *6*(1), 95-99.

Chauhan, B. C., Mikelberg, F. S., Balaszi, A. G., LeBlanc, R. P., Lesk, M. R., & Trope, G. E.

(2008). Canadian Glaucoma Study 3:Risk factors for the progression of Open-Angle Glaucoma. *Archives of Ophthalmology*, *126*(8), 1030–1037. doi: 10.1001/archopht.126.8.1030.

Dane, S., Koçer, I., Demirel, H., Ucok, K., & Tan, U. (2006a). Effect of acute submaximal exercise on intraocular pressure in athletes and sedentary subjects. *International Journal of Neuroscience*, *116*(10), 1223–1230. doi: 10.1080/00207450500522501.

Era, P., Parssinen, O., Kallinen, M., & Suominen, H. (1993). Effect of bicycle ergometer test on intraocular pressure in elderly athletes and controls. *Acta Ophthalmologica* (Copenhagen), *71*(3), 301-307.

Friedman, D. S., Quigley, H. A., & Gelb, L., Tan, J., Margolis, J., Shah, S. N. … Hahn, S. R. (2007). Using pharmacy claims data to study adherence to glaucoma medications: Methodology and findings of the Glaucoma Adherence and Persistency Study (GAPS) *Investigative Ophthalmology & Visual Science*, *48*, 5052–5057. doi:10.1167/iovs.07-0290.

Gale, J., Wells, A. P., & Wilson, G. (2009). Effects of ocular physiology and disease. *Survey of Ophthalmology, 54*(3), 349-355. doi: 10.1016/j.survophthal.2009.02.005.

Gibbons, T., Mulligan, S., Wilber, R., Rundell, K., Shannon, M., & Kearney, J. (1996). Presented by the Sport Science and Technology Division of the United States Olympic Committee. *Lactate Threshold: Application to training and performance.* http://www.coachr.org/lactate_threshold_application_to_training_and_performance.htm. Accessed June 18, 2012.

Gordon, M.O., & Kass, M. A. (1999). The Ocular Hypertension Treatment Study: design and baseline description of the participants. *Archives of Ophthalmology*, *117*(5), 573-583. doi:10.1001/archopht.117.5.573.

Guyton, A. C., Hall, J. E. (2006b). Energetics and Metabolic Rate, Body temperature, temperature regulation and fever. In: Schmitt W, Gruliow, R. (Eds.), *Textbook of Medical Physiology.* (11th ed., pp. 889-900), Philadelphia, PA; Elsevier Saunders.

Guyton, A. C., Hall, J. E. (2006c). The Body fluid compartments: Extracellular and intracellular fluids; interstiitial fluid and edema. In: Schmitt W, Gruliow, R. (Eds.), *Textbook of Medical Physiology.* (11th ed., pp. 291-299), Philadelphia, PA; Elsevier Saunders.

Guyton, A. C., Hall, J. E. (2006d). Sports Physiology. In: Schmitt W, Gruliow, R. (Eds.), *Textbook of Medical Physiology.* (11th ed., p. 1065), Philadelphia, PA; Elsevier Saunders.

Hamilton-Maxwell, K. E., & Feeney, L. (2012). Walking for a short distance at a brisk pace reduces IOP. *Journal of Glaucoma*, *21*(6), 421–425. doi: 10.1097/IJG.0b013e31821826d0.

Hamilton, K. E., Pye, D. C., Aggarwala, S., Evian, S., Khosla, J., & Perera, R. (2007). Diurnal variation of central corneal thickness and Goldmann applanation tonometry estimates of intraocular pressure. *Journal of Glaucoma*, *16*(1), 29-35. doi: 10.1097/IJG.0b013e31802b350f.

Harris, A., Malinovsky, V. E., Cantor, L., Henderson, P. A., & Martin, B. J. (1992). Isocapnia Blocks Exercise-Induced Reductions in Ocular Tension. *Investigative Ophthalmology & Visual Science, 33*(7), 2229-2232.

Harris, A., Malinovsky, V. E., Martin, B. J. (1994). Correlates of acute exercise-induced ocular hypotension. *Investigative Ophthalmology & Visual Science, 35*(11), 3852-3857.

Haynes, W., Johnson, A., & Alward, W. (1992). Effects of jogging exercise on patients with the pigmentary dispersion syndrome and pigmentary glaucoma. *Ophthalmology*, *99*(7),

1096–1103.

Higgins, J. P. T., & Altman, D. G. (2011). Assessing risk of bias in included studies. In: Higgins, J. P. T., & Green, S., (Eds.), *Cochrane handbook for systematic reviews of interventions.* [Version 5.1.0, updated March 2011]. The Cochrane Collaboration. Available from www.cochrane-handbook.org. Accessed June 30,2012.

Higgins, J. P. T., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta analyses. *British Medical Journal*, *327*(7414), 557-560. doi: 10.1136/bmj.327.7414.557.

Hoffman, J. (2006). Aerobic Power and Endurance. Norms for Fitness Performance and Health. In: Bahrke MS, Ewing AS. (Eds.), USA: Human Kinetics.

Jay, J. L., & Murdoch, J. R. (1993). The rate of visual field loss in untreated primary open angle glaucoma. *British Journal of Ophthalmology*, *77*(3), 176-178.

Karabatakis, V., Natsis, K., Chatzibalis, T., Lake, S. L., Bisbas, I. T., Kallinderis, K. A., & Stangos, N. T. (2004). Correlating intraocular pressure, blood pressure, and heart rate changes after jogging. *European Journal of Ophthalmology*, *14*(2), 117–122.

Kaufmann. C., Bachmann, L. M., & Thiel, M. A. (2004). Contour Tonometry with Goldmann Applanation Tonometry. *Investigative Ophthalmology & Visual Science*, *45*(9), 3118-3121. doi:10.1167/iovs.04-0018.

Kielar, R. A., Teraslinna, P., Rowe, D. G., & Jackson, J. (1975). Standardized aerobic and anaerobic exercise: differential effects on intraocular tension, blood pH, and lactate. *Investigative Ophthalmology & Visual Science*, *14*(10), 782-785.

Kiuchi, Y., Mishima, H. K., Hotehama, Y., Furumoto, A., Hirota, A., & Onari, K. (1994). Exercise intensity determines the magnitude of IOP decrease after running. *Japanese Journal of Ophthalmology*, *38*(2), 191–195.

Klein, B. E., & Klein, R. (1981). Intraocular pressure and cardiovascular risk variables. *Archives of Ophthalmology, 99*(5), 837-839. doi:10.1001/archopht.1981.03930010837009.

Leske, M. C., Heijl, A., Hussein, M., Bengtsson, B., Hyman, L., & Komaroff, E. (2003). Factors for glaucoma progression and the effect of treatment: The Early Manifest Glaucoma Trial. *Archives of Ophthalmology*, *121*(1), 48-56. doi:10.1001/archopht.121.1.48.

Li, M., Wang, M., Guo, W., Wang, J., & Sun, X. (2011). The effect of caffeine on intraocular pressure: a systematic review and meta-analysis. *Graefe's Archive for Clinical and Experimental Ophthalmology*, *249*(3), 435-442. doi: 10.1007/s00417-010-1455-1.

Liu, J, H. K., Zhang, X., Kripke, D. F., & Weinreb, R. N. (2003). Twenty-four-hour intraocular pressure pattern associated with early glaucomatous changes. *Investigative Ophthalmology & Visual Science*, *44*(4), 1586-1590.

Martin, B., Harris, A., Hammel, T., & Malinovsky, V. (1999). Mechanism of exercise-induced ocular hypotension. *Investigative Ophthalmology & Visual Science, 40*(5), 1011-1015.

Marcus, D. F., Krupin, T., Podos, S. M., & Becker, B. (1970). The effect of exercise on intraocular pressure. I. Human beings. *Investigative Ophthalmology*, *9*(10), 749-752.

McArdle, W. D., Katch, F. I., & Katch, V. L. (2006). Essentials of exercise physiology. In: Lupash E., Kiefer R (Eds.), *Human Energy Transfer during exercise.* (3rd ed., p. 204). Philadelphia, PA; Lippincott Williams & Wilkins.

Molina, N., Milla, E., Bitrian, E., Larena, C., & Martíneza, L. (2010). Comparison of Goldmann tonometry, pneumotonometry and the effect of the central corneal thickness. *Archivos de la Sociedad Española de Oftalmología (English), 85*(10), 325-328. doi: 10.1016/j.oftal.2010.09.003.

Moura, M. A., Rodrigues, L. O. C., Waisberg, Y., de Almeida, H. G., & Silami-Garcia, E. (2002). Effects of submaximal exercise with water ingestion on intraocular pressure in healthy human males. *Brazilian Journal Of Medical and Biological Research, 35*(1), 121-125.

Ogbuehi, K. C. (2006). Assessment of the accuracy and reliability of the Topcon CT80 non-contact tonometer. *Clinical and Experimental Optometry*, *89*(5), 310–314. doi: 10.1111/j.1444-0938.2006.00068.x.

Orgül, S., & Flammer, J. (1994). Moderate exertion lasting only seconds reduces intraocular pressure. *Graefe's Archive for Clinical and Experimental Ophthalmology, 232*(5), 262-264.

Passo, M. S., Goldberg, L., Elliot, D. L., & Van Buskirk, E. M. (1987). Exercise conditioning and intraocular pressure. *American Journal of Ophthalmology, 103*(6), 754–757.

Qureshi, I. A. (1995a). Effects of mild, moderate and severe exercise on intraocular pressure of sedentary subjects. *Annals of Human Biology*, *22*, 545–553.

Qureshi, I. A. (1995b). The effects of mild, moderate, and severe exercise on intraocular pressure in glaucoma patients. *Japanese Journal of Physiology*, *45*(4), 561-569.

Qureshi, I. A. (1995c). Age and intraocular pressure: how are they correlated? *Journal of Pakistan Medical Association*, 45(6), 150-152.

Qureshi, I. A. (1996a). Effects of exercise on IOP in physically fit subjects, *Clinical and Experimental Pharmacology and Physiology, 23*(8), 648–652.

Qureshi, I. A., Xi, X., Huang, Y., & Wu, X. (1996b). Magnitude of decrease in intraocular pressure depends upon intensity of exercise. *Korean Journal of Ophthalmology, 10*(2), 109-115.

Qureshi, I. A., Xi, X. R., Lu, H. J., Wu, X. D., Huang, Y. B., & Shiarkar, E. (1996c). Effect of seasons upon intraocular pressure in healthy population of China. *Korean Journal Ophthalmology*, *10*(1), 29-33.

Qureshi, I. A., Wu, X. D., Xi, X. R., Yang, J., & Huang, Y. B. (1997a). Resting intraocular pressure of steel factory workers is related to their physical fitness. Industrial Health, 35(2), 259-263.

Quigley, H. A. (2011). Glaucoma. *The Lancet, 377*(9774), 1367-1377. doi: 10.1016/S0140-6736(10)61423-7.

Quigley, H. A., & Broman, A. T. (2006). The number of people with glaucoma worldwide in 2010 and 2020. *British Journal of Optholmolgy*, *90*(3), 262–267. doi: 10.1136/bjo.2005.081224.

Read, S. A., & Collins, M. J. (2011). The short-term influence of exercise on axial length and intraocular pressure. *Eye* (London), *25*(6), 767–774. doi: 10.1038/eye.2011.54.

Risner, D., Ehrlich, R., Kheradiya, N. S., Siesky, B., McCranor, L., & Harris, A. (2009). Effects of exercise on intraocular pressure and ocular blood flow: a review. *Journal of Glaucoma, 18*(6), 429-436. doi: 10.1097/IJG.0b013e31818fa5f3.

Schulzer, M., & Drance, S. M. (1987). Intraocular pressure, systemic blood pressure and age: A correlational study. *British Journal of Opthalmology, 71*(4), 245-249.

Schwartz, G. F., & Quigley, H. A. (2008). Adherence and Persistence with Glaucoma Therapy. *Survey of Ophthalmology*, *53*(Supplement 1), S57-S68. doi: 10.1016/j.survophthal.2008.08.002.

Shah, P., Whittaker, K., Wells, A., & Khaw, P. T. (2001). Exercise-induced visual loss associated with advanced glaucoma in young adults. *Eye (London)*, *15*(Part 5), 616-620. doi: 10.1038/eye.2001.196.

Swain, D., Abernathy, K. S., Smith, C. S., Lee, S. J., & Bunn, S. A. (1994). Target heart rates for the development of cardiorespiratory fitness. *Medicine & Science in Sports & Exercise*, *26*(1), 112-116.

Tonnu, P. A., Ho, T., Sharma, K., White, E., Bunce, C., & Garway-Heath, D. (2005). A comparison of four methods of tonometry: method agreement and interobserver variability. *British Journal of Opthalmology, 89*(7), 847-850. doi: 10.1136/bjo.2004.056614.

Vermeire, E., Hearnshaw, H., Van Royen, P., & Denekens, J. (2001). Patient adherence to treatment: three decades of research. A comprehensive review. *Journal of Clinical Pharmacy and Therapeutics*, *26*(5), 331-342.

Whitacre, M. M. & Stein, R. A. (1993). Sources of error with use of Goldmann-type tonometers. *Survey of Ophthalmology*, *38*, 1-30. doi: 10.1016/0039-6257(93)90053-A.

Wilson, M. R. (1997). The Myth of "21". *Journal of Glaucoma*, 6(2), 75–77.

Wimpissinger, B., Resch, H., Berisha, F., Weigert, G., Polak, K., Schmetterer, L. (2003). Effects of Isometric Exercise on Subfoveal Choroidal Blood Flow in Smokers and Nonsmokers. *Investigative Ophthalmology & Visual Science, 44*(11), 4859-4863.

Williams, P. T. (2009). Relationship of incident glaucoma versus physical activity and fitness in male runners. Medicine & Science in Sports & Exercise, *41*(8), 1566-1572. doi: 10.1249/MSS.0b013e31819e420f.

Winters, J. E., & Pihos, A. M. (2008). Sight for seniors: A summary of findings and challenges to providing community-based eye care to low-income seniors. *Optometry*, *79*(12), 718-723

6.5 Article 2

The Progression of Exercise Induced Changes in Intraocular Pressure as a Function of Dehydration

The Progression of Exercise Induced Changes in Intraocular Pressure as a Function of Dehydration

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ABSTRACT

Purpose. A transient reduction in IOP after a single bout of aerobic exercise is found time and again across studies of exercise-induced change in intraocular pressure (IOP). There is a suggestion in the literature that the mechanisms implicated in the hypotensive effect of exercise on IOP involve metabolic changes that occur during the progression to systemic dehydration.

Methods. In the current study, 13 participants rode an ergocycle in a temperate room for 90 minutes, at 59% of their maximal aerobic capacity, in a state of either hyper- or hypohydration. IOP was measured at 0, 5, 30, 60 and 90 minutes, and 30 minutes after exercise. Body weight was measured at 0, 30, 60 and 90 minutes.

Results. There is an initial drop in IOP under both conditions followed by a rise in IOP at 30 minutes that is nearly equal to baseline. From that point on, IOP hovers around baseline values in the hypo-hydrated condition and increases until the end of the exercise protocol in the hyper-hydrated condition. There was a reduction in body weight in both conditions, however it was significantly greater in the hypo-hydrated condition and was not significantly correlated with change in IOP in either condition.

Conclusions. Fluctuations in IOP during and after exercise are likely a homeostatic response to dysregulation of the aqueous humor caused by fluid intake, posture changes and large changes in activity level and do not seem to be related to physical exercise on its own.

Keywords: intraocular pressure, exercise, physical fitness, dehydration, fluid intake, homeostasis

Introduction

There are over five decades of research on the hypotensive effect of aerobic exercise on intraocular pressure (IOP). In general, researchers find a transient reduction from baseline IOP (10 to 21 mm Hg) on the order of 1.2 to 8.0 mm Hg, in a normal population, after a single bout of moderate to vigorous exercise (Gale, Wells, & Wilson, 2009; Risner et al., 2009; Roddy, Curnier, & Ellemberg, 2014). A meta-analysis conducted by our group confirmed a mean post exercise change in IOP of -2.340 mm Hg 95% CI [-3.305, -1.375] for normally active participants and -4.18 mm Hg 95% CI [-5.151, -3.245] for sedentary participants (Roddy et al., 2014).

The mechanism driving post exercise reductions in IOP is still unknown but one suggestion is that it involves metabolic changes that occur during the progression to systemic dehydration (Hunt, Feigl, & Stewart, 2012; Martin, Harris, Hammel, & Malinovsky, 1999, Sollanek et al., 2012). As a person sweats electrolytes are lost and plasma osmolarity or hyperosmolarity increases (low electrolytes as compared to water), as does colloid osmotic pressure (pressure exerted by the increased proteins in blood plasma) if fluids are not maintained. Both of these homeostatic processes have the potential to cause osmotic changes in the retinal and uveal vasculature that could ultimately reduce the volume and formation of intraocular fluids, thereby reducing IOP (Guyton & Hall, 2006b, Martin et al., 1999). Given this proposed relationship between decreasing IOP values and individual levels of hydration, it is suggested that IOP measurements could provide immediate and useful information regarding a person's hydration status at a given point in time, such as during sport activities (Ashkenazi, Melamed, & Blumenthal, 1992; Hunt et al., 2012; Sollanek et al., 2012).

Hunt, Feigl and Stewart (2102) explored how room temperature changes the relationship between aerobic exercise and IOP. Participants were asked to perform 90 minutes of walking on a treadmill in two climate conditions, 22°C (temperate) and 43°C (hot). All participants were pre-hydrated with an isotonic solution the night before testing and 250 ml at least 60 minutes before exercise. The researchers found that IOP decreased to a significantly greater extent in the hot compared to the temperate condition (≈ -3.4 versus -1.1 mm Hg,

respectively). Weight loss due to an increased volume of sweat was also significantly greater during the hot condition (≈-3.13 versus -.78 kg, respectively) and accounted for 51% of the variance when results were normalized for baseline IOP. The authors of the study attributed the post exercise change in IOP to mechanisms associated with dehydration in the hot condition only.

It is suggested that without manipulation (e.g. room temperature) to induce increased sweating, dehydration might not affect post exercise IOP (Buckingham & Young 1986; Harris, Malinovsky, & Martin, 1994; Moura, Rodrigues, Waisberg, de Almeida, & Silami-Garcia, 2012). Moura, Rodrigues, Waisberg, de Almeida and Silami-Garcia (2002) explored the combined effect of water intake, water temperature and exercise on IOP. Participants were asked to ingest 600 ml of water 15 minutes before either 45 minutes of seated rest or before 90 minutes of exercise on an ergocycle. Participants also ingested 240 ml of water at 15, 30 and 45 minutes over the course of both the exercise and rest conditions, for a total 1320 ml of water ingested. IOP was measured during six different experimental sessions, pre- and post exercise or rest at one of three different water temperatures.

IOP increased from an average of 12.4 mm Hg to 14.3 mm Hg in both the exercise and rest conditions and the participants lost an average of 0.3 kg body weight during the exercise condition and gained 0.5 kg body weight in the resting condition. The fluctuation in IOP was the same in both the exercise and rest conditions and returned to basal values after both exercise and rest. There was no effect of water temperature on IOP. Moura et al. (2002) concluded that changes in IOP were largely attributable to the 1320 mL of water ingested pre- and during exercise and rest.

The relationship between exercise induced fluctuations in IOP and systemic dehydration is complicated by at least three factors. Firstly, the range of fluid ingestion protocols before and during exercise does not allow for an accurate comparison of progressive change from baseline across studies (Harris et al., 1994; Hunt et al., 2012; Moura et al., 2002; Sollanek et al., 2012). This is further complicated by individual variations based on physical

fitness, the temperature of the room and the composition of the fluid (water or isotonic) ingested (Hunt et al., 2012; Sawka et al., 2007; Sollanek et al., 2012).

Secondly, the duration of exercise required to bring a participant to a minimum level of dehydration (e.g., ≥ 2% reduction in body weight) also varies with the manipulation of the temperature and fluid ingestion protocols, as well as exercise intensity (Casa, Armstrong, Hillman, Montain et al., 2000; Sawka et al., 2007). The majority of studies on exercise and IOP include only 10 to 60 minutes of low to vigorous bouts of exercise in a temperate room, with varying levels of control on pre-exercise fluid intake (Gale et al., 2009; Risner et al., 2009; Roddy et al., 2014). Ten to 20 minutes in a temperate room is too short a duration to cause dehydration, however, across the literature, many studies find reductions in IOP despite the short durations and large variation in fluid ingestion protocols (Roddy et al., 2014).

Orgül and Flammer (1994) found that IOP and heart rate were positively correlated in an aerobic test of 8 seconds (deep knee bends) suggesting that those reductions in IOP were more likely related to the immediate responses of the parasympathetic nervous system that ultimately affect choroidal blood flow and vascular resistance. It is possible that the reported decreases in IOP when a person initiates exercise is the result of the parasympathetic nervous system producing homeostatic responses to sudden changes in energy demands (Guyton & Hall, 2006b,c,d).

Finally, the results of a number of studies suggest that increased physical fitness reduces the hypotensive effect of exercise on IOP (Gale et al., 2009; Harris et al., 1994; Qureshi, 1996a, 1997b; Risner et al., 2009; Roddy et al., 2014). When a person engages in chronic exercise the efficacy of the sweating mechanism increases. Plasma volume increases instead of osmolarity, diminishing the loss of electrolytes through the sweat and urine (Guyton & Hall, 2006b,c). The state of being Hypo- (a water deficit) versus Hyper- (a water surplus) hydrated before and during exercise could modulate the overall volume and composition of a participant's sweat and affect the speed of electrolyte loss which would influence the time it takes for systemic dehydration (Guyton & Hall, 2006b; Moura et al., 2002).

The current study uses a within subject experimental design to investigate the relationship between IOP and hydration during aerobic exercise. Participants rode an ergocycle in a temperate room for 90 minutes in a state of either hyper- or hypo-hydration. IOP was measured at 0, 5, 30, 60 and 90 minutes, and 30 minutes after exercise. Body weight was measured at 0, 30, 60 and 90 minutes.

Using change in body weight as a measure of hydration, we propose that IOP will correlate with loss of body weight when fluids are restricted and that there will be little movement in IOP when fluids are held constant. It is possible that we will also replicate initial reductions in IOP when the exercise begins that are unrelated to dehydration and more likely related to homeostatic responses to changes in level of activity.

Methods

The current study was approved by the ethics committee for research in health sciences of the University of Montreal. Ten females and six males were recruited from the University of Montreal, QC, Canada and from the city of Montreal, QC, Canada, via posters and social media. One female and one male did not validate the Test of Maximal Oxygen Intake (VO_2max) and could not be included in the experiment. Another female participant could not complete the final day of exercise and her data were excluded from the analyses. The remaining 13 participants were between 20 and 46 years of age (M = 32.2, SD = 7.0), were free of ocular and systemic diseases that affect IOP and had no history of steroid use (Quigley, 2011). Characteristic data are presented in Table 2.1. Weekly exercise routines and physical demands with regard to occupation were monitored via self-report on all three days of the experimental procedure.

The experiment required three visits from each participant. Day 1 was a test of VO_2max to determine the relative intensity of the exercise protocol over the next two test days. On days 2 and 3 participants began the session with baseline readings of IOP, heart rate, blood pressure (BP) and weight followed by a 90-minute ride on an ergocycle. The experiment

was a within subjects design, as such, the two hydration conditions were counterbalanced across the two days. Measurement protocols and intervals are described in detail below.

Table 2.1.

Descriptive statistics

Variable	Mean	*SD*
Age	32.23	7.05
*IOP Baseline (mm Hg)	14.11	4.03
Baseline Body weight (Kg)	65.96	10.43
VO_2max (ml•kg•min)	40.56	5.65
Height (cm)	167.48	6.79

*Baseline IOP was not significantly different between conditions therefore the value is an average of both conditions at Time 0.

Test of Maximal Oxygen Intake (VO_2max)

Aerobic capacity was determined with a VO_2max test performed on a Lode ergocycle (Corival 906900, LODE B.V. Medical Technology, Groningen, The Netherlands). During the test, the Ultima™ CardiO2® (790705-006, 12 lead ECG CPX Testing, Medgraphics Cardiorespiratory Diagnostics, St Paul, MI) was used to monitor the gas exchange via the exhaled breath of the participant. Data were collected with the Breeze Suite software (V. 7.2.0.52, 2001-2011, Medgraphics Corporation, St Paul, MI). To validate the test we measured both the respiratory exchange rate (less oxygen inhaled and more carbon dioxide exhaled) and the plateau in VO_2 as the workload increased (Poole, Wilkerson, & Jones, 2008).

To begin the test, participants warmed up on the bike for 5 minutes at 50 watts (1 watt = 3600 J/hour, or 6.1183 kg-m/min). After the warm up, intensity was increased by 25 watts at 2-minute intervals until the participant could no longer maintain a range of 80 to 90

revolutions per minute (RPMs). Participants were monitored via their heart rate (T31 coded™ Transmitter, Polar® Electro, Lachine, Qc) and the BORG scale of perceived exertion for the duration of the ride (Borg, 1982). Blood pressure was measured with a stethoscope and sphygmomanometer to monitor participants for excessive increases greater than 250 mm Hg in systolic BP and greater than 115 mm Hg in diastolic BP or decreases in baseline BP (>10 mm Hg) during exercise (American College of Sports Medicine [ACSM] 2010b).

The results of the VO_2max test were used to calculate the intensity at which the participants would ride on their next two testing days, using the formula 40-59% VO_2R [$VO2_{max}$ - resting VO_2] (ACSM, 2010a,c).

After the VO_2max test the participants were given a standardized water bottle for the pre-hydration protocol to be followed during the three hours before each of the two testing days.

Pre-test Criteria

To ensure that the pre-hydration protocol could be fulfilled on each of the two testing days, and to mitigate the effects of diurnal fluctuation, the participants were instructed to be awake for 3 hours preceding the test (Hamilton et al., 2007). They were further instructed to abstain from a) contact lens wear for the 24 hours preceding the exercise portion of the test, b) drinking liquids such as caffeine, alcohol or sports drinks for 12 hours preceding exercise (Buckingham & Young, 1986; Li, Wang, Guo, Wang, & Sun, 2011), and c) tobacco, food or medication for a minimum of 3 hours preceding exercise (Wimpissinger et al., 2003).

To ensure that the participants were fully hydrated before starting to cycle they were asked to drink 7 $mL.kg^{-1}$ of water per kilogram of body weight, 2 hours before arriving at the lab (Casa et al., 2000; Cheuvront, Kenefick, Charkoudian, & Sawka, 2013; Sawka et al., 2007). This amount is based on recommendations made in the "Position Stand on Exercise and Fluid Replacement" put forth by the ACSM (Casa et al., 2007). All participants used the same model and size of water bottle.

Exercise Protocol

The participants performed two 90-minute rides on an ergocycle (Lode, Covivial Ergometer, LODE B.V. Medical Technology, Groningen, The Netherlands) at a *moderate* intensity (≈59%) of their VO_2max. The ergocycle was chosen to replicate the only study in a previous meta-analysis (Roddy et al., 2014) that looked at exercise protocols including durations of longer than 20 minutes. A moderate intensity as defined by the American College of Sports Medicine (2010a) is equal to 40-59% $V0_2R$ [$VO2_{max}$ - resting VO_2] or 64-76% of maximal HR (ACSM, 2010a). This intensity was chosen for the current study to best replicate the majority of studies that looked specifically at exercise, IOP and factors of hydration (Hunt et al., 2014; Moura et al., 2002). It is also the range of intensity that is most prevalent in the literature on exercise and IOP as a whole (Roddy et al., 2014).

The exercise protocol was performed on two different days, separated by no less than one week and no more than four weeks. The riding was done between the hours of 9:00:00 and 12:00:00 to mitigate the effects of diurnal fluctuation on IOP (Hamilton et al., 2007). The room was maintained at an average temperature of 22.2º (*SD* = 1.0) and the humidity was kept within 21º and 53º Celsius (deVries & Housh, 1994d,e). A 5-minute warm up was performed at the lower of 50 watts or 40% of the participant's VO_2max.

To ensure that participants were riding in their target range, heart rate was measured throughout the test using a monitor worn around the chest (T31 coded™ Transmitter, Polar Electro, Lachine, Qc). Blood pressure was measured with a stethoscope and sphygmomanometer to monitor participants for excessive increases in systolic or diastolic BP or decreases in baseline BP (>10 mm Hg) during exercise (ACSM, 2010b).

IOP Measurement Protocol

The same researcher, using the iCare® TA01i rebound tonometer (Icare Finland Oy, Vantaa, Finland), took all IOP measurements. A previous meta-analysis from this lab found

that across studies all reported measurement tools were those that required anaesthesia and had the potential to produce increased outflow from repeated measures (Roddy et al., 2014). The surface area applanated by the Rebound tonometer is much smaller than other methods (e.g., approximately 1.80 mm versus 3.06 mm for the GAT) and requires no anaesthetic thereby mitigating some of those measurement difficulties (Kim, Jeoung, Park, Yang, & Kim, 2013). Further the rebound tonometer is a fully portable and self-contained unit. The iCare® has an accuracy of ±1.2 mm Hg at ≤20 mm Hg and ±2.2 mm Hg at >20 mm Hg (Kim et al., 2013; Molina, Milla, Bitrian, Larena, & Martíneza, 2010; Tonnu et al., 2005). The recorded IOP values are an average of six measures per eye at each measurement. Measurements occurred at 0, 5, 30, 60 and 90 minutes and 30 minutes after the exercise stopped.

Participants were seated on the ergocycle for all IOP measurements. The first measurement was taken immediately before participants started pedalling (0 minutes). For each measurement thereafter the resistance of the bike was decreased over 60 seconds and the participant sat still for 60 seconds while the IOP measurement occurred. After the measurement, participants were brought back to the wattage at which they left off with the exception of the 90-minute measure. A final measure was made 30 minutes post exercise. At all time points, IOP was measured before any other measure was taken or the participant dismounted to be weighed.

Hyper- and Hypo- Hydration Protocol

For each of the two testing days, a nude weight measurement was obtained at 0, 30, 60 and 90 minutes immediately after the IOP. Hydration was measured as a function of weight loss. The participants began each of their two rides two hours after finishing their prescribed water amount and then either ingested water as per the hyper-hydration condition, or ingested no water during exercise (hypo-hydration condition).

In the hyper-hydration condition, participants drank 5 $mL.kg^{-1}$ (per body weight) of water at 30 and 60 minutes during exercise in addition to their pre-exercise amount (Casa et al., 2000; Sawka et al., 2007). Fluid replacement was calculated to approximate sweat and

urine losses and maintain hydration at less than a 2% body weight reduction. The water temperature averaged 17.6ºC (*SD* = 3.9) (Casa et al., 2000; Sawka et al., 2007).

Body Weight Measurements

Participants were instructed to void their bladders completely before their initial weight measurement. Body weight was measured at all time points with a Tanita BF-350 Body Composition Analyzer calibrated for accuracy up to 200 kg in increments of .1 kg (Tanita Corporation, Tokyo Japan).

Data Collection

Each IOP data point represents an average of 6 readings. The average was corrected for corneal thickness using the following formula:

IOP *Corrected* = IOP +0.02*(545-CCT).

The manufacturer's correction is based on the results of Ehlers, Bramsen and Sperling (1975).

There was no significant difference between the IOP readings of the two eyes, therefore only the right eye data were used.

Body weight loss was calculated with the following equation:

> % change in body weight (Kg) = {[baseline weight (kg) - post exercise body weight (kg)] - urine volume (L) (Casa et al., 2000; Sawka et al., 2007).

To account for the dry and saturated weight of the heart monitor, the weight

measurements of each participant include .06 kg. For the final nude weight .1 kg was deducted to reflect the saturated weight.

Statistical Analysis

A repeated-measures Analyses of Variance (ANOVA) was conducted for IOP with condition (hyper- and hypo-hydrated) and time (0, 5, 30, 60, 90 and 120 minutes) as factors. A separate ANOVA was also conducted for body weight with condition (hyper- and hypo-hydrated) and time (0, 30, 60, and 90 minutes) as factors. Simple effect analyses were performed to decompose any interaction. Effect sizes for significant ANOVAs were estimated by calculating a partial eta-squared and, for simple effects, they were estimated using Cohen's *d* statistic. Finally, we carried out a bivariate correlation to verify the relationship between change in IOP and bodyweight over time. Statistical analyses were performed with IBM® SPSS® Statistics V22.0.

Results

Intraocular Pressure

Figure 2.1 presents mean IOP for the hyper- and hypo-hydrated conditions as a function of time. Inspection of the figure indicates that IOP at baseline and at 5 minutes into the exercise protocol is the same for the both conditions. Interestingly, there is an initial and similar drop in IOP under both conditions followed by a rise in IOP 30 minutes into the exercise protocol that is nearly equal to baseline. From that point on, IOP hovers around baseline values for the hypo-hydrated condition, whilst it increases continuously until the end of the exercise protocol for the hyper-hydrated condition. Although IOP decreases 30 minutes post-exercise in the hyper-hydrated condition, it is still well above baseline. The ANOVA indicates a significant interaction between time and condition $F(5, 60) = 3.99$, $p = .003$, $\eta_p^2 = .25$, as well as a main effect of time $F(5,60) = 7.90$, $p < .001$, $\eta_p^2 = .40$ and a main effect of condition $F(1,12) = 5.83$, $p = .033$, $\eta_p^2 = .33$.

A series of planned comparisons were conducted to identify the origin of the interaction. IOP was significantly higher in the hyper-hydrated condition as compared to the hypo-hydrated condition at 60 and 90 minutes into the exercise protocol (M = 1.50, SD = 1.87, p = .013, d = .81, 95% CI [.376, 2.624]; M = 2.15, SD = 2.24, p = .005, d = .96, 95% CI [.795, 3.513], respectively) and also at 30 minutes post-exercise (M = 1.85, SD = 2.49, p = .018, d = .05, 95% CI [.369, 3.323]. In the hyper-hydrated condition, there was a significant increase in IOP at the end of the exercise protocol compared to baseline (M = 1.96, SD = 1.77, p = .028, d = -1.10, 95% CI [.15, 3.77] and a significant difference between the first measure taken 5 minutes into the exercise session and the measures taken 60 (M = 2.65, SD = 1.80, p = .003, d = -1.48, 95% CI [.84, 4.47] and 90 (M = 3.00, SD = 1.84, p = .001, d = -1.62, 95% CI [1.13, 4.87] minutes into the exercise and 30 minutes post-exercise (M = 2.15, SD = 1.88, p = .021, d = -1.14, 95% CI [.24, 4.06]. Finally, at no time point was IOP significantly different than baseline in the hypo-hydrated condition.

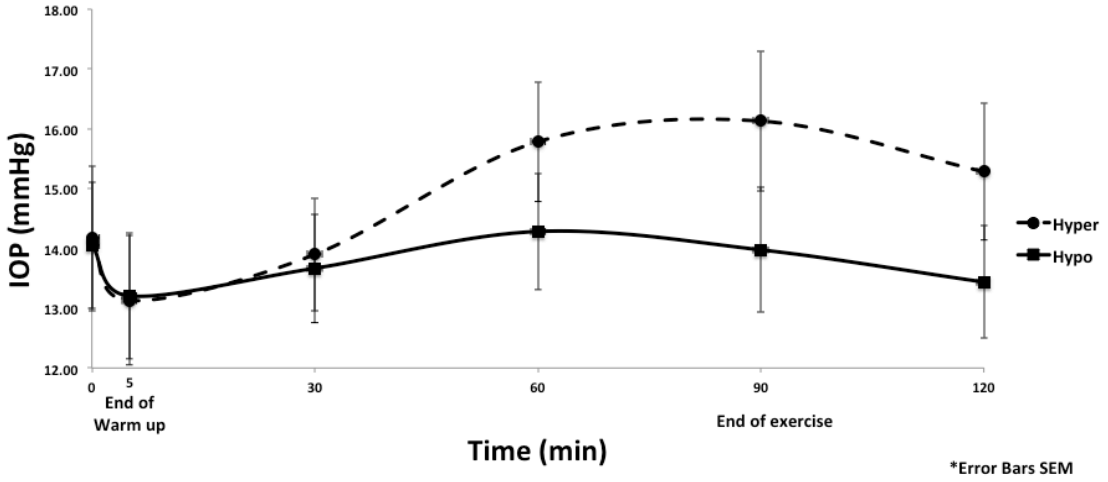

Figure 2.1. Change in IOP pre-, during and 30 minutes post exercise for the hyper and hypo-hydrated conditions, plotted as a function of time. The error bars represent one standard error of the mean.

Body Weight Loss

Figure 2.2 presents the mean body weight at baseline and throughout the exercise protocol for the hyper- and hypo-hydrated conditions. Inspection of the figure shows that body weight changes very little over time in the hyper-hydrated condition, whilst it decreases constantly over time in the hypo-hydrated condition. The ANOVA found a significant interaction between time and condition $F(3, 36) = 82.14$, $p < 001$, $\eta_p^2 = .87$; a main effect of time $F(3,36) = 50.95$, $p < .001$, $\eta_p^2 = .81$; and a main effect of condition $F(1,12) = 5.34$, $p = .039$, $\eta_p^2 = .31$.

A series of planned comparisons were conducted to identify the origin of the interaction. Body weight was significantly lower in the hypo-hydrated condition as compared to the hyper-hydrated condition at 60 and 90 minutes into the exercise protocol ($M = -.55$, $SD = .79$, $p = .024$, $d = -.71$, 95% CI [-1.02, -.08]; $M = -.93$, $SD = .83$, $p = .001$, $d = -1.15$, 95% CI [-1.42, -.44, respectively]). In the hyper-hydrated condition, bodyweight was significantly reduced from baseline at 30 ($M = -.27$, $SD = .07$, $p < .001$, $d = -3.10$, 95% CI [-.34, -1.9], 60 ($M = -.34$, $SD = .22$, $p = .001$, $d = -1.17$, 95% CI [-.53, -.15] and 90 minutes ($M = -.43$, $SD = .29$, p = .001, $d = -1.51$, 95% CI [-.69, -.18]. Body weight was also significantly lower at 90 minutes compared to 60 minutes into the exercise protocol ($M = -.09$, $SD = .11$, $p = .044$, $d = -.90$, 95% CI [-1.86, -.002].

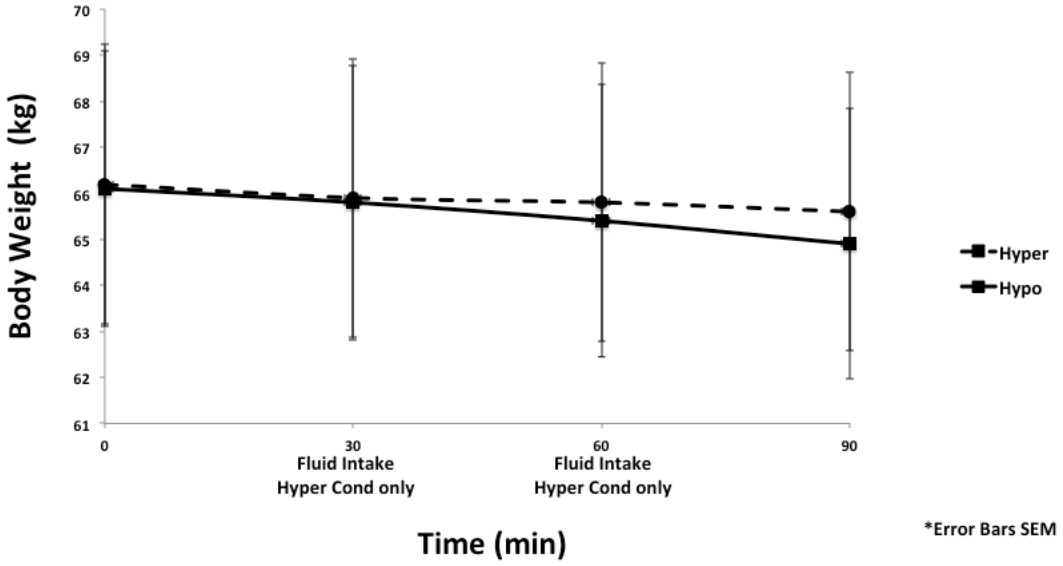

Figure 2.2. Change in body weight pre-, during and post exercise for the hyper- and hypo-hydrated conditions plotted as a function of time. The error bars represent one standard error of the mean.

In the hypo-hydrated condition, bodyweight was significantly reduced from baseline at 30 (M = -.25, SD = .11, p < .001, d = -2.13, 95% CI [-.35, -1.49], 60 (M = -.65, SD = .29, p < .001, d = -2.21, 95% CI [-.90, -.39], and 90 minutes (M = -1.12, SD = .47, p < .001, d = -2.36, 95% CI [-1.53, -.70]. There was also a significant decrease in body weight for each time point compared to the previous measure taken. Specifically, body weight was significantly lower at 60 minutes compared to 30 minutes into the exercise protocol (M = -.39, SD = .18, p < .001, d = -2.09, 95% CI [-.56, -.23], and at 90 minutes compared to 30 minutes (M = -.86, SD = .36, p < .001, d = -2.32, 95% CI [-1.19, -.54] and 60 minutes (M = -.47, SD = .22, p < .001, d = -2.29, 95% CI [-.65, -.29].

A bivariate correlation was used to verify the relationship between change in IOP and body weight. No significant correlation was found.

Room Temperature and Humidity

There were no significant differences between the hyper- and hypo-hydrated

conditions in room temperature and humidity over the duration of the experiment.

Discussion

The post-exercise reduction in IOP is a well-documented phenomenon, however, the mechanisms driving those reductions remains unknown. The aim of the current study was to verify a possible relationship between exercise-induced changes in IOP and dehydration during aerobic exercise. Participants rode an ergocycle in a temperate room for 90 minutes, at 59% of their maximal aerobic capacity, in a state of either hyper- or hypo-hydration. Contrary to much of the literature, we did not find a significant post exercise reduction in IOP in either condition. The decrease in IOP, after 90 minutes of exercise in the hypo-hydrated condition, was only -.08 mm Hg (*SD* = 1.80) despite a 1.12 kg (*SD* = .47) reduction in body weight. Further, even though participants also lost weight at the end of the 90-minute exercise protocol in the hyper-hydrated condition (*M* = -.432 kg, *SD* = .29), we found an increase in IOP of 1.962 mm Hg (*SD* = 1.77) likely caused by the continued ingestion of water.

Relationship Between Post Exercise Body Weight and IOP

In the hypo-hydrated condition, the participants in the current study lost an average 39% more body weight than did the participants in the hyper-hydrated condition. We can assume from this outcome that the hydration protocol was sufficient to create a bimodal distribution and induce dehydration in the experimental group. However, we observed no correlation between loss of body weight and reductions in IOP.

These results are interesting when we consider that the participants lost an average 30% more body weight than did the participants in the temperate condition (22ºC) in the study by Hunt et al. (2012), in which they compare room temperature differences on post exercise IOP. Yet, the participants of Hunt et al. produced a significant post exercise reduction in IOP of -1.1 mm Hg, contrary to our results in which IOP was not significantly reduced post exercise. If dehydration, as measured by loss of body weight, is implicit in the mechanisms driving post exercise IOP we should have observed an even greater decrease than Hunt et al.

In other words, either dehydration is not a factor in post exercise reductions in IOP or it is possible that the relationship between dehydration and post exercise IOP is not a linear one.

The Influence of Water Intake on IOP

In the hyper-hydrated condition there was a significant increase in IOP at the end of the 90-minute exercise protocol as compared to baseline. At 30 and 60 minutes into the exercise protocol IOP was significantly higher than the first measure taken at 5 minutes. These increases in IOP are in accord with Moura et al. (2002) who suggested that change in IOP is due to fluid ingestion pre- and during exercise regardless of the relative level of hydration. In the current study, in both conditions, participants were required to finish their prescribed water two hours before the exercise portion of the test. At 30 and 60 minutes, in the hyper-hydrated condition only, participants ingested a further 5 $mL.kg^{-1}$ (per body weight) of water and IOP rose accordingly, whereas in the hypo-hydrated condition it hovered around baseline. Moura et al. observed that their participants exhibited the same magnitude and pattern of fluctuation in IOP during the 45-minute rest condition as when they were in the exercise condition if water was consumed in the same intervals. The results of both studies taken together suggest that ingestion of water causes IOP increase whether the participant is resting, exercising or in the first stages of dehydration.

Given the robust effect of water consumption on IOP, it is possible that we did not find a significant post exercise reduction in the hypo-hydrated condition because we over-hydrated our participants before they started the exercise protocol. The pre-exercise criteria for both experimental days of this study required that most participants finish drinking nearly half a litre of water (average 432 ml of water per participant, *SD* = 142), two hours before beginning to exercise, to allow time for fluid induced increases in IOP to subside. It is possible that two hours was not enough time and therefore the participants were over-hydrated at the start of the exercise protocol. This would prevent the degree of dehydration necessary to cause the increase in plasma osmolarity and colloid osmotic pressure implicated in post exercise reductions in IOP (Martin et al., 1999). In contrast to our results, Hunt et al. (2012) required all participants to drink 250 ml of an isotonic sports drink upon rising and no later than 60

minutes before the trial. Although this is 90 ml less than the amount of water drank by our smallest participant and closer to the start of the exercise protocol, none of their participants exhibited an increase in IOP.

Habitual water intake and IOP. It seems that water consumption alone does not explain the difference in results between the current study and that of Hunt et al. (2012). There is also the possibility that a post-exercise reduction in IOP was prevented not just by the water ingestion on the test day but also by a discrepancy between habitual water intake and the pre-exercise criteria of the current study. In the hyper-hydrated condition, the IOP of our participants remained significantly elevated even 30 minutes after exercise ceased. There is evidence that hydration, as measured via urine and plasma osmolarity, is responsive to changes in habitual fluid ingestion, and only stabilizes within 24 hours of modifying the volume of water consumed (Perrier et al., 2013a; Perrier et al., 2013b). Although the relative volume of water for each participant was chosen based on the recommendations made by the American College of Sports Medicine (Sawka et al., 2007) on the ingestion of fluid during physical activity and sports it is possible that IOP was too greatly elevated for those participants that do not habitually drink a lot of water upon rising in the morning (Perrier et al., 2013a; Perrier et al., 2013b; Sawka et al., 2007).

The Initial Drop in Post Exercise IOP

There was an initial drop in IOP at 5 minutes in both the hyper- and hypo-hydration conditions on the order of -.846 to -1.038 mm Hg, respectively (SD = 1.13, SD = 1.52, respectively) that replicates a pattern in the literature whereby the initiation of exercise produces an immediate reduction in IOP (Roddy et al., 2014). This initial drop in IOP might occur because when the body changes posture or changes dynamic intensity, such as when initiating exercise, IOP fluctuates (Barkana, 2014; Orgül & Flammer, 1994). Barring pathology of the eye, the fluctuations eventually move towards basal values or an adjusted plateau until the next major postural or physiological change (Acott, Kelley, Keller, & Vranka et al., 2014; Barkana, 2014; Johnstone, 2013; Hamilton et al., 2007; Moura et al., 2002).

If fluctuations in IOP predominantly reflect homeostatic processes, it is also possible that, like other systems of the human body, the ocular system can overshoot the return to basal levels (Guyton & Hall, 2006d; Roberts, Reiss, & Monger, 2000). For example, in most cases, IOP rises when a person lies down and it settles at an elevated plateau. After waking and sitting, IOP gradually returns to baseline within a couple of hours. Jumping up quickly or a short intense bout of movement could produce a reduction in IOP that overshoots the baseline before its ascent back to basal values (Barkana, 2014; Guyton & Hall, 2006d; Roberts et al., 2000; Orgül & Flammer, 1994). Measurements taken too soon after the cessation of intense exercise could be simply reflecting this fluctuation, such as in studies whereby the post exercise measures of IOP occur at10 minutes post exercise or less (Conte, Baldin, Russo, & Storti, 2014; Hunt et al., 2012).

Limitations

There were two possible limitations with the current study. Firstly, our participants were relatively high on the continuum of VO_2max and were under represented at the lower end of the VO_2max scale. A recent meta-analysis revealed that sedentary participants experience an almost twofold reduction in post exercise IOP than is seen in the normally active group, confirming a pattern often seen in the literature (Gale et al., 2009; Risner et al., 2009; Roddy et al., 2014). In the current study, the high fitness level of the participants may have elevated the average post exercise IOP.

Secondly, there is research to show that a valsalva manoeuvre (a forced exhalation when the airway is closed) during intense isometric exercises or weight lifting elevates IOP (Aykan, Erdurmus, Yilmaz, Bilge et al., 2010; Bakke, Hisdal, & Semb, 2009; Harris, Malinovsky, Cantor, Henderson, & Martin, 1992; Rüfer et al., 2014; Vieira, Oliveira, de Andrade, Bottaro, & Ritch, 2006). In the current study, this could have prevented the reduction in IOP observed in other studies that used walking, such as on a treadmill, as the exercise mode (Gale et al., 2009; Hunt et al., 2012; Risner et al., 2009; Roddy et al., 2014). When using a test of maximal aerobic capacity to establish a target range for exercise, it happens that those

participants at the higher end of the fitness scale achieve power settings on the ergocycle that exceed 150 watts. The duration of a VO_2max test is usually no more than 10 to 12 minutes. The protocol of the current study called for 90 minutes of riding at 59% of one's VO_2max. A combination of subjective reporting by the participants and their responses on the Borg scale (Borg, 1982) suggested that leg fatigue was causing increased muscular effort to press down on the pedals. Increased effort from exerting pressure, such as that which occurs during weightlifting, might have begun to elevate rather than reduce IOP (Bakke et al., 2009; Vieira et al., 2006). Although this does not explain the difference between the hypo- and hyper-condition of the current study and does not affect our main conclusions, it is relevant to the overall discussion of appropriate exercise protocols for the study of aerobic exercise on changes in IOP.

Conclusion

One of the mechanisms implicated in the hypotensive effect of exercise on IOP is hyperosmolarity potentially caused by systemic dehydration. The results of the current study did not support that theory. IOP remained close to baseline for the duration of exercise when fluid was restricted, and increased with water consumption when participants drank during exercise. Reductions in body weight (dehydration) were not significantly correlated in either the hyper- or hypo-hydrated conditions. The results of the current study suggest that fluctuations in IOP during and after exercise are likely a homeostatic response to dysregulation of the aqueous humor caused by fluid intake and large changes in activity level that initiate a parasympathetic response and do not seem to be related to physical exercise on its own.

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REFERENCES

Acott, T. S., Kelley, M. J., Keller, K. E., Vranka, J. A., Abu-Hassan DW, Li X … Bradley, J. M. (2014). Intraocular pressure homeostasis: maintaining balance in a high-pressure environment. *Journal of Ocular Pharmacology and Therapeutics*, *30*(2-3), 94-101. doi: 10.1089/jop.2013.0185.

American College of Sports Medicine. (2010a). Health Appraisal and Risk Assessment. In: Walter Thompson (Ed.), *Guidelines for Exercise Testing and Prescription*, (8th ed., pp. 4-6), USA: Walters Kluwer: Lippincott Williams and Wilkin.

American College of Sports Medicine [ACSM] (2010b). Health Related Physical Fitness Testing and Interpretation. In: Walter Thompson (Ed.), *Guidelines for Exercise Testing and Prescription*, (8th ed., pp. 82-87). USA: Walters Kluwer: Lippincott Williams and Wilkin.

American College of Sports Medicine. (2010c). General Principles of Exercise Prescription. In: Walter Thompson (Ed.), *Guidelines for Exercise Testing and Prescription*, (8th ed., pp. 156-163). USA: Walters Kluwer: Lippincott Williams and Wilkin.

Ashkenazi, I., Melamed, S., & Blumenthal, M. (1992). The effect of continuous strenuous exercise on intraocular pressure. *Investigative Ophthalmology & Visual Science, 33*(10), 2874-2877.

Aykan, U., Erdurmus, M., Yilmaz, B., & Bilge, A. H. (2010). Intraocular pressure and ocular pulse amplitude variations during the valsalva manoeuvre. *Graefe's Archive for Clinical and Experimental Ophthalmology*, *248*(8), 1183-1186. doi: 10.1007/s00417-010-1359-0.

Bakke, E. F., Hisdal, J., & Semb, S. O. (2009). Intraocular pressure increases in parallel with systemic blood pressure during isometric exercise. *Investigative Ophthalmology & Visual Science*, *50*(2), 760-764. doi: 10.1167/iovs.08-2508.

Barkana, Y. (2014). Postural change in intraocular pressure: a comparison of measurement with a Goldmann tonometer, Tonopen XL, pneumatonometer, and HA-2. *Journal of Glaucoma*, *23*(1), e23-28. doi: 10.1097/IJG.0b013e3182a0762f.

Borg, G. A. (1982). Psychophysical bases of perceived exertion. *Medicine & Science in Sports & Exercise*, *14*(5), 377-381.

Buckingham, T., & Young, R. (1986). The rise and fall of intra-ocular pressure: the influence of physiological factors. *Ophthalmic and Physiological Optics*, *6*(1), 95-99.

Casa, D. J., Armstrong, L. E., Hillman, S. K., Montain, S. J., Reiff, R. V., Rich, B. S. ... Stone, J. A. (2000). National Athletic Trainers' Association Position Statement: Fluid Replacement for Athletes. *Journal of Athletic Training, 35*(2), 212-224.

Cheuvront, S. N., Kenefick, R. W., Charkoudian, N., & Sawka, M. N. (2013). Physiologic basis for understanding quantitative dehydration assessment. *The American Journal of Clinical Nutrition*, *97*(3), 455-462. doi:10.3945/ajcn.112.044172.

Conte, M., Baldin, A. D., Russo, M. R., Storti, L. R., Caldara, A. A., Cozza, H. F., & Ciolac, E. G. (2014). Effects of high-intensity interval vs. continuous moderate exercise on intraocular pressure. *International Journal of Sports Medicine, 35*(10), 874-878. doi: 10.1055/s-0033-1364025.

deVries, H. A., & Housh, T. J. (1994d). Physiology of Training and Conditioning Athletes, Physical Fitness Testing. *Physiology of Exercise-For physical education athletics and exercise science.* (5th Ed., p. 258), WCB Brown and Benchmark Publishing: Madison, Wisconsin; Dubuque, Iowa.

deVries, H. A., & Housh, T. J. (1994e). Physiology of Training and Conditioning Athletes, Chapter 28, Environment and Exercise. *Physiology of Exercise-For physical education*

athletics and exercise science. (5th ed., p. 551-552), WCB Brown and Benchmark Publishing: Madison, Wisconsin; Dubuque, Iowa.

Ehlers, N., Bramsen, T., & Sperling, S. (1975). Applanation tonometry and central corneal thickness. *Acta Ophthalmologica (Copenhagen), 53*(1), 34-43.

Gale, J., Wells, A. P., & Wilson, G. (2009). Effects of ocular physiology and disease. *Survey of Ophthalmology, 54*(3), 349-355. doi: 10.1016/j.survophthal.2009.02.005.

Guyton, A. C., Hall, J. E. (2006b). In: Schmitt W, Gruliow, R. (Eds.), Energetics and Metabolic Rate, Body temperature, temperature regulation and fever. *Textbook of Medical Physiology.* (11th ed., pp. 881-900), Philadelphia, PA; Elsevier Saunders.

Guyton, A. C., Hall, J. E. (2006c). In: Schmitt W, Gruliow, R. (Eds.), The Body fluid compartments: Extracellular and intracellular fluids; interstiitial fluid and edema. *Textbook of Medical Physiology.* (11th ed., pp. 291-293), Philadelphia, PA; Elsevier Saunders.

Guyton, A. C., Hall, J. E. (2006d). In: Schmitt W, Gruliow, R. (Eds.), Membrane Potentials and Action Potentials. *Textbook of Medical Physiology.* (11th ed., p. 61), Philadelphia, PA; Elsevier Saunders.

Hamilton, K. E., Pye, D. C., Aggarwala, S., Evian, S., Khosla, J., & Perera, R. (2007). Diurnal variation of central corneal thickness and Goldmann applanation tonometry estimates of intraocular pressure. *Journal of Glaucoma*, *16*(1), 29-35. doi: 10.1097/IJG.0b013e31802b350f.

Harris, A., Malinovsky, V. E., Cantor, L., Henderson, P. A., & Martin, B. J. (1992). Isocapnia Blocks Exercise-Induced Reductions in Ocular Tension. *Investigative Ophthalmology & Visual Science, 33*(7), 2229-2232.

Harris, A., Malinovsky, V. E., Martin, B. J. (1994). Correlates of acute exercise-induced ocular hypotension. *Investigative Ophthalmology & Visual Science, 35*(11), 3852-3857.

Hunt, A. P., Feigl, B., & Stewart, I. B. (2012). The intraocular pressure response to dehydration: a pilot study. *European Journal of Applied Physiology, 112*(5), 1963-1966. doi: 10.1007/s00421-011-2143-5.

Johnstone, M. A. (2014). Intraocular pressure regulation: findings of pulse-dependent trabecular meshwork motion lead to unifying concepts of intraocular pressure homeostasis. *Journal of Ocular Pharmacology and Therapeutics, 30*(2-3), 88-93. doi: 10.1089/jop.2013.0224.

Kim, K. N., Jeoung, J. W., Park, K. H., Yang, M. K., & Kim, D. M. (2013). Comparison of the new rebound tonometer with Goldmann applanation tonometer in a clinical setting. *Acta Ophthalmologica, 91*(5), e392-396. doi: 10.1111/aos.12109.

Li, M.,Wang, M., Guo, W., Wang, J., & Sun, X. (2011). The effect of caffeine on intraocular pressure: a systematic review and meta-analysis. *Graefe's Archive for Clinical and Experimental Ophthalmology*, *249*(3), 435-442. doi:10.1007/s00417-010-1455-1.

Martin, B., Harris, A., Hammel, T., & Malinovsky, V. (1999). Mechanism of exercise-induced ocular hypotension. *Investigative Ophthalmology & Visual Science, 40*(5), 1011-1015.

Molina, N., Milla, E., Bitrian, E., Larena, C., & Martíneza, L. (2010). Comparison of Goldmann tonometry, pneumotonometry and the effect of the central corneal thickness. *Archivos de la Sociedad Española de Oftalmología (English), 85*(10), 325-328. doi: 10.1016/j.oftal.2010.09.003.

Moura, M. A., Rodrigues, L. O. C., Waisberg, Y., de Almeida, H. G., & Silami-Garcia, E. (2002). Effects of submaximal exercise with water ingestion on intraocular pressure in healthy human males. *Brazilian Journal Of Medical and Biological Research, 35*(1), 121-

125.

Orgül, S., & Flammer, J. (1994). Moderate exertion lasting only seconds reduces intraocular pressure. *Graefe's Archive for Clinical and Experimental Ophthalmology, 232*(5), 262-264.

Perrier, E., Demazières, A., Girard, N., Pross, N., Osbild, D., Metzger, D. … Klein, A. (2013a). Circadian variation and responsiveness of hydration biomarkers to changes in daily water intake. *European Journal of Applied Physiology, 113*(8), 2143-2151. doi: 10.1007/s00421-013-2649-0.

Perrier, E., Vergne, S., Klein, A., Poupin, M., Rondeau, P., Le Bellego, L. …Tack, I. (2013b). Hydration biomarkers in free-living adults with different levels of habitual fluid consumption. *British Journal of Nutrition, 109*(9), 1678-1687. doi: 10.1017/S0007114512003601.

Poole, D. C., Wilkerson, D. P., & Jones, A. M. (2008). Validity of criteria for establishing maximal O 2 uptake during ramp exercise tests. *European Journal of Applied Physiology*, *102*(4), 403- 410. doi: 10.1007/s00421-007-0596-3.

Qureshi, I. A. (1996a). Effects of exercise on IOP in physically fit subjects, *Clinical and Experimental Pharmacology and Physiology, 23*(8), 648–652.

Qureshi, I. A. (1997b). Does physical fitness influence intraocular pressure? *Journal of Pakistan Medical Association*, *47*(3), 81-84.

Quigley, H. A. (2011). Glaucoma. *The Lancet, 377*(9774), 1367-1377. doi: 10.1016/S0140-6736(10)61423-7.

Risner, D., Ehrlich, R., Kheradiya, N. S., Siesky, B., McCranor, L., & Harris, A. (2009). Effects of exercise on intraocular pressure and ocular blood flow: a review. *Journal of Glaucoma, 18*(6), 429-436. doi: 10.1097/IJG.0b013e31818fa5f3.

Roberts, M., Reiss, M. J., & Monger, G. (2000). Homeostasis and the Control of Glucose. In: Nelson Thornes (Ed), *Advanced Biology*, (p. 272). Cheltenham: United Kingdom.

Roddy, G., Curnier, D., & Ellemberg, D. (2014). Reductions in intraocular pressure after acute aerobic exercise: A Meta Analysis, *Journal of Vision, 12*(9), 483-483. doi: 10.1167/12.9.483.

Rüfer, F., Schiller, J., Klettner, A., Lanzl, I., Roider, J., & Weisser, B. (2014). Comparison of the influence of aerobic and resistance exercise of the upper and lower limb on intraocular pressure. *Acta Ophthalmologica, 92*(3), 249-252. doi:10.1111/aos.12051.

Sawka, M. N., Burke, L. M., Eichner, E. R., Maughan, R. J., Montain, S. J., & Stachenfeld, N. S. (2007). ACSM Position Stand ‘‘Exercise and Fluid Replacement,’’ *Medicine & Science in Sports & Exercise*, *39*(2), 377-390. Review.

Sollanek, K. J., Kenefick, R. W., Walsh, N. P., Fortes, M. B., Esmaeelpour, M., & Cheuvront, S. N. (2012). Assessment of thermal dehydration using the human eye: What is the potential? *Journal of Thermal Biology, 37*(2), 111–117. doi:10.1016/j.jtherbio.2011.12.006.

Tonnu, P. A., Ho, T., Sharma, K., White, E., Bunce, C., & Garway-Heath, D. (2005). A comparison of four methods of tonometry: method agreement and interobserver variability. *British Journal of Opthalmology, 89*(7), 847-850. doi: 10.1136/bjo.2004.056614.

Vieira, G. M., Oliveira, H. B., de Andrade, D. T., Bottaro, M., & Ritch, R. (2009). Intraocular pressure variation during weight lifting. *Archives of Ophthalmology*, *124*(9), 1251–1254.

doi:10.1001/archopht.124.9.1251.

Wimpissinger, B., Resch, H., Berisha, F., Weigert, G., Polak, K., Schmetterer, L. (2003). Effects of Isometric Exercise on Subfoveal Choroidal Blood Flow in Smokers and Nonsmokers. *Investigative Ophthalmology & Visual Science, 44*(11), 4859-4863.

6.6 Article 3

Is There a Relationship Between IOP and Physical Fitness?

Is There a Relationship Between IOP and Physical Fitness?

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ABSTRACT

Across the majority of the literature on the hypotensive effect of aerobic exercise on intraocular pressure (IOP) a consistent pattern is found. Baseline IOP is often lower in those who are physically fit as compared those who are sedentary. In addition, acute post exercise reductions in IOP are attenuated. Long-term physiological changes that occur with physical conditioning make it important to correctly define the fitness level of participants when conducting research on the possible mechanisms driving the acute hypotensive effects of exercise on IOP.

Thirty-one participants were included in the current study. The objective was to determine the degree of correlation between IOP, reported as an average of four discrete measures conducted over an eight-week period, and a single test of maximal aerobic capacity (VO_2max) used to determine the participant's level of conditioning.

A significant negative correlation was observed between Absolute VO_2max and baseline IOP, such that, as Absolute VO_2max increased baseline IOP decreased, but only in the upper third of the VO_2max continuum. There was no significant correlation between Relative VO_2max and baseline IOP contrary to existing literature. Across the 4 measures baseline IOP measurements were significantly correlated with each other, potentially reflecting the high fitness level of the participants. There was a small range of VO_2max scores in the current study. Therefore, although it is possible that a relationship between VO_2max and baseline IOP only exists within the elite levels of the physically fit, it is equally possible that there were not enough participants represented at the low end of the fitness continuum.

Keywords: intraocular pressure, exercise, aerobic, VO_2max, physical fitness, homeostasis

Introduction

A vast literature exists on the relationship between changes in intraocular pressure (IOP) and aerobic exercise. The majority of the research centres on 10 to 60 minutes of moderate to vigorous exercise and, in general, there is a transient reduction from normal baseline IOP (10 to 21 mm Hg, see Quigley, 2011) on the order of 1.2 to 8.0 mm Hg (Gale, Wells, & Wilson, 2009; Risner et al., 2009; Roddy, Curnier, & Ellemberg, 2014). However, there are a few notable exceptions in which researchers found no change or an increase in IOP (Dane, Koçer, Demirel, Ucok & Tan, 2006a; Moura, Rodrigues, Waisberg, de Almeida &. Garcia, 2002; Shah, Whittaker, Wells, & Khaw, 2001). One factor that causes variability across studies is the physical fitness of the participants.

In studies wherein the participants were stratified by level of physical conditioning, people at the higher end of the fitness continuum experience less of a reduction in IOP after acute aerobic exercise, or even an increase (see Dane et al., 2006a), than do people who are sedentary (Harris, Malinovsky, & Martin, 1994; Passo, Goldberg, Elliot, & Van Buskirk, 1987; Qureshi, 1996a).

A meta-analysis on reductions in IOP after acute aerobic exercise conducted by this group revealed that sedentary participants experience an almost twofold reduction in IOP, post exercise, than do the normally active groups (Roddy et al., 2014). In addition group differences (Sedentary versus Normally Active) explained 27.60% of the between-study variability (R^2 *adj*). Another finding was that characterization of fitness level varied across studies, and often, participants deemed normally active were actually at the high end of the fitness continuum.

There is also the suggestion in the literature that it is not only acute post-exercise reductions in IOP that are blunted in those who are physically fit, but that baseline IOP is also lower than in those who are sedentary (Harris et al., 1994; Passo et al. 1987; Qureshi, 1996a). A correlational study by Qureshi, Wu, Xi, Yang and Huang (1997a) found that the relative

VO_2max of steel workers who performed a moderate or vigorous task at work was 5.1 (*SD* = 1.1) ml/kg/min ($p < 0.001$) higher than those who worked sedentary desk jobs. Further, baseline IOP was 1.9 (*SD* = 0.7) mm Hg ($p < 0.001$) lower in the more active group.

The observations of Qureshi et al. (1997a) concur with three studies that used exercise interventions of three months to determine both the effect of long-term physical conditioning on baseline and the acute effects of post exercise IOP. These studies found reductions in baseline IOP of .31 to 1.5 mm Hg in normal participants and up to 4.6 mm Hg for those participants with Glaucoma (Passo et al. 1987, 1991; Qureshi, 1996a; Qureshi, 1995b). Further, there was at least a threefold difference between the control and experimental groups, across the three studies, after long-term physical conditioning.

Conversely, Sargent, Blair and Magun (1981) found no difference in acute post-exercise changes in IOP between the experimental and control group after a 6-month exercise intervention. They did, however, find a reduction in baseline IOP for both groups, after the six months, of a similar magnitude found in the aforementioned studies. It was suggested by the authors that the reductions in baseline IOP were caused by seasonal fluctuation (Sargent, Blair, & Magun, 1981). IOP can fluctuate as much as 0.14 to 0.39 mmHg ($P \leq 0.02$; Gardiner, Demirel, Gordon, & Kass, 2013) with a peak in January or February (Bengtsson, 1973; Gardiner et al., 2013; Qureshi, Xi, Lu, Wu, Huang, & Shiarkar, 1996c). This factor is also important when considering the exercise protocol of research on physical conditioning over time and the resultant effects on baseline IOP.

The observations made by Qureshi et al. (1997a) are pertinent to a common suggestion running through the literature, that post exercise reductions in IOP could potentially offset the increase in IOP seen in a subtype of a group of degenerative diseases, known as Glaucoma, a disease characterized by consistently high baseline IOP values (Gale et al., 2009; Risner et al., 2009; Roddy et al., 2014; Qureshi, 1997b). It should be noted, that although elevated IOP remains the most easily controllable risk factor for this disease, research is inconclusive as to whether or not the addition of chronic aerobic exercise will impact the course of the disease in a person at risk (Bengtsson & Heijl, 2005; Gale et al., 2009; Passo et al., 1991; Qureshi,

1995b; Williams, 2009). That said if there is a potential application in preventative therapy the relationship between physical fitness and baseline IOP must be made clear.

When conducting research on the mechanisms driving the hypotensive effects of exercise on IOP it is important to understand that many of the proposed mechanisms driving the hypotensive effect of exercise on IOP are themselves a part of physiological systems that work differently in a physically conditioned body as opposed to a sedentary one (deVries & Housh, 1994a, b, c, d; Guyton and Hall, 2006b, d). For example, highly trained athletes show an increased efficacy of the sweating mechanism and a delay in lactic acid increases during vigorous exercise allowing them to perform longer than sedentary people (deVries & Housh, 1994a,b; Guyton and Hall, 2006b,d). These changes that occur with physical conditioning are often representative of an increase in the body's efficiency to regulate different physiological systems when they are provoked by different exercises, changes in posture, fluid ingestion or deprivation, stress and many other factors (Buckingham & Young, 1986; Li, Wang, Guo, Wang, & Sun, 2011; Loewen, Liu, & Weinreb, 2010; Read & Collins, 2011; Roddy et al., 2014; Sollanek, Kenefick, Walsh, Fortes, Esmaeelpour, & Cheuvront, 2012). Not only do these changes lead to a lower baseline IOP, they seem to also have an effect on acute post exercise reductions in IOP (Hunt, Feigl, & Stewart, 2012; Sollanek et al., 2012). Averaging IOP measurements across participants, even within a small range of the fitness continuum, could be obscuring changes in baseline IOP that correlate with fitness level.

Another factor in the relationship between long-term physical conditioning and IOP is that reductions in baseline IOP are not permanent and the return to basal values is imminent when the conditioning stops. Most studies that include one acute aerobic exercise session show a return to baseline IOP within 60 minutes post-exercise (Risner et al., 2009; Roddy et al., 2014). Long-term physical conditioning is shown to maintain a reduction in baseline IOP for up to three weeks after the cessation of a three-month exercise intervention (Passo et al., 1987) but those results have not been replicated. It is important to note that across the literature on exercise-induced reductions in IOP there is a return to basal levels, without exception. This occurs whether IOP is elevated or reduced immediately after the manipulation,

regardless of the magnitude of the fluctuation, or the duration or intensity of exercise (Gale et al., 2009; Risner et al., 2009; Roddy et al., 2014).

There is a another complicating factor when it comes to research on exercise and IOP and that is the fact that the majority of studies on the hypotensive effects of exercise use single measures of IOP for the baseline measure or, in the case of the rebound tonometer, an average of six or more values taken in quick succession, one set in each eye (Risner et al., 2009; Roddy et al., 2014). A possible issue arises in that every discrete measure of IOP is affected by the season (Gardiner et al., 2013), time of day (Hamilton et al., 2007, Liu & Weinreb, 2011), amount and type of liquid ingested pre-measure (Buckingham & Young, 1986; Li et al., 2011; Moura et al., 2002), how long a participant was awake (Hamilton et al., 2007; Liu & Weinreb, 2011; Liu, Zhang, Kripke, & Weinreb, 2003a; Liu, Bouligny, Kripke, & Weinreb, 2003b), and any number of physiological factors (Loewen et al., 2010; Read & Collins, 2011; Sollanek et al., 2012).

The current study explores further the relationship between physical fitness and baseline IOP. Four baseline IOP measures will be obtained over an eight-week period, with regular intervals between days, all measures performed between the hours of 12:00:00 and 17:00:00. The measures will be compared, as 4 discrete measures and as a series of compounding averages, to a single test of VO_2max on an ergo cycle. We propose that there will be a negative correlation between baseline IOP and $V0_2$max such that the higher a person's $V0_2$max the lower the baseline IOP.

Given the enormous amount of factors that affect IOP a single measure, or a group of measures taken in one sitting, might not register a true baseline. It is possible that sedentary people might exhibit greater fluctuation in IOP caused by external factors such as rushing to the lab for testing, water deprivation or stress. Conversely, if long-term physical conditioning has the effect of maintaining a low, or even optimal baseline IOP, the values of those participants at the higher end of the fitness continuum could be quite stable across measures taken on different days.

Method

Participants and Recruitment

The current study was approved by the ethics committee for research in health sciences of the University of Montreal. The 23 women and 8 men included in the study were recruited from the University of Montreal, QC, Canada and from the city of Montreal, QC, Canada, via posters and social media. Participants were between 20 and 43 years of age (*SD* = 6.87). Characteristic data are presented in Table 3.1.

Control questionnaires. Before being eligible for participation all interested persons filled in questionnaires to ensure that they were free of i) ocular disease and previous ocular surgery, ii) Diabetes Type II, cardiovascular conditions and hypertension, iii) and that they did not currently use steroids, beta blockers or medication for elevated IOP (Schulzer & Drance, 1987). Participants also completed a questionnaire to determine their physical readiness to undertake the VO_2max test (the PAR-Q in English/Q-AAAP in French).

The experiment required a total of four visits, to be done within eight weeks of the first visit no closer than 5 days apart and no farther than 10 days apart, to the School of Optometry at the University of Montreal. On each visit the participant sat for one minute and then their baseline IOP was measured with the iCare® TA01i rebound tonometer (Icare Finland Oy, Vantaa, Finland). One visit to the department of kinesiology for a test of maximal aerobic capacity (VO_2max), during that same eight-week period, was also required. Weekly exercise routines and physical demands with regard to occupation were monitored via self-report on all five days of the experimental procedure. Measurement protocols and intervals are described in detail below.

Intraocular Pressure Measurements

A single researcher, using the iCare® TA01i rebound tonometer (Icare Finland Oy, Vantaa, Finland), took all IOP measurements. The iCare® has an accuracy of ±1.2 mm Hg at

≤20 mm Hg and ±2.2 mm Hg at >20 mm Hg (Kim, Jeoung, Park, Yang, & Kim, 2013; Molina, Milla, Bitrian, Larena, & Martíneza, 2010; Tonnu, Ho, Sharma, White, Bunce, & Garway-Heath, 2005). The recorded values are an average of six measures per eye at each measurement interval. All measurements were performed in both eyes.

Participants were required to be awake for a minimum of two hours before IOP measures were taken on each testing day. All visits were conducted between the hours of 12:00:00 and 17:00:00, Tuesday, Wednesday or Thursday, during the months of September, October and November of 2014 too avoid the effects of diurnal and seasonal fluctuation (Hamilton et al., 2007; Liu & Weinreb, 2011; Liu et al., 2003a; Sit, 2014 and Gardiner et al., 2013, respectively).

In the 24 hours leading up to each of the four IOP measurements participants were asked to abstain from contact lens wear, alcohol (Buckingham & Young, 1986) or exercise.

Tests of Physical Fitness

Test of maximal oxygen uptake. Aerobic capacity was determined with a test of maximum oxygen consumption (VO_2max) performed on a Lode ergocycle (Corival 906900, LODE B.V. Medical Technology, Groningen, The Netherlands). During the test, the Ultima™ CardiO2® (790705-006, 12 lead ECG CPX Testing, Medgraphics Cardiorespiratory Diagnostics, St Paul, MI) was used to monitor the gas exchange via the exhaled breath of the participant. Data were collected with the Breeze Suite software (V. 7.2.0.52, 2001-2011, Medgraphics Corporation, St Paul, MI). To validate the test we measured both the respiratory exchange rate (less oxygen inhaled and more carbon dioxide exhaled) and the plateau in VO_2 as the workload increased (Poole, Wilkerson, & Jones, 2008).

To begin the test, participants warmed up on the bike for 5 minutes at 50 watts (1 watt = 3600 J/hr, or 6.1183 kg-m/min). After the warm up, intensity was increased by 25 watts at 2-minute intervals until the participant could no longer maintain a range of 80 to 90 revolutions per minute (RPMs). Participants were monitored via their heart rate (T31 coded™

Transmitter, Polar® Electro, Lachine, Qc) and the BORG scale of perceived exertion for the duration of the ride (Borg, 1982). Blood pressure was measured with a stethoscope and sphygmomanometer to monitor participants for excessive increases greater than 250 mm Hg in systolic BP and greater than 115 mm Hg in diastolic BP or decreases in baseline BP (>10 mm Hg) during exercise (ACSM, 2010b).

Self-Reports of health and fitness. Weekly exercise routines and physical demands with regard to physical exertion were monitored via self-report on all five days of the experimental procedure to ensure that there were no extreme changes in the pattern of physical activity since the last measurement.

Table 3.1. *Characteristic Data*

Variable	Mean (Female) N = 23	*SD*	Mean (Male) N = 8	*SD*
Age (year)	25.1	6.4	26.5	8.4
Weight (Kg)	59.9	8.0	73.8	10.1
Height (cm)	164.5	6.1	177.4	5.5
Resting Heart Rate (BPM)	92.0	17.6	88.8	21.0

*N = 31

Statistical Analysis

Correlational analysis was used to assess the relationship between relative and absolute VO_2max and baseline IOP. Separate bivariate correlations were conducted for each of the four discrete measures (IOPT1, IOPT2, IOPT3 and IOPT4) and for the cumulative measure (IOP1234), and Relative and Absolute VO_2max.

In the final analysis, the Relative VO_2max scores were trichotomized in the following manner, below 36.08 mL/kg/min, 36.08 - 41.83 mL/kg/min and greater than 41.83 kg/mL/min and a correlational analysis was performed with each level and (IOPT1, IOPT2, IOPT3, IOPT4 and IOP1234) and (absolute or relative) VO_2max. The cut-off criteria was chosen so that all Relative VO_2max scores in the lower third of the range were confined to the 3 lower categories of VO_2max normative data (by age), Very Poor, Poor and Fair (Table Reference: Heyward, 1998 [revised in 1997 from The Physical Fitness Specialist Certification Manual]). There were no men represented in this category. The values in the upper third of the range were confined to the upper 3 categories of VO_2max normative data, Good, Excellent and Superior. Five men and five women comprised the upper category. The remaining men (3) and women (8) straddled the upper four categories.

Although trichotomization of data is an imperfect analysis the impetus in this case was to compare more directly the results of this study to that of Moura et al. (2002) whose 6 young male participants averaged 47.8 ± 9.1 (kg^1min^1) and Hunt et al. (2012) whose 7 young male participants 59.7 ± 7.2 (kg^1min^1). Although the top third of our participants in terms of their $V0_2$max test results are of mixed gender (5 men and 5 women) the range of 42.8 to 55.6 (kg^1min^1) is a closer approximation to the results of the aforementioned studies.

Results

There were no significant differences between the right and left eye measurements of IOP; therefore, the results are for the right eye only. Five females and one male presented with IOP readings between 21 and 29 mm Hg for three of the four visits. In all cases the participants were given a complete optical examination at the School of Optometry, University of Montreal. There were no pathologies or historical risk factors present for any of the participants. Because the purpose of the current study is to examine a relationship between IOP and VO_2max along a fitness continuum, all 5 participants were included in the study.

Stability of Baseline Measures

Baseline IOP at Time 1 (IOPT1) was significantly correlated with IOPT2, IOPT3 and IOPT4 (r (31) = .764, .806 and .813, $p < .001$), IOP2 was significantly correlated with IOPT3 and IOPT4(r (31) = .781 and .861, $p < .001$) and IOPT3 was significantly correlated with IOPT4 (r (31) = .833, $p < .001$), suggesting that IOP values were stable over the weekly measures. Relative $V0_2$max and Absolute $V0_2$max were also significantly positively correlated (r (31) = .743, $p < .001$), confirming that the two values reflect the same parameter.

IOP and VO_2max

Separate bivariate correlations were carried out for each of the four discrete measures (IOPT1, IOPT2, IOPT3 and IOPT4) and Relative and Absolute VO_2max, and for the cumulative measure (IOP1234) and Relative and Absolute VO_2max. Relative VO_2max was not significantly correlated with IOPT1, IOPT2, IOPT3 or IOPT4, or the cumulative measure IOPT1234 (Table 3.2). Absolute VO_2max was significantly correlated with IOP at IOPT4 (r(31) = -.360, p = .047) but was not correlated at IOPT1, IOPT2, IOPT3 or IOPT1234 (Table 3.2).

Table 3.2.

Pearson Correlation table between VO_2max *and IOP measurements at each time point.*

	IOPT1	*p*	IOPT2	*p*	IOPT3	*p*	IOPT4	*p*	IOPT1234	*p*
VO_2maxREL	.018	.924	-.102	.585	.005	.980	-.166	.372	-.065	.730
VO_2maxABS	-.198	.286	-.335	.065	-.322	.077	-.360**	.047**	-.326	.073

VO_2maxREL = Relative VO_2max (mL/kg/min)
VO_2maxABS = Absolute VO_2max (mL/min)
N = 31

IOP and Fitness Level

When the Relative VO_2max data was trichotomized (Table 3.3) there was a significant negative correlation between Absolute VO_2max values greater than 41.83 mL/min (N = 10) and baseline IOP, such that, as Absolute VO_2max increases, for both men and women,

baseline IOP decreases, IOPT1 ($r(10) = -.673$, $p = .033$, $R^2 = .452$), IOPT2 ($r(10) = -.727$, $p = .017$, $R^2 = .528$), IOPT3 ($r(10) = -.800$, $p = .005$, $R^2 = .640$), IOPT4 ($r(10) = -.859$, $p = .001$, $R^2 = .696$) (Figures 3.1 to 3.4) and IOPT1234 ($r(10) = -.798$, $p = .006$) (Figure 3.5).

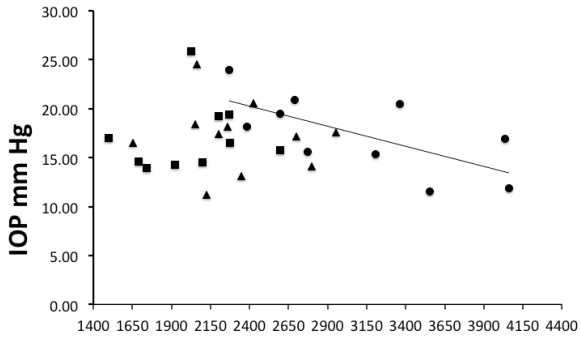

Figure 3.1 Time 1

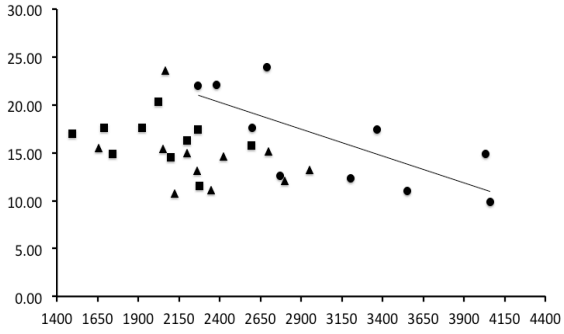

Figure 3.2 Time 2

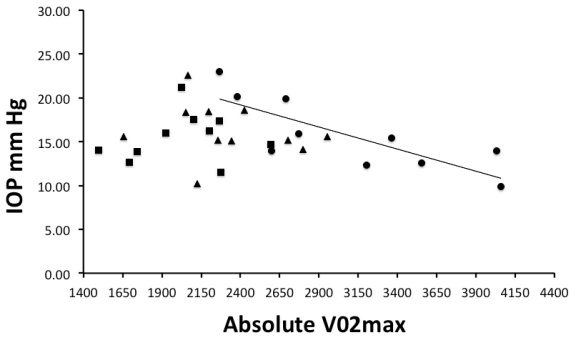

Figure 3.3 Time 3

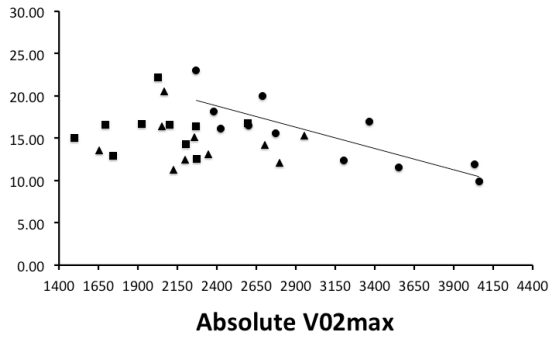

Figure 3.4 Time 4

Figures 3.1 to 3.4. Scatterplots showing data trichotomized by Relative $V0_2$max. IOP is plotted as a function of Absolute $V0_2$max at Times 1 to 4. Squares represent IOP values below 36.08 mm Hg, triangles represent IOP values between 36.08 and 41.83 mm Hg and circles represent IOP scores above 41.83 mm Hg. The linear trendline is presented for the scores above 41.83 mm Hg only. The R^2 values are as follows, .053, .528, .640 and .696, respectively. See Table 3.3.

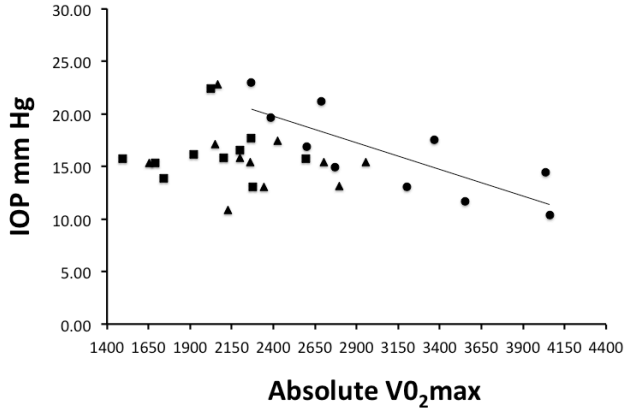

Figure 3.5. Scatterplot showing data trichotomized by Relative $V0_2max$. IOP is averaged over Times 1 to 4 and plotted as a function of Absolute $V0_2max$. Squares represent IOP values below 36.08 mm Hg, triangles represent IOP values between 36.08 and 41.83 mm Hg and circles represent IOP scores above 41.83 (R^2 = .636). See Table 3.3.

There were no correlations between Relative VO_2max and baseline measures of IOP, below 36.08 mL/kg/min Relative VO_2max for IOPT1 ($r(10) = .120$, $p = .741$), IOPT2 ($r(10) = -.313$, $p = .379$), IOPT3 ($r(10) = .005$, $p = .990$), IOPT4 ($r(10) = -.282$, $p = .430$) and IOPT1234 ($r(10) = -.104$, $p = .776$). Neither were there significant correlations between Relative VO_2max and baseline measures of IOP in the middle third of the dataset, 36.08 to 41.83 mL/kg/min Relative VO_2max, for IOPT1 ($r(10) = .307$, $p = .359$), IOPT2 ($r(10) = .008$, $p = .981$), IOPT3 ($r(10) = .432$, $p = .185$), IOPT4 ($r(10) = .273$, $p = .416$) and IOPT1234 ($r(10) = .264$, $p = .433$) (Table 3.3).

There were no correlations between Absolute VO_2max and baseline measures of IOP, below 36.08 mL/kg/min Relative VO_2max for IOPT1 ($r(10) = .175$, $p = .629$), IOPT2 ($r(10) = -.282$, $p = .431$), IOPT3 ($r(10) = .178$, $p = .623$), IOPT4 ($r(10) = -.064$, $p = .862$) and IOPT1234 ($r(10) = .064$, $p = .861$). Neither were there significant correlations between Absolute VO_2max and baseline measures of IOP in the middle third of the dataset, 36.08 to 41.83 mL/kg/min Relative VO_2max, for IOPT1 ($r(11) = -.122$, $p = .720$), IOPT2 ($r(11) = -.324$, $p = .330$), IOPT3 ($r(11) = -.199$, $p = .558$), IOPT4 ($r(11) = --.125$, $p = .713$) and IOPT1234 ($r(11) = -.246$, $p = .543$) (Table 3.3).

Finally, there were no correlations between Relative VO_2max and baseline measures of IOP values greater than 41.83 mL/min Relative VO_2max (N = 10) for IOPT1 (r(10) = -.287, p = .421), IOPT2 (r(10) = -.331, p = .351), IOPT3 (r(10) = -.239, p = .506), IOPT4 (r(10) = -.425, p = .221) and IOPT1234 (r(10) = -.336, p = .342) (Table 3.3).

Table 3.3.

Pearson Correlation (r) table of VO_2max *at 3 levels and IOP measurements at each time point*

¥VO_2max RELATIVE	VO_2max Category	IOPT1 *r*	*p*	IOPT2 *r*	*p*	IOPT3 *r*	*p*	IOPT4 *r*	*p*	IOPT1234 *r*	*p*
< 36,08 *N* = 10	Relative	.120	.741	-.313	.379	.005	.990	-.282	.430	-.104	.776
	Absolute	.175	.629	-.282	.431	.178	.623	.064	.862	.064	.861
36,08 - 41,83 *N* = 11	Relative	.307	.359	.008	.981	.432	.185	.273	.416	.264	.433
	Absolute	-.122	.720	-.324	.330	-.199	.558	-.125	.713	-.206	.533
> 41,83 *N* = 10	Relative	-.287	.421	-.331	.351	-.239	.506	-.425	.221	-.336	.342
	Absolute	-.673	.003*	-.727	.017*	-.800	.005**	-.859	.001***	-.798	.006**

¥VO_2max Relative values were used to divide the data into three groups.

Discussion

Across decades of research on the hypotensive effects of exercise and IOP a consistent pattern emerges. Participants at the higher end of the physical fitness continuum do not produce the same magnitude of acute post exercise reductions in IOP, and often exhibit lower baseline IOP, than do sedentary and clinical populations (Gale et al., 2009; Risner et al., 2009; Roddy et al., 2014). The current study was conducted to ascertain whether physical fitness, as measured by a VO_2max test, correlates negatively with baseline IOP values. There was a significant negative correlation between Absolute $V0_2$max and baseline IOP but only in highly fit participants (the upper third of the $V0_2$max continuum). There was no correlation between Relative $V0_2$max and IOP.

IOP and Relative versus Absolute VO_2max

At first glance the results are somewhat perplexing because unlike Relative VO_2max, Absolute VO_2max does not consider a person's weight. This seems contrary to the literature that suggests that the acute post exercise reductions in IOP are more affected by relative than by absolute exercise intensity (Harris et al., 1994; Kiuchi, Mishima, & Hotehama et al., 1994; Qureshi, Xi, Huang, & Wu, 1996b). However, VO_2max generally does not vary linearly with body mass and further improvements in performance can still occur once a VO_2max plateau is reached **(**deVries & Housh, 1994a,b). This is because athletes are able to perform at a higher percentage of their VO_2max for prolonged periods (deVries & Housh, 1994a,b; Bryant & Green, 2010). For example, highly trained runners can use more than 90% of their VO_2max for 25 to 30 minutes with only small amounts of lactate build up compared to sedentary people **(**deVries & Housh, 1994b). Therefore, it is possible then that an optimal baseline IOP can only be maintained when people continue to train close to the VO_2max threshold.

Our results concur with a previous questionnaire-based study conducted to assess the dose-response relationship of exercise to the risk of Glaucoma in 29,854 middle-aged men (Willams, 2009). Among other considerations, declining glaucoma risk suggests consistently lower IOP values than those at risk for the disease or already diagnosed. After following the

sample for 7.7 years, Willams (2009) found that the risk for reported glaucoma declined as the distance run per week increased and acute performance on a10-km footrace improved. Relevant to the current study is the fact that the top tier of 781 men who exceeded 5.0 m/s (p = 0.03) on the footrace reported 0% glaucoma diagnoses. Further, the risk for reported glaucoma decreased 5% per kilometer-per-day run (p = 0.04). The results of the study suggest that to maintain the hypotensive effects of exercise on IOP one must train vigorously and consistently.

IOP and Superior Physical Fitness

As in many recent studies, the majority of our participants were at the high end of the fitness continuum (e.g., Conte et al., 2014; Hunt et al., 2012; Moura et al., 2002; Rüfer, Schiller, & Klettner et al., 2014). The average Relative $V0_2$max value for the female participants (average 25.09 years of age, SD = 6.4) is 37.11 mL/kg/min (SD = 6.3). This places the results at Excellent on the $V0_2$max Normative Scale for the age range (ACSM, 2010b; Heyword, 1998). The average Relative $V0_2$max value for the men (average 26.05 years of age, SD = 8.4) is 44.4 mL/kg/min (SD = 5.6) (ACSM, 2010b; Heyword, 1998). Further, only 5 of the 23 female participants and 2 of the 8 male participants fell into the bottom three categories while the other 24 participants are considered to possess good, excellent or superior $V0_2$max (ACSM, 2010b; Heyword, 1998). The relatively high fitness level, and by extension the superior aerobic conditioning, of the majority of the participants likely explains the stability of the IOP measures from week to week.

IOP and Exercise Modality

It is difficult to adequately quantify the intensity and duration of exercise conditioning required to develop and maintain low baseline IOP. In the few studies that exist the long-term exercise interventions include hockey, supervised group aerobics and various jogging protocols (Passo et al. 1987; Qureshi, 1996a; Sargent et al. 1991). Similarly, in the current study, the habitual exercise practices of the participants varied from yoga to running to a

variation of full body aerobic and muscle conditioning programs.

There is evidence that the type of exercise does play a role in both the acute and long-term hypotensive effect of exercise on IOP (Gale et al., 2009; Harris et al., 1994; Roddy et al., 2014). An observation of the studies included in a meta analysis by this group revealed that cycling produced an almost two-fold greater average reduction in IOP than the treadmill for the sedentary participants across studies ($\bar{x}$ = -4.53 vs. $\bar{x}$ = -2.49 mm Hg, respectively). That trend was reversed for the normally active group ($\bar{x}$ = -2.21 vs. $\bar{x}$ = -3.16 mm Hg, respectively) (Buckingham & Young 1986; Dane et al., 2006a; Harris et al., 1994; Karabatakis et al., 2004; Kiuchi et al, 1994; Passo et al., 1987; Qureshi, 1996a; Qureshi, 1995a; Read & Collins, 2011). Many factors could be at play here that relate to demands placed on the body because of increasingly localized muscle fatigue in the legs, increased metabolic needs, and reduced peripheral blood flow across different modalities of exercise, all of which affect the efficacy of the test to determine a true $V0_2$max (Miles et al., 1980). For some participants VO_2max values are as much as 5% lower on an ergocyle (Heyword, 1998). Although participants at the higher end of the scale would be less susceptible to these effects it could still affect results, especially for those who do not ride a bike regularly.

Low Baseline IOP and VO_2max

The current study could not establish a correlation between VO_2max values in the lower third of the sample and baseline IOP, possibly because the VO_2max values were not low enough. As previously mentioned the range of fitness in our sample tended towards the high end of the fitness continuum. The relationship between exercise and IOP would likely be clearer where the aerobic range extends to lower VO_2max values so that a full progression, from extremely sedentary to extremely physically fit, can be established. It is possible that the same relationship exists for high baseline IOP values and very low VO_2max values, as exists for low baseline IOP and very high VO_2max values in the current study. It is also possible that the relationship between baseline IOP and physical fitness occurs only at the very top of the fitness continuum and that there is no relationship between the two for people who are more sedentary.

The hypotensive effect of physical conditioning on IOP could also be subject to floor effect because baseline IOP can only be reduced so far without having incurred damage to the eye. Ocular hypotony occurs when intraocular pressure is equal to or less than 6.5 mm Hg. Such low values can adversely impact the eye in many ways, including corneal decomposition, accelerated cataract formation, macular irregularities and fluid leakage (Costa & Arcieri, 2007). In no study reviewed by this team over the course of a meta-analysis and our own lab research do baseline IOP values drop below 8 mm Hg after exercise or long-term conditioning (Roddy et al., 2014). In other words, the hypotensive effect of exercise on IOP might correlate with VO_2max at the high end of the fitness continuum but only to the physiological lower boundary of IOP.

Conclusion

The current study explored further the relationship between physical fitness and baseline IOP. Four baseline IOP measures were obtained over an eight-week period and compared to a single test of VO_2max on an ergo cycle. We did find a relationship between baseline IOP and physical fitness but only in the top third of the fitness continuum and only when absolute VO_2max values were used in the comparison. It is unknown whether the range of fitness levels was too small to create a full progression of baseline values or if the relationship only exists in those who are at the top end of the VO_2max scale. Continued research on the mechanisms driving the hypotensive effect of exercise on IOP should explore further the pattern of change across the fitness continuum and include participants at the lower end of the range. The attenuated response observed in the physically fit possibly reflects the improved efficacy of parasympathetic responses to exercise.

REFERENCES

American College of Sports Medicine [ACSM] (2010a). Health Appraisal and Risk Assessment. In: Walter Thompson (Ed.), *Guidelines for Exercise Testing and Prescription*, (8th ed., pp. 4-6), USA: Walters Kluwer: Lippincott Williams and Wilkin.

American College of Sports Medicine [ACSM] (2010b). Health Related Physical Fitness Testing and Interpretation. In: Walter Thompson (Ed.), *Guidelines for Exercise Testing and Prescription*, (8th ed., pp. 82-87). USA: Walters Kluwer: Lippincott Williams and Wilkin.

Bengtsson, B., & Heijl, A. (2005). A long-term prospective study of risk factors for glaucomatous visual field loss in patients with ocular hypertension. *Journal of Glaucoma*, *14*(2), 135.

Borg, G. A. (1982). Psychophysical bases of perceived exertion. *Medicine & Science in Sports & Exercise*, *14*(5), 377-381.

Bryant, C. X., & Green, D. J. (2010). *ACE Essentials of Exercise Science for Fitness Professionals. American Council on Exercise*, 76-77.

Buckingham, T., & Young, R. (1986). The rise and fall of intra-ocular pressure: the influence of physiological factors. *Ophthalmic and Physiological Optics*, *6*(1), 95-99.

Conte, M., Baldin, A. D., Russo, M. R., Storti, L. R., Caldara, A. A., Cozza, H. F., & Ciolac, E. G. (2014). Effects of high-intensity interval vs. continuous moderate exercise on intraocular pressure. *International Journal of Sports Medicine, 35*(10), 874-878. doi: 10.1055/s-0033-1364025.

Costa, V. P., & Arcieri, E. S. (2007). Hypotony maculopathy. *Acta Ophthalmologica (Scandanavia), 85*(6), 586-597. doi: 10.1111/j.1600-0420.2007.00910.x.

Dane, S., Koçer, I., Demirel, H., Ucok, K., & Tan, U. (2006a). Effect of acute submaximal exercise on intraocular pressure in athletes and sedentary subjects. *International Journal of Neuroscience*, *116*(10), 1223–1230. doi:10.1080/00207450500522501.

deVries, H. A., & Housh, T. J. (1994a). Basic physiology underlying the study of physiology and exercise, Circulatory system and exercise. *Physiology of Exercise-For physical education athletics and exercise science.* (5th ed., pp. 129-130), WCB Brown and Benchmark Publishing: Madison, Wisconsin; Dubuque, Iowa.

deVries, H. A., & Housh, T. J. (1994b). Basic physiology underlying the study of physiology and exercise, Exercise Metabolism. *Physiology of Exercise-For physical education athletics and exercise science.* (5th ed., p. 225), WCB Brown and Benchmark Publishing: Madison, Wisconsin; Dubuque, Iowa.

deVries, H. A., & Housh, T. J. (1994c). Basic physiology underlying the study of physiology and exercise, The Heart and Exercise. *Physiology of Exercise-For physical education athletics and exercise science.* (5th ed., pp. 95; 108-109), WCB Brown and Benchmark Publishing: Madison, Wisconsin; Dubuque, Iowa.

deVries, H. A., & Housh, T. J. (1994d). Physiology of Training and Conditioning Athletes, Physical Fitness Testing. *Physiology of Exercise-For physical education athletics and exercise science.* (5th Ed., p. 258), WCB Brown and Benchmark Publishing: Madison, Wisconsin; Dubuque, Iowa.

Gale, J., Wells, A. P., & Wilson, G. (2009). Effects of ocular physiology and disease. *Survey of Ophthalmology, 54*(3), 349-355. doi: 10.1016/j.survophthal.2009.02.005.

Gardiner, S. K., Demirel, S., Gordon, M. O., & Kass, M. A. (2013) Seasonal changes in visual field sensitivity and intraocular pressure in the ocular hypertension treatment study. Ocular Hypertension Treatment Study Group. *Ophthalmology*, *120*(4), 724-730. [Gardiner et al., 2012, ARVO Abstract 1751; ahead of print]. doi: 10.1016/j.ophtha.2012.09.056.

Guyton, A. C., Hall, J. E. (2006b). Energetics and Metabolic Rate, Body temperature, temperature regulation and fever. In: Schmitt W, Gruliow, R. (Eds.), *Textbook of Medical Physiology.* (11th ed., pp. 889-900), Philadelphia, PA; Elsevier Saunders.

Guyton, A. C., Hall, J. E. (2006d). Sports Physiology. In: Schmitt W, Gruliow, R. (Eds.), *Textbook of Medical Physiology.* (11th ed., p. 1065), Philadelphia, PA; Elsevier Saunders.

Hamilton, K. E., Pye, D. C., Aggarwala, S., Evian, S., Khosla, J., & Perera, R. (2007). Diurnal variation of central corneal thickness and Goldmann applanation tonometry estimates of intraocular pressure. *Journal of Glaucoma*, *16*(1), 29-35. doi: 10.1097/IJG.0b013e31802b350f.

Harris, A., Malinovsky, V. E., Martin, B. J. (1994). Correlates of acute exercise-induced ocular hypotension. *Investigative Ophthalmology & Visual Science, 35*(11), 3852-3857.

Heyword, Vivian, H. (1998). Advance Fitness Assessment & Exercise Prescription. (3rd ed., p. 48). Reprinted from: The Physical Fitness Specialist Certification Manual, The Cooper Institute for Aerobics Research, Dallas TX, revised 1997.

Hunt, A. P., Feigl, B., & Stewart, I. B. (2012). The intraocular pressure response to dehydration: a pilot study. *European Journal of Applied Physiology, 112*(5), 1963-1966. doi:10.1007/s00421-011-2143-5.

Karabatakis, V., Natsis, K., Chatzibalis, T., Lake, S. L., Bisbas, I. T., Kallinderis, K. A., & Stangos, N. T. (2004). Correlating intraocular pressure, blood pressure, and heart rate changes after jogging. *European Journal of Ophthalmology*, *14*(2), 117–122.

Kim, K. N., Jeoung, J. W., Park, K. H., Yang, M. K., & Kim, D. M. (2013). Comparison of the new rebound tonometer with Goldmann applanation tonometer in a clinical setting. *Acta Ophthalmologica, 91*(5), e392-396. doi: 10.1111/aos.12109.

Kiuchi, Y., Mishima, H. K., Hotehama, Y., Furumoto, A., Hirota, A., & Onari, K. (1994). Exercise intensity determines the magnitude of IOP decrease after running. *Japanese Journal of Ophthalmology*, *38*(2), 191–195.

Li, M.,Wang, M., Guo, W., Wang, J., & Sun, X. (2011). The effect of caffeine on intraocular pressure: a systematic review and meta-analysis. *Graefe's Archive for Clinical and Experimental Ophthalmology*, *249*(3), 435-442. doi:10.1007/s00417-010-1455-1.

Liu, J. H. K., & Weinreb, R. N. (2011). Monitoring intraocular pressure for 24 h. *British Journal of Opthalmology, 95*(5), 599–600. doi:10.1136/bjo.2010.199737.

Liu, J, H. K., Zhang, X., Kripke, D. F., & Weinreb, R. N. (2003a). Twenty-four-hour intraocular pressure pattern associated with early glaucomatous changes. *Investigative Ophthalmology & Visual Science*, *44*(4), 1586-1590.

Liu, J. H., Bouligny, R. P., Kripke, D. F., & Weinreb, R. N. (2003b). Nocturnal elevation of intraocular pressure is detectable in the sitting position. *Investigative Ophthalmology & Visual Science*, *44*(10), 4439-4442. doi:10.1167/iovs.03-0349.

Loewen, N. A., Liu, H. K., & Weinrub, R. N. (2010). Increased 24-Hour Variation of Human Intraocular Pressure with Short Axial Length. *Investigative Ophthalmology & Visual Science*, *51*(2), 933-937. doi:10.1167/iovs.09-4218.

Miles D. S., Critz, J. B. & Knowlton, R. G. (1980) Cardiovascular, metabolic, and ventilatory responses of women to equivalent cycle ergometer and treadmill exercise. *Medicine and Science in Sports and Exercise,12*, 14-19.

Molina, N., Milla, E., Bitrian, E., Larena, C., & Martíneza, L. (2010). Comparison of Goldmann tonometry, pneumotonometry and the effect of the central corneal thickness. *Archivos de la Sociedad Española de Oftalmología (English), 85*(10), 325-328. doi: 10.1016/j.oftal.2010.09.003.

Moura, M. A., Rodrigues, L. O. C., Waisberg, Y., de Almeida, H. G., & Silami-Garcia, E. (2002). Effects of submaximal exercise with water ingestion on intraocular pressure in healthy human males. *Brazilian Journal Of Medical and Biological Research, 35*(1), 121-125.

Passo, M. S., Goldberg, L., Elliot, D. L., & Van Buskirk, E. M. (1987). Exercise conditioning and intraocular pressure. *American Journal of Ophthalmology, 103*(6), 754–757.

Passo, M. S., Goldberg, L., & Elliot, D. L., & Van Buskirk, E. M. (1991). Exercise training reduces intraocular pressure among subjects suspected of having glaucoma. *Archives of Ophthalmology, 109*, 1096–1098. doi:10.1001/archopht.1991.01080080056027.

Poole, D. C., Wilkerson, D. P., & Jones, A. M. (2008). Validity of criteria for establishing maximal O 2 uptake during ramp exercise tests. *European Journal of Applied Physiology*, *102*(4), 403- 410. doi: 10.1007/s00421-007-0596-3.

Qureshi, I. A. (1995a). Effects of mild, moderate and severe exercise on intraocular pressure of sedentary subjects. *Annals of Human Biology*, *22*, 545–553.

Qureshi, I. A. (1995b). The effects of mild, moderate, and severe exercise on intraocular pressure in glaucoma patients. *Japanese Journal of Physiology*, *45*(4), 561-569.

Qureshi, I. A. (1996a). Effects of exercise on IOP in physically fit subjects, *Clinical and Experimental Pharmacology and Physiology, 23*(8), 648–652.

Qureshi, I. A., Xi, X., Huang, Y., & Wu, X. (1996b). Magnitude of decrease in intraocular pressure depends upon intensity of exercise. *Korean Journal of Ophthalmology, 10*(2), 109-115.

Qureshi, I. A., Xi, X. R., Lu, H. J., Wu, X. D., Huang, Y. B., & Shiarkar, E. (1996c). Effect of seasons upon intraocular pressure in healthy population of China. *Korean Journal Ophthalmology*, *10*(1), 29-33.

Qureshi, I. A., Wu, X. D., Xi, X. R., Yang, J., & Huang, Y. B. (1997a). Resting intraocular pressure of steel factory workers is related to their physical fitness. *Industrial Health*, 35(2), 259-263.

Qureshi, I. A. (1997b). Does physical fitness influence intraocular pressure? *Journal of Pakistan Medical Association*, *47*(3), 81-84.

Quigley, H. A. (2011). Glaucoma. *The Lancet, 377*(9774), 1367-1377. doi: 10.1016/S0140-6736(10)61423-7.

Read, S. A., & Collins, M. J. (2011). The short-term influence of exercise on axial length and intraocular pressure. *Eye* (London), *25*(6), 767–774. doi: 10.1038/eye.2011.54.

Risner, D., Ehrlich, R., Kheradiya, N. S., Siesky, B., McCranor, L., & Harris, A. (2009). Effects of exercise on intraocular pressure and ocular blood flow: a review. *Journal of Glaucoma, 18*(6), 429-436. doi: 10.1097/IJG.0b013e31818fa5f3.

Roddy, G., Curnier, D., & Ellemberg, D. (2014). Reductions in intraocular pressure after acute aerobic exercise: A Meta Analysis, *Journal of Vision, 12*(9), 483-483. doi: 10.1167/12.9.483.

Rüfer, F., Schiller, J., Klettner, A., Lanzl, I., Roider, J., & Weisser, B. (2014). Comparison of the influence of aerobic and resistance exercise of the upper and lower limb on intraocular pressure. *Acta Ophthalmologica, 92*(3), 249-252. doi:10.1111/aos.12051.

Sargent, R. G., Blair, S. N., Magun, J. C., Krejci, R. C., Sacoco, C., Langley, T. D., & Taylor, R. L. (1981). Physical fitness and intraocular pressure. *American Journal of Optometry and Physiological Optics*, *58*(6), 460-466.

Schulzer, M., & Drance, S. M. (1987). Intraocular pressure, systemic blood pressure and age: A correlational study. *British Journal of Opthalmology, 71*(4), 245-249.

Shah, P., Whittaker, K., Wells, A., & Khaw, P. T. (2001). Exercise-induced visual loss associated with advanced glaucoma in young adults. *Eye (London)*, *15*(Part 5), 616-620. doi: 10.1038/eye.2001.196.

Sit, A. J. (2014) Intraocular pressure variations: causes and clinical significance. *Canadian Journal of Ophthalmology*, *49*(6), 484-488. doi: 10.1016/j.jcjo.2014.07.008.

Sollanek, K. J., Kenefick, R. W., Walsh, N. P., Fortes, M. B., Esmaeelpour, M., & Cheuvront, S. N. (2012). Assessment of thermal dehydration using the human eye: What is the potential? *Journal of Thermal Biology, 37*(2), 111–117. doi:10.1016/j.jtherbio.2011.12.006.

Tonnu, P. A., Ho, T., Sharma, K., White, E., Bunce, C., & Garway-Heath, D. (2005). A comparison of four methods of tonometry: method agreement and interobserver variability. *British Journal of Opthalmology, 89*(7), 847-850. doi: 10.1136/bjo.2004.056614.

Williams, P. T. (2009). Relationship of incident glaucoma versus physical activity and fitness in male runners. Medicine & Science in Sports & Exercise, *41*(8), 1566-1572. doi: 10.1249/MSS.0b013e31819e420f.

Chapter 7

General Discussion

The general objective of this thesis was to tease apart factors that influence the aerobic effect of exercise on IOP. After over 100 papers on the subject of exercise and IOP it is known that in the majority of cases, aerobic exercise produces a reduction in IOP, both the chronic and acute effects of exercise are attenuated in the physically fit and for all populations IOP always returns to baseline. The lack of standardization with regard to exercise protocols and stratification of participants across the literature to date complicates generalization and application of study results in a clinical or sports related setting.

The first study included in the thesis was designed as a meta-analysis to bring greater statistical power to a quantitative estimation of the overall contributions of intensity, duration and physical fitness to the effect of acute aerobic exercise on IOP. Large variations across studies with regard to control of pre-exercise fluid ingestion were observed during the literature search for Study 1. How hydrated one is before beginning an exercise protocol is necessarily a factor in dehydration, one of the many proposed mechanisms driving the hypotensive effect of exercise. To explore this interaction further in Study 2, the progressive changes in hydration levels, as per body weight, and in IOP were measured in both a hypo-hydrated (water restricted) and hyper-hydrated condition. Study 3 was designed to further elucidate the relationship between physical fitness and IOP. The following section provides a summary of the results of the three studies contained herein.

7.1 Summary of Study 1 Results. Reductions in intraocular pressure after acute aerobic exercise: a meta-analysis

The objective of the meta-analysis was to combine the results of studies that looked specifically at the effect of acute aerobic exercise on IOP, in normally active and sedentary people, and to examine the influence of factors implicated in that relationship. There was a

significant hypotensive effect of acute aerobic exercise on IOP that was almost two-fold greater for sedentary populations than for normally active populations, -4.2 mm Hg 95% CI [-5.151, -3.245] versus -2.3 mm Hg 95% CI [-3.305, -1.375], respectively, values that are in accord with much of the literature (Gale at el., 2009; Harris et al., 1994; Passo et al., 1987; Passo et al., 1991; Qureshi, 1996a; Qureshi et al., 1996b; Risner et al., 2009). A multiple regression revealed that group differences were not be explained by exercise intensity or duration. Only group allocation (sedentary or normally active) contributed significantly to the overall effect size (B = -1.886, SE = - 0.818, p = 0.043). This is an important finding as many studies on the acute effect of exercise in IOP show a decrease in IOP, relative to the intensity of exercise (e.g., Harris et al., 1994; Kiuchi et al., 1994; Qureshi, 1995b; Qureshi, 1996a).

Other important findings of this analysis were the sheer number of variables mediating the effect of exercise on IOP and the variation in exercise parameters and protocol and participant characterization across studies.

7.2 Summary of Study 2 Results. The Progression of Exercise Induced Changes in Intraocular Pressure as a Function of Dehydration

One of the mechanisms implicated in the hypotensive effect of exercise on IOP is systemic dehydration leading to ocular hyperosmolarity (Hunt et al., 2012; Martin et al., 1999; Sollanek et al., 2012). The results of this study did not support that theory. Thirteen participants rode an ergocycle for 90 minutes in either a hypo- or hyper-hydrated condition. IOP was measured at 5, 30, 60, and 90 minutes and hydration, as a function of reduction in body weight, was measured at 0, 30, 60 and 90 minutes.

As exercise began there was an initial drop in IOP under both conditions, in accord with observations made in Study 1 that often IOP decreases significantly in the first 5 minutes of initiating exercise. Subsequently, IOP hovered close to baseline for the duration of exercise when fluid was restricted, and increased with water consumption when participants drank during exercise.

There was a reduction in body weight in both conditions that was significantly greater in the hypo-hydrated condition but was not significantly correlated with change in IOP in either condition. The results of the current study suggest that fluctuations in IOP during and after exercise, regardless of duration, are likely a homeostatic response to dysregulation of the aqueous humor caused by fluid intake and large changes in activity level. The hypotensive effect of IOP does not seem to be related to dehydration caused by exercise.

7.3 Summary of Study 3 Results. Is There a Relationship Between IOP and Physical Fitness?

Across the literature participants at the higher end of the physical fitness continuum exhibit lower baseline IOP and do not produce the same magnitude of acute post exercise reductions in IOP, as do sedentary and clinical populations (Gale et al., 2009; Risner et al., 2009; Study 1: Roddy, Curnier, & Ellemberg, et al., 2014). Study 3 attempted to clarify the relationship between physical fitness and baseline IOP by performing four discrete baseline measures conducted over an eight-week period, and a single test of VO_2max on an ergocycle.

The results showed a significant negative correlation between Absolute VO_2max and baseline IOP but only in the upper third of the VO_2max continuum. There was no correlation between Relative VO_2max and baseline IOP. Across participants, baseline IOP measurements were stable from week to week.

The three studies combined add some degree of clarification to the ongoing exploration of exercise and IOP. Study 1 found that post exercise reductions in IOP are not explained by either exercise intensity or duration and only group allocation (normally active versus sedentary) contributes significantly to the effect of exercise on IOP. Study 3 breaks down the relationship between fitness and baseline IOP further and reveals that baseline IOP is lower when VO_2max is higher but only for participants in the top third of the fitness continuum.

Study 2 did not support the idea that systemic dehydration causing hyperosmolarity is involved in post exercise reductions in IOP, even after 90 minutes of riding. It is more likely

that fluctuations in IOP immediately after starting exercise, as well as during and after exercise are various homeostatic responses to dysregulation of the aqueous humor caused by pre-exercise fluid intake and large changes in activity level.

The remainder of Chapter 7 incorporates the results of the Studies 1, 2 and 3 into the literature on exercise and IOP in a general discussion that covers 1) post exercise reductions in IOP and homeostatic balance in the physically fit versus the sedentary, 2) the usefulness of IOP as a marker of hydration 3) and the clinical usefulness of post exercise reductions in IOP.

7.4 The Homeostatic Balance of IOP During Exercise in The Physically Fit and the Sedentary

It is important to note that across the literature on exercise-induced reductions in IOP there is a return to basal levels, without exception. This homeostatic correction occurs whether IOP is elevated or reduced, regardless of the magnitude of the fluctuation, or the duration or intensity of exercise (Gale et al., 2009; Hunt et al., 2012; Moura et al., 2002; Risner et al., 2009; Study 1: Roddy et al., 2014). Even after 5-minute headstands, which produce twofold increases from baseline IOP, there is a return to basal values within 30 minutes (Baskaran et al., 2006).

Study 2 found no significant reductions in IOP after a 90-minute ride without water (hypo-hydrated condition). In fact, after the initial decrease, IOP hovered around baseline. We did find that IOP increased significantly in the hyper-hydrated conditioned as the participants continued to ingest water throughout the duration of the exercise protocol (Study 2) and began to descend towards baseline 30 minutes after the last drink of water. The results of this study concur with those of Moura et al. (2002) in that fluctuations in IOP after exercise have a great deal to due with the fluid ingested pre-exercise and the body's attempt to absorb it and restore basal values.

Mechanisms driving the hypotensive effect of exercise on IOP proposed across the literature are often part of homeostatic systems that improve with conditioning. The most

common suggested mechanism, ocular hyperosmolarity as caused by systemic dehydration, is possibly linked to the sweating mechanism, which becomes increasingly efficient at preserving electrolytes to delay dehydration (deVries & Housh, 1994b,d; Guyton & Hall, 2006b,c,d; Martin et al., 1999). The preservation of electrolytes is a function of homeostatic correction and when that correction is successful reductions in post exercise IOP do not occur (Martin et al., 1999; Study 2 this Thesis).

Finally, the initial decrease in IOP observed in Study 2, in both conditions, speaks to the homeostatic theory in that when moderate to vigorous exercise is initiated metabolic demands on the body immediately change. These results compliment the results of Orgül and Flammer (1994) who found decreases in IOP after approximately 8 to 10 seconds. The parasympathetic nervous system produces responses to sudden changes in energy demands, some of which present immediately such as an increase in heart rate (Guyton & Hall, 2006e) and some of which present over longer durations, such as the increased efficacy of the sweat mechanism (Guyton & Hall, 2006b,d). In all cases, as previously mentioned IOP eventually returns to its current baseline.

In Study 3 we found that a relationship between increased physical fitness and lowered baseline values only existed for the top third of the absolute VO_2max values of the participants. With regard to the maintenance of optimal baseline IOP, it is possible that for physical fitness to impact these processes in the long-term, the training must be intense and frequent enough to exact change in the efficacy of all systems involved in homeostatic balance (This concept is discussed further in 7.3).

7.5 The Usefulness of IOP as a Biomarker of Hydration

There is renewed interest in IOP and exercise in the field of exercise science. The possibility that ocular hyperosmolarity as a function of systemic dehydration is involved in reductions in IOP over longer durations of exercise suggests that, in turn, decreasing IOP should indicate the level of hydration of the participants. However, the results of Study 3,

along with those of Moura, Rodrigues, Waisberg, de Almeida, and Silami-Garcia (2002) suggest that there are a number of complications.

The most obvious complication is pre-exercise fluid control. This includes fluid ingestion not just in the few hours before, but also habitual water intake over the long term. Homeostatic balance is such that when water is scarce dehydration occurs and when water is ingested it must at some point be absorbed. However, the homeostatic balance of fluid is individually conditioned through physiological concerns such as habitual water intake and sweat rate, in addition to the individual level of physical conditioning (Perrier et al., 2013a; Perrier et al., 2013b). In other words, different people dehydrate at different rates for many reasons. To use fluctuations of IOP during exercise as a marker of hydration requires that individual patterns of sweat rate and habitual water intake are calculated and continuously monitored for changes in these parameters which could potentially obscuring results. Further, if IOP is used as a biomarker of hydration in the physically fit the attenuated changes in IOP could be obscured by any number of other factors including diurnal and seasonal variation.

After exercise begins, the physically fit should be closer to homeostatic balance and therefore produce parallel reductions in IOP and total body weight (as a measure of hydration) when water is restricted. Study 2 did not confirm that correlation however, in accord with Moura et al. (2002) and converse to Hunt, Feigl and Stewart (2012). None of the three aforementioned studies, including Study 2 in this thesis, included sedentary controls to see if a relationship between dehydration and IOP is more or less prevalent in that population. It is possible that sedentary participants would simply exhibit a greater magnitude of fluctuation in IOP as the parasympathetic nervous system works to maintain homeostatic balance. By example, Dane et al. (2006a) found that extremely fit participants actually incurred an increase in IOP of .33 mm Hg after 5 minutes of exercise therefore, if the exercise continues post exercise reductions would be calculated from a value higher than baseline. The post exercise fluctuations of IOP might simply be too small in the physically fit to be separated from other extenuating factors and would not therefore reflect the true relationship between hydration and IOP.

7.6 The Clinical Usefulness of Post Exercise Reductions in IOP

The implications of the hypotensive effects of exercise on IOP are often presented in the context of a lifestyle change that could offset the increase in IOP that characterizes high tension POAG (Gale et al., 2009; Harris et al., 1994; Risner et al., 2009; Study 1: Roddy et al., 2014). It is important that this concept be addressed realistically. Elevation of IOP is largely controlled through pharmacology and when treatment is administered early, and adhered to, the outcome is usually successful (Friedman et al., 2003; Leske et al., 2003; Leske, 2007; Quigley, 2011; Schwartz & Quigley, 2008; Vermeire, Hearnshaw, Van Royen, & Denekens, 2001). Research is inconclusive as to whether or not the addition of chronic aerobic exercise will significantly lower baseline IOP to a degree that would impact the course of the disease in a person at risk (Gale et al., 2009; Harris et al., 1994; Quigley, 2011).

Based on the degree of target reduction set for some patients in the early stages of Glaucoma there is a distant possibility that exercise could help maintain a lower baseline. However, if exercise could be considered a complimentary therapy to maintain reductions in IOP, as for any intervention, dose response must be considered. Study 1 revealed a vast array of pre-exercise protocols that would need to be standardized and replicated until a specific intensity, frequency and mode of exercise produces a reliable (and adjustable) magnitude of reduction in IOP. Also, as group allocation was the most significant predictor of the magnitude of reduction in post exercise IOP, exercise prescription guidelines would need to reflect the fitness continuum.

Although it is unlikely that exercise would be prescribed specifically for ocular health there is still evidence that staying at the top end of the fitness continuum will promote a healthy baseline IOP the same way it promotes healthy baselines in other systems of the body (Passo et al., 1987; Qureshi, 1996a, Qureshi et al, 1997a; Qureshi, 1997b; Williams, 2009). The majority of studies on acute exercise find a return to baseline within an hour or two dependent on the exercise protocol. Passo et al. (1987) found some participants did not return to baseline until three weeks after the cessation of a 3-month intervention of regular hockey games; further, the hypotensive effect after acute exercise was still attenuated after 3 weeks.

Williams (2009) found that the possible long-term benefits of exercise on baseline IOP were most robust at the top end of the fitness continuum of a group of highly trained runners. Qureshi et al. (1997a) found lower baseline IOP values in the relative VO_2max of steel workers who performed a moderate or vigorous task at work than those who worked sedentary desk jobs. The results of Study 3 together with Passo, Williams and Qureshi and colleagues (1987, 2009, & 1997a,b, respectively) suggest that being fit could potentially help maintain a lower baseline IOP. However, the dose response of such an intervention remains unknown. It is possible that consistent moderate exercise improves the efficacy of mechanisms that drive the hypotensive effects of exercise on IOP and that those gains are lost when physical conditioning is no longer maintained.

7.7 Limitations of the Thesis

Across the literature on the acute effects of exercise on IOP the methodological differences range from variations in participant categorization, intensity and duration differences in exercise protocols, to the control of variables that cause IOP fluctuation beyond that which is caused by exercise. With regard to Study 1, lack of standardization of exercise protocol and pre-exercise criteria and under reporting of variance constrained the meta-analysis to a small number of studies. This in turn constrained the number of variables that we could include and factors such as age and gender might have changed the results somewhat (Dane et al., 2006a,b; Leske & Podger, 1983; Qureshi, 1995c).

Studies 2 and 3 suffered from the same limitations as much of the literature on the hypotensive effects of exercise and IOP. In both studies participants were relatively high on the continuum of VO_2max and were under represented at the lower end of the VO_2max scale. It is likely a bias created by the fact that sedentary people are not interested in either riding a bicycle for 90 minutes or performing the VO_2max test itself.

In fact, using only a bicycle for both tests of VO_2max (Studies 1 and 2) and the exercise protocol of Study 2 might also have changed our pattern of results by not allowing all participants to achieve a true VO_2max. Many more people walk than do ride a bicycle and

VO_2max values are regularly shown to be almost 5% higher when a test of maximal aerobic capacity is performed on a treadmill rather than an ergocycle (Heyword, 1998). As reported in Study 2 of this paper (pg. 106), increasingly localized muscle fatigue in the legs, increased metabolic needs, and reduced peripheral blood flow across different modalities of exercise, could affect $V0_2$max test results (Miles et al., 1980).

7.8 The Future of this Research

The results of the 3 studies included in this thesis, taken together with the literature to date, suggest that greater attention must be paid to a possible relationship between physical conditioning and posited mechanisms that potentially drive the hypotensive effects of exercise. It would be interesting to know how the results of Study 2 would have changed if we had been able to compare dehydration in a sedentary group, over the course of 90 minutes of exercise, to the level of dehydration experienced in our sample of relatively fit people.

It would also be of interest to expand the correlational analysis of Study 3 to include participants at the lower end of the fitness continuum. Whether the mechanisms involved act directly on the hypotensive effect of exercise or are simply a part of homeostatic systems compensating for the initial change in activity as exercise begins, it would be interesting to know at what level of fitness do these changes take place. It is quite possible that relationship between physical conditioning and baseline IOP is not a linear one partly because of the physiological constraints of the floor effect. IOP can only be reduced to 6.5 mm Hg without having incurred trauma to the eye, (Costa & Arcieri, 2007).

Conclusion

The three studies that comprise this thesis add some degree of clarification to the ongoing exploration of exercise and IOP. Study 1 found that group allocation (normally active or sedentary) made the greatest contribution to post exercise reductions in IOP. Study 3 breaks down the relationship between fitness and baseline IOP further and reveals that baseline IOP is lower when VO_2max is higher with but only for participants in the top third of the fitness

continuum. The inclusion of more sedentary participants might have created a clearer progression of that relationship.

Study 2 could not confirm the hypothesis that systemic dehydration causing hyperosmolarity is involved in post exercise reductions in IOP, even after 90 minutes of riding. It is more likely that the observed fluctuations in IOP immediately after starting exercise, as well as during and after exercise were caused by pre-exercise fluid intake and large changes in activity level. It is also possible that the relatively high fitness level of our participants obscured our results in both Studies 2 and 3.

The results of this thesis suggest that the hypotensive effect of exercise on IOP is likely a homeostatic response to dysregulation of the aqueous humor caused by the initiation of exercise and exercise fluid intake protocols. It is important to understand how the magnitude of fluctuation in IOP changes as physical fitness improves. The attenuated response of IOP after an exercise protocol possibly reflects the improved efficacy of parasympathetic responses to exercise. Continued research on the mechanisms driving the hypotensive effect of exercise on IOP should explore further the pattern of change across the fitness continuum and include participants of all levels.

REFERENCES

Ainsworth, B. E., Haskell, W. L., & Leon, A. S., Jacobs, D. R. Jr., Montoye, H. J., Sallis, J. F., & Paffenbarger, R. S. Jr. (1993). Compendium of physical activities: Classification of energy costs of human physical activities. *Medicine & Science in Sports & Exercise*, *25*, 71-80.

Ainsworth, B. E., Haskell, W. L., Herrmann, S. D., Meckes, N., Bassett, D. R. Jr., Tudor-Locke, C. … Leon, A. S. (2011). Compendium of Physical Activities: a second update of codes and MET values. *Medicine & Science in Sports & Exercise*, *43*(8), 1575-1581.

Acott, T. S., Kelley, M. J., Keller, K. E., Vranka, J. A., Abu-Hassan DW, Li X … Bradley, J. M. (2014). Intraocular pressure homeostasis: maintaining balance in a high-pressure environment. *Journal of Ocular Pharmacology and Therapeutics*, *30*(2-3), 94-101. doi: 10.1089/jop.2013.0185.

American College of Sports Medicine [ACSM] (1991). Health Appraisal and Risk Assessment. In: Walter Thompson (Ed.), *Guidelines for Exercise Testing and Prescription*, (4th ed., pp. 93-119). Philadelphia: Lea and Febiger.

American College of Sports Medicine [ACSM] (2010a). Health Appraisal and Risk Assessment. In: Walter Thompson (Ed.), *Guidelines for Exercise Testing and Prescription*, (8th ed., pp. 4-6), USA: Walters Kluwer: Lippincott Williams and Wilkin.

American College of Sports Medicine [ACSM] (2010b). Health Related Physical Fitness Testing and Interpretation. In: Walter Thompson (Ed.), *Guidelines for Exercise Testing and Prescription*, (8th ed., pp. 82-87). USA: Walters Kluwer: Lippincott Williams and Wilkin.

American College of Sports Medicine. (2010c). General Principles of Exercise Prescription. In: Walter Thompson (Ed.), *Guidelines for Exercise Testing and Prescription*, (8th ed., pp.

156-163). USA: Walters Kluwer: Lippincott Williams and Wilkin.

Ashkenazi, I., Melamed, S., & Blumenthal, M. (1992). The effect of continuous strenuous exercise on intraocular pressure. *Investigative Ophthalmology & Visual Science, 33*(10), 2874-2877.

Avunduk, A. M., Yilmaz, B., Sahin, N., Kapicioglu, Z., & Dayanir, V. (1999). The comparison of intraocular pressure reductions after isometric and isokinetic exercises in normal individuals. *Ophthalmologica*, *213*(5), 290-294.

Aykan, U., Erdurmus, M., Yilmaz, B., & Bilge, A. H. (2010). Intraocular pressure and ocular pulse amplitude variations during the valsalva manoeuvre. *Graefe's Archive for Clinical and Experimental Ophthalmology*, *248*(8), 1183-1186. doi: 10.1007/s00417-010-1359-0.

Bakke, E. F., Hisdal, J., & Semb, S. O. (2009). Intraocular pressure increases in parallel with systemic blood pressure during isometric exercise. *Investigative Ophthalmology & Visual Science*, *50*(2), 760-764. doi: 10.1167/iovs.08-2508.

Barkana, Y. (2014). Postural change in intraocular pressure: a comparison of measurement with a Goldmann tonometer, Tonopen XL, pneumatonometer, and HA-2. *Journal of Glaucoma*, *23*(1), e23-28. doi: 10.1097/IJG.0b013e3182a0762f.

Baskaran, M., Raman, K., Ramani, K. K., Roy, J., Vijaya, L., & Badrinath, S. S. (2006). Intraocular pressure changes and ocular biometry during Sirsasana (headstand posture) in yoga practitioners, *Ophthalmology*, *113*(8), 1327-1332. doi:10.1016/j.ophtha.2006.02.063

Bengtsson, B., & Heijl, A. (2005). A long-term prospective study of risk factors for glaucomatous visual field loss in patients with ocular hypertension. *Journal of Glaucoma*, *14*(2), 135.

Bertschinger, D. R., Mendrinos, E., & Dosso, A. (2007). Yoga can be dangerous—glaucomatous visual field defect worsening due to postural yoga British Journal of Ophthalmology, *91*(10), 1413–1414. doi: 10.1136/bjo.2007.114546

Borg, G. A. (1982). Psychophysical bases of perceived exertion. *Medicine & Science in Sports & Exercise*, *14*(5), 377-381.

Brody, S., Erb, C., Veit, R., & Rau, H. (1999). Intraocular pressure changes: the influence of psychological stress and the Valsalva manoeuvre. *Biological Psychology*, *51*, 43–57. doi:10.1016/S0301-0511(99)00012-5

Brubaker, R. F. (1991). Flow of aqueous humour in humans. [The Friedenwald Lecture]. *Investigative Ophthalmology & Visual Science*, *32*(13), 3145–3166.

Bryant, C. X., & Green, D. J. (2010). *ACE Essentials of Exercise Science for Fitness Professionals. American Council on Exercise*, 76-77.

Buckingham, T., & Young, R. (1986). The rise and fall of intra-ocular pressure: the influence of physiological factors. *Ophthalmic and Physiological Optics*, *6*(1), 95-99.

Casa, D. J., Armstrong, L. E., Hillman, S. K., Montain, S. J., Reiff, R. V., Rich, B. S. ... Stone, J. A. (2000). National Athletic Trainers' Association Position Statement: Fluid Replacement for Athletes. *Journal of Athletic Training, 35*(2), 212-224.

Chauhan, B. C., Mikelberg, F. S., Balaszi, A. G., LeBlanc, R. P., Lesk, M. R., & Trope, G. E. (2008). Canadian Glaucoma Study 3: Risk factors for the progression of Open-Angle Glaucoma. *Archives of Ophthalmology*, *126*(8), 1030–1037. doi: 10.1001/archopht.126.8.1030.

Cheuvront, S. N., Kenefick, R. W., Charkoudian, N., & Sawka, M. N. (2013). Physiologic basis for understanding quantitative dehydration assessment. *The American Journal of*

Clinical Nutrition, *97*(3), 455-462. doi:10.3945/ajcn.112.044172.

Chromiak, J. A., Abadie, B. R., Braswell, R. A., Koh, Y. S., & Chilek, D. R. (2003). Resistance training exercises acutely reduce intraocular pressure in physically active men and women. *Journal of Strength and Conditioning Research*, *17*(4), 715-720.

Conte, M., Baldin, A. D., Russo, M. R., Storti, L. R., Caldara, A. A., Cozza, H. F., & Ciolac, E. G. (2014). Effects of high-intensity interval vs. continuous moderate exercise on intraocular pressure. *International Journal of Sports Medicine, 35*(10), 874-878. doi: 10.1055/s-0033-1364025.

Cooper, K., Lempert, P., & Culver, J. (1965). Effect of exercise on intraocular tension and its relationship to open angle glaucoma. *Aerospace Medicine*, *36*, 51-53.

Costa, V. P., & Arcieri, E. S. (2007). Hypotony maculopathy. *Acta Ophthalmologica (Scandanavia), 85*(6), 586-597. doi: 10.1111/j.1600-0420.2007.00910.x.

Dane, S., Koçer, I., Demirel, H., Ucok, K., & Tan, U. (2006a). Effect of acute submaximal exercise on intraocular pressure in athletes and sedentary subjects. *International Journal of Neuroscience*, *116*(10), 1223–1230. doi:10.1080/00207450500522501.

Dane, S., Koçer, I., Demirel, H., Ucok, K., & Tan, U. (2006b). Long-term effects of mild exercise on intraocular pressure in athletes and sedentary subjects. *International Journal of Neuroscience*, *116*(10), 1207–1214. doi:10.1080/00207450500516461.

deVries, H. A., & Housh, T. J. (1994a). Basic physiology underlying the study of physiology and exercise, Circulatory system and exercise. *Physiology of Exercise-For physical education athletics and exercise science.* (5th ed., pp. 129-130), WCB Brown and Benchmark Publishing: Madison, Wisconsin; Dubuque, Iowa.

deVries, H. A., & Housh, T. J. (1994b). Basic physiology underlying the study of physiology and exercise, Exercise Metabolism. *Physiology of Exercise-For physical education athletics and exercise science.* (5th ed., p. 225), WCB Brown and Benchmark Publishing: Madison, Wisconsin; Dubuque, Iowa.

deVries, H. A., & Housh, T. J. (1994c). Basic physiology underlying the study of physiology and exercise, The Heart and Exercise. *Physiology of Exercise-For physical education athletics and exercise science.* (5th ed., pp. 95; 108-109), WCB Brown and Benchmark Publishing: Madison, Wisconsin; Dubuque, Iowa.

deVries, H. A., & Housh, T. J. (1994d). Physiology of Training and Conditioning Athletes, Physical Fitness Testing. *Physiology of Exercise-For physical education athletics and exercise science.* (5th Ed., p. 258), WCB Brown and Benchmark Publishing: Madison, Wisconsin; Dubuque, Iowa.

deVries, H. A., & Housh, T. J. (1994e). Physiology of Training and Conditioning Athletes, Chapter 28, Environment and Exercise. *Physiology of Exercise-For physical education athletics and exercise science.* (5th ed., p. 551-552), WCB Brown and Benchmark Publishing: Madison, Wisconsin; Dubuque, Iowa.

Dickerman, R. D., Smith, G. H., Langham-Roof, L., McConathy, W. J., East, J. W., & Smith, A. B. (1999). Intraocular pressure changes during maximal isometric contraction: does this reflect intra-cranial pressure or retinal venous pressure? *Neurological Research*, *21*(3), 243-246.

Diestelhorst, M., Krieglstein, G. K. (1994). The effect of the water-drinking test on aqueous humor dynamics in healthy volunteers. *Graefe's Archive for Clinical and Experimental Ophthalmology*, *232*(3), 145-147.

Ehlers, N., Bramsen, T., & Sperling, S. (1975). Applanation tonometry and central corneal thickness. *Acta Ophthalmologica (Copenhagen), 53*(1), 34-43.

Era, P., Parssinen, O., Kallinen, M., & Suominen, H. (1993). Effect of bicycle ergometer test on intraocular pressure in elderly athletes and controls. *Acta Ophthalmologica* (Copenhagen), *71*(3), 301-307.

Farrell, P. A., Wilmore, J. H., Coyle, E. F., Billing, J. E., & Costill, D. L. (1993). Plasma lactate accumulation and distance running performance. *Medicine and Science in Sports and Exercise, 11*(4), 338-344. doi: 10.1249/00005768-199310000-00002.

Feitl, M. E., & Krupin, T. (1996). Hyperosmotic agents. In: Ritch, R., Shields, M. B., Krupin, T. (Eds.). (pp. 1483–1488), *The Glaucomas*. St Louis: Mosby.

Francis, B. A., Hsieh, A., Lai, M. Y., Chopra, V., Pena, F., Azen, S., & Varma, R. (2007). Los Angeles Latino Eye Study Group. Effects of corneal thickness, corneal curvature, and intraocular pressure level on Goldmann applanation tonometry and dynamic contour tonometry. *Ophthalmology*, *114*(1), 20-26. doi:10.1016/j.ophtha.2006.06.047.

Friedman, D. S., Quigley, H. A., & Gelb, L., Tan, J., Margolis, J., Shah, S. N. … Hahn, S. R. (2007). Using pharmacy claims data to study adherence to glaucoma medications: Methodology and findings of the Glaucoma Adherence and Persistency Study (GAPS) *Investigative Ophthalmology & Visual Science*, *48*, 5052–5057. doi:10.1167/iovs.07-0290.

Gale, J., Wells, A. P., & Wilson, G. (2009). Effects of ocular physiology and disease. *Survey of Ophthalmology, 54*(3), 349-355. doi: 10.1016/j.survophthal.2009.02.005.

Gallardo, M. J., Aggarwal, N., Cavanagh, H. D., & Whitson, J. T. (2006). Progression of glaucoma associated with the Sirsasana (headstand) yoga posture. *Advances in Therapy*, *23*(6), 921-925.

Gardiner, S. K., Demirel, S., Gordon, M. O., & Kass, M. A. (2013). Seasonal changes in visual field sensitivity and intraocular pressure in the ocular hypertension treatment study. Ocular Hypertension Treatment Study Group. *Ophthalmology*, *120*(4), 724-730. [Gardiner et al., 2012, ARVO Abstract 1751; ahead of print]. doi: 10.1016/j.ophtha.2012.09.056.

Gibbons, T., Mulligan, S., Wilber, R., Rundell, K., Shannon, M., & Kearney, J. (1996). Presented by the Sport Science and Technology Division of the United States Olympic Committee. *Lactate Threshold: Application to training and performance.* http://www.coachr.org/lactate_threshold_application_to_training_and_performance.htm. Accessed June 18, 2012.

Gordon, M.O., & Kass, M. A. (1999). The Ocular Hypertension Treatment Study: design and baseline description of the participants. *Archives of Ophthalmology*, *117*(5), 573-583. doi:10.1001/archopht.117.5.573.

Güngör, K., Beydağı, H., Bekir, N., Arslan, C., Süer, C., Erbağci, I. … Aynacioğlu, A. S. (2002). The impact of acute dynamic exercise on intraocular pressure: role of the beta 2-adrenergic receptor polymorphism. *Journal of International Medical Research*, *30*(1), 26-33.

Guyton, A. C., Hall, J. E. (2006a). The Nervous System: B. The Special Senses: Fluid System of the Eye—Intraocular Fluid. In: Schmitt W, Gruliow, R. (Eds.), *Textbook of Medical Physiology.* (11th ed., pp. 623-624), Philadelphia, PA; Elsevier Saunders.

Guyton, A. C., Hall, J. E. (2006b). Energetics and Metabolic Rate, Body temperature, temperature regulation and fever. In: Schmitt W, Gruliow, R. (Eds.), *Textbook of Medical Physiology.* (11th ed., pp. 889-900), Philadelphia, PA; Elsevier Saunders.

Guyton, A. C., Hall, J. E. (2006c). The Body fluid compartments: Extracellular and intracellular fluids; interstiitial fluid and edema. In: Schmitt W, Gruliow, R. (Eds.),

Textbook of Medical Physiology. (11th ed., pp. 291-299), Philadelphia, PA; Elsevier Saunders.

Guyton, A. C., Hall, J. E. (2006d). Sports Physiology. In: Schmitt W, Gruliow, R. (Eds.), *Textbook of Medical Physiology.* (11th ed., p. 1065), Philadelphia, PA; Elsevier Saunders.

Guyton, A. C., Hall, J. E. (2006e). Muscle Blood flow and cardiac output during exercise; the coronary circulation and ischemic heart disease. In: Schmitt W, Gruliow, R. (Eds.), *Textbook of Medical Physiology.* (11th ed., pp. 247-248), Philadelphia, PA; Elsevier Saunders.

Guyton, A. C., Hall, J. E. (2006f). In: Schmitt W, Gruliow, R. (Eds.), Membrane Potentials and Action Potentials. *Textbook of Medical Physiology.* (11th ed., p. 61), Philadelphia, PA; Elsevier Saunders.

Hamilton-Maxwell, K. E., & Feeney, L. (2012). Walking for a short distance at a brisk pace reduces IOP. *Journal of Glaucoma*, *21*(6), 421–425. doi: 10.1097/IJG.0b013e31821826d0.

Hamilton, K. E., Pye, D. C., Aggarwala, S., Evian, S., Khosla, J., & Perera, R. (2007). Diurnal variation of central corneal thickness and Goldmann applanation tonometry estimates of intraocular pressure. *Journal of Glaucoma*, *16*(1), 29-35. doi: 10.1097/IJG.0b013e31802b350f.

Harris, A., Malinovsky, V. E., Cantor, L., Henderson, P. A., & Martin, B. J. (1992). Isocapnia Blocks Exercise-Induced Reductions in Ocular Tension. *Investigative Ophthalmology & Visual Science, 33*(7), 2229-2232.

Harris, A., Malinovsky, V. E., Martin, B. J. (1994). Correlates of acute exercise-induced ocular hypotension. *Investigative Ophthalmology & Visual Science, 35*(11), 3852-3857.

Haynes, W., Johnson, A., & Alward, W. (1992). Effects of jogging exercise on patients with the pigmentary dispersion syndrome and pigmentary glaucoma. *Ophthalmology*, *99*(7), 1096–1103.

Heyword, Vivian, H. (1998). Advance Fitness Assessment & Exercise Prescription. (3rd ed., p. 48). Reprinted from: The Physical Fitness Specialist Certification Manual, The Cooper Institute for Aerobics Research, Dallas TX, revised 1997.

Higgins, J. P. T., & Altman, D. G. (2011). Assessing risk of bias in included studies. In: Higgins, J. P. T., & Green, S., (Eds.), *Cochrane handbook for systematic reviews of interventions.* [Version 5.1.0, updated March 2011]. The Cochrane Collaboration. Available from www.cochrane-handbook.org. Accessed June 30,2012.

Higgins, J. P. T., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta analyses. *British Medical Journal*, *327*(7414), 557-560. doi:10.1136/bmj.327.7414.557.

Hoffman, J. (2006). Aerobic Power and Endurance. Norms for Fitness Performance and Health. In: Bahrke MS, Ewing AS. (Eds.), USA: Human Kinetics.

Hunt, A. P., Feigl, B., & Stewart, I. B. (2012). The intraocular pressure response to dehydration: a pilot study. *European Journal of Applied Physiology, 112*(5), 1963-1966. doi: 10.1007/s00421-011-2143-5.

Imms, F. J. & Mehta, D. (1989). Respiratory responses to sustained isometric muscle contractions in man: the effect of muscle mass. *Journal of Physiology (London), 419*, 1-14. doi: 10.1113/jphysiol.1989.sp017857.

Jain, A. K., Saini, J. S., & Gupta, R. (2000). Tonometry in normal and scarred corneas, and in postkeratoplasty eyes: a comparative study of the Goldmann, the ProTon and the Schiotz

tonometers. *Indian Journal of Ophthalmology* [serial online; cited 2015 Jul 24], *48*(1), 25-32. Available from: http://www.ijo.in/text.asp?2000/48/1/25/14859

Janiszewska, Z. (1963). Changes of the intraocular pressure after effort. *Klinika Oczna*, *33*, 385 [In: Risner et al., 2009, p.429]).

Jay, J. L., & Murdoch, J. R. (1993). The rate of visual field loss in untreated primary open angle glaucoma. *British Journal of Ophthalmology*, *77*(3), 176-178.

Johnstone, M. A. (2014). Intraocular pressure regulation: findings of pulse-dependent trabecular meshwork motion lead to unifying concepts of intraocular pressure homeostasis. *Journal of Ocular Pharmacology and Therapeutics, 30*(2-3), 88-93. doi: 10.1089/jop.2013.0224.

Jonas, J. B. (2007). Intraocular pressure during headstand. *Ophthalmology*, *114*, 1791. [Comment on: Baskaran, M., Raman, K., Ramani, K. K., Roy, J., Vijaya, L., & Badrinath, S. S. (2006)].

Karabatakis, V., Natsis, K., Chatzibalis, T., Lake, S. L., Bisbas, I. T., Kallinderis, K. A., & Stangos, N. T. (2004). Correlating intraocular pressure, blood pressure, and heart rate changes after jogging. *European Journal of Ophthalmology*, *14*(2), 117–122.

Kaufmann. C., Bachmann, L. M., & Thiel, M. A. (2004). Contour Tonometry with Goldmann Applanation Tonometry. *Investigative Ophthalmology & Visual Science*, *45*(9), 3118-3121. doi:10.1167/iovs.04-0018.

Kielar, R. A., Teraslinna, P., Rowe, D. G., & Jackson, J. (1975). Standardized aerobic and anaerobic exercise: differential effects on intraocular tension, blood pH, and lactate. *Investigative Ophthalmology & Visual Science*, *14*(10), 782-785.

Kim, K. N., Jeoung, J. W., Park, K. H., Yang, M. K., & Kim, D. M. (2013). Comparison of the new rebound tonometer with Goldmann applanation tonometer in a clinical setting. *Acta Ophthalmologica, 91*(5), e392-396. doi: 10.1111/aos.12109.

Kiss, B., Dallinger, S., Polak, K., Findl, O., Eichler, H.G., Schmetterer, L. (2001). Ocular hemodynamics during isometric exercise. *Microvascular Research*, *61*(1), 1-13. doi:10.1006/mvre.2000.2269.

Kiuchi, Y., Mishima, H. K., Hotehama, Y., Furumoto, A., Hirota, A., & Onari, K. (1994). Exercise intensity determines the magnitude of IOP decrease after running. *Japanese Journal of Ophthalmology*, *38*(2), 191–195.

Klein, B. E., & Klein, R. (1981). Intraocular pressure and cardiovascular risk variables. *Archives of Ophthalmology, 99*(5), 837-839. doi:10.1001/archopht.1981.03930010837009.

Klein, B. E., Klein, R., & Knudtson, M. D. (2005). Intraocular pressure and systemic blood pressure: longitudinal perspective: the Beaver dam eye study. *British Journal of Ophthalmology*, *89*, 284–287. doi:10.1136/bjo.2004.048710.

Kotecha, A., White, E.T., Shewry, J. M., & Garway-Heath, D. F. (2005). The relative effects of corneal thickness and age on Goldmann applanation tonometry and dynamic contour tonometry, *British Journal of Opthomology, 89,* 1572–1575. doi:10.1136/bjo.2005.075580

Krejci, R. C., Gordon, R. B., Moran, C. T., Sargent, R. G., & Magun, J. C. (1981). Changes in intraocular pressure during acute exercise. *American Journal of Optometry and Physiological Optics*, *58*(2), 144-148.

Lee, G. A., Khaw, P. T., Ficker, L. A., & Shah, P. (2002). The corneal thickness and intraocular pressure story: where are we now? *Clinical & Experimental Ophthalmology*, *30*(5), 334-337. doi:10.1046/j.1442-9071.2002.00551.x.

Leske, M. C. (2007). Open-angle glaucoma - an epidemiologic overview. *Ophthalmic Epidemiology*, *14*(4), 166-172. Review. doi: 10.1080/09286580701501931.

Leske, M. C., Heijl, A., Hussein, M., Bengtsson, B., Hyman, L., & Komaroff, E. (2003). Factors for glaucoma progression and the effect of treatment: The Early Manifest Glaucoma Trial. *Archives of Ophthalmology*, *121*(1), 48-56. doi:10.1001/archopht.121.1.48.

Leske, M. C., & Podgor, M. J. (1983). Intraocular pressure, cardiovascular risk variables, and visual field defects. *American Journal of Epidemiology*, *118*(2), 280-287.

Li, M., Wang, M., Guo, W., Wang, J., & Sun, X. (2011). The effect of caffeine on intraocular pressure: a systematic review and meta-analysis. *Graefe's Archive for Clinical and Experimental Ophthalmology*, *249*(3), 435-442. doi: 10.1007/s00417-010-1455-1.

Liu, J. H. K., & Weinreb, R. N. (2011). Monitoring intraocular pressure for 24 h. *British Journal of Opthalmology, 95*(5), 599–600. doi:10.1136/bjo.2010.199737.

Liu, J, H. K., Zhang, X., Kripke, D. F., & Weinreb, R. N. (2003a). Twenty-four-hour intraocular pressure pattern associated with early glaucomatous changes. *Investigative Ophthalmology & Visual Science*, *44*(4), 1586-1590.

Liu, J. H., Bouligny, R. P., Kripke, D. F., & Weinreb, R. N. (2003b). Nocturnal elevation of intraocular pressure is detectable in the sitting position. *Investigative Ophthalmology & Visual Science*, *44*(10), 4439-4442. doi:10.1167/iovs.03-0349.

Loewen, N. A., Liu, H. K., & Weinrub, R. N. (2010). Increased 24-Hour Variation of Human Intraocular Pressure with Short Axial Length. *Investigative Ophthalmology & Visual Science*, *51*(2), 933-937. doi:10.1167/iovs.09-4218.

Martin, B., Harris, A., Hammel, T., & Malinovsky, V. (1999). Mechanism of exercise-induced ocular hypotension. *Investigative Ophthalmology & Visual Science, 40*(5), 1011-1015.

Marcus, D. F., Edelhauser, H. F., Maksud, M. G., & Wiley, R. L. (1974). Effects of a sustained muscular contraction on human intraocular pressure. *Clinical Sci*ence, *47*, 249–257.

Marcus, D. F., Krupin, T., Podos, S. M., & Becker, B. (1970). The effect of exercise on intraocular pressure. I. Human beings. *Investigative Ophthalmology*, *9*(10), 749-752.

McLeod, S. D., West, S. K., Quigley, H. A., & Fozard, J. L. (1990). A longitudinal study of the relationship between intraocular and blood pressures. *Investigative Ophthalmology & Visual Science*, *31*(11), 2361-2366.

McArdle, W. D., Katch, F. I., & Katch, V. L. (2006). Essentials of exercise physiology. In: Lupash E., Kiefer R (Eds.), *Human Energy Transfer during exercise.* (3rd ed., p. 204). Philadelphia, PA; Lippincott Williams & Wilkins.

Miles D. S., Critz, J. B. & Knowlton, R. G. (1980). Cardiovascular, metabolic, and ventilatory responses of women to equivalent cycle ergometer and treadmill exercise. *Medicine and Science in Sports and Exercise, 12*, 14-19.

Molina, N., Milla, E., Bitrian, E., Larena, C., & Martíneza, L. (2010). Comparison of Goldmann tonometry, pneumotonometry and the effect of the central corneal thickness. *Archivos de la Sociedad Española de Oftalmología (English), 85*(10), 325-328. doi: 10.1016/j.oftal.2010.09.003.

Mosaed, S., Liu, J. H., & Weinreb, R. N. (2005). Correlation between office and peak nocturnal intraocular pressures in healthy subjects and glaucoma patients. *American Journal of Ophthalmology*, *139*, 320–324. doi:10.1016/j.ajo.2004.09.062.

Moura, M. A., Rodrigues, L. O. C., Waisberg, Y., de Almeida, H. G., & Silami-Garcia, E. (2002). Effects of submaximal exercise with water ingestion on intraocular pressure in healthy human males. *Brazilian Journal Of Medical and Biological Research, 35*(1), 121-125.

Movaffaghy, A., Chamot, S. R., Petrig, B. L., & Riva, C. E. (1998). Blood flow in the human optic nerve head during isometric exercise, *Experimental Eye Research*, *67*(5), 561-568. doi:10.1006/exer.1998.0556.

Ogbuehi, K. C. (2006). Assessment of the accuracy and reliability of the Topcon CT80 non-contact tonometer. *Clinical and Experimental Optometry*, *89*(5), 310–314. doi: 10.1111/j.1444-0938.2006.00068.x.

Okimi, P. H., Sportsman, S., Pickard, M. R., & Fritsche, M. B. (1991). Effects of caffeinated coffee on intraocular pressure. *Applied Nursing Research*, *4*(2), 72-76.

Orgül, S., & Flammer, J. (1994). Moderate exertion lasting only seconds reduces intraocular pressure. *Graefe's Archive for Clinical and Experimental Ophthalmology, 232*(5), 262-264.

Ozmerdivenli, R., Simsek, E., Bulut, S., Karacabey, K., & Saygin, O. (2006). Comparison of the effects of acute and regular exercise on intraocular pressure in Turkish athlete and sedentarians. *International Journal of Neuroscience*, *116*, 351–360. doi: 10.1080/00207450500442288.

Passo, M. S., Goldberg, L., Elliot, D. L., & Van Buskirk, E. M. (1987). Exercise conditioning and intraocular pressure. *American Journal of Ophthalmology, 103*(6), 754–757.

Passo, M. S., Goldberg, L., & Elliot, D. L., & Van Buskirk, E. M. (1991). Exercise training reduces intraocular pressure among subjects suspected of having glaucoma. *Archives of Ophthalmology, 109*, 1096–1098. doi:10.1001/archopht.1991.01080080056027.

Perrier, E., Demazières, A., Girard, N., Pross, N., Osbild, D., Metzger, D. … Klein, A. (2013a). Circadian variation and responsiveness of hydration biomarkers to changes in daily water intake. *European Journal of Applied Physiology, 113*(8), 2143-2151. doi: 10.1007/s00421-013-2649-0.

Perrier, E., Vergne, S., Klein, A., Poupin, M., Rondeau, P., Le Bellego, L. …Tack, I. (2013b). Hydration biomarkers in free-living adults with different levels of habitual fluid consumption. *British Journal of Nutrition, 109*(9), 1678-1687. doi: 10.1017/S0007114512003601.

Poole, D. C., Wilkerson, D. P., & Jones, A. M. (2008). Validity of criteria for establishing maximal O 2 uptake during ramp exercise tests. *European Journal of Applied Physiology*, *102*(4), 403- 410. doi: 10.1007/s00421-007-0596-3.

Portmann, N., Gugleta, K., Kochkorov, A., Polunina, A., Flammer, J., & Orgul, S. (2011). Choroidal blood flow response to isometric exercise in glaucoma patients and patients with ocular hypertension. *Investigative Ophthalmology & Visual Science, 52*(10), 7068-7073. doi:10.1167/iovs.11-7758.

Qureshi, I. A. (1995a). Effects of mild, moderate and severe exercise on intraocular pressure of sedentary subjects. *Annals of Human Biology*, *22*, 545–553.

Qureshi, I. A. (1995b). The effects of mild, moderate, and severe exercise on intraocular pressure in glaucoma patients. *Japanese Journal of Physiology*, *45*(4), 561-569.

Qureshi, I. A. (1995c). Age and intraocular pressure: how are they correlated? *Journal of Pakistan Medical Association*, 45(6), 150-152.

Qureshi, I. A. (1996a). Effects of exercise on IOP in physically fit subjects, *Clinical and Experimental Pharmacology and Physiology, 23*(8), 648–652.

Qureshi, I. A., Xi, X., Huang, Y., & Wu, X. (1996b). Magnitude of decrease in intraocular pressure depends upon intensity of exercise. *Korean Journal of Ophthalmology, 10*(2), 109-115.

Qureshi, I. A., Xi, X. R., Lu, H. J., Wu, X. D., Huang, Y. B., & Shiarkar, E. (1996c). Effect of seasons upon intraocular pressure in healthy population of China. *Korean Journal Ophthalmology*, *10*(1), 29-33.

Qureshi, I. A., Wu, X. D., Xi, X. R., Yang, J., & Huang, Y. B. (1997a). Resting intraocular pressure of steel factory workers is related to their physical fitness. *Industrial Health*, 35(2), 259-263.

Qureshi, I. A. (1997b). Does physical fitness influence intraocular pressure? *Journal of Pakistan Medical Association*, *47*(3), 81-84.

Quigley, H. A. (2011). Glaucoma. *The Lancet, 377*(9774), 1367-1377. doi: 10.1016/S0140-6736(10)61423-7.

Quigley, H. A., & Broman, A. T. (2006). The number of people with glaucoma worldwide in 2010 and 2020. *British Journal of Optholmolgy*, 90(3), 262–267. doi: 10.1136/bjo.2005.081224.

Read, S. A., & Collins, M. J. (2011). The short-term influence of exercise on axial length and intraocular pressure. *Eye* (London), *25*(6), 767–774. doi: 10.1038/eye.2011.54.

Risner, D., Ehrlich, R., Kheradiya, N. S., Siesky, B., McCranor, L., & Harris, A. (2009). Effects of exercise on intraocular pressure and ocular blood flow: a review. *Journal of Glaucoma, 18*(6), 429-436. doi: 10.1097/IJG.0b013e31818fa5f3.

Roberts, M., Reiss, M. J., & Monger, G. (2000). Homeostasis and the Control of Glucose. In: Nelson Thornes (Ed), *Advanced Biology*, (p. 272). Cheltenham: United Kingdom.

Roddy, G., Curnier, D., & Ellemberg, D. (2014). Reductions in intraocular pressure after acute aerobic exercise: A Meta Analysis, *Journal of Vision, 12*(9), 483-483. doi: 10.1167/12.9.483.

Rüfer, F., Schiller, J., Klettner, A., Lanzl, I., Roider, J., & Weisser, B. (2014). Comparison of the influence of aerobic and resistance exercise of the upper and lower limb on intraocular pressure. *Acta Ophthalmologica, 92*(3), 249-252. doi:10.1111/aos.12051.

Sargent, R. G., Blair, S. N., Magun, J. C., Krejci, R. C., Sacoco, C., Langley, T. D., & Taylor, R. L. (1981). Physical fitness and intraocular pressure. *American Journal of Optometry and Physiological Optics*, *58*(6), 460-466.

Sawka, M. N., Burke, L. M., Eichner, E. R., Maughan, R. J., Montain, S. J., & Stachenfeld, N. S. (2007). ACSM Position Stand ‘‘Exercise and Fluid Replacement,’’ *Medicine & Science in Sports & Exercise*, *39*(2), 377-390. Review.

Schulzer, M., & Drance, S. M. (1987). Intraocular pressure, systemic blood pressure and age: A correlational study. *British Journal of Opthalmology, 71*(4), 245-249.

Schwartz, G. F., & Quigley, H. A. (2008). Adherence and Persistence with Glaucoma Therapy. *Survey of Ophthalmology*, *53*(Supplement 1), S57-S68. doi: 10.1016/j.survophthal.2008.08.002.

Sesso, H, D., Paffenbarger, R. S., & Lee, I. M. (2000). Physical activity and coronary heart

disease in men: the Harvard Alumni Health Study. *Circulation*. *102*, 975–980. doi: 10.1161/01.CIR.102.9.975.

Shah, P., Whittaker, K., Wells, A., & Khaw, P. T. (2001). Exercise-induced visual loss associated with advanced glaucoma in young adults. *Eye (London)*, *15*(Part 5), 616-620. doi: 10.1038/eye.2001.196.

Shapiro, A., Wolf, E., Ferber, I., Merin, S. (1983). The effect of physical activity on the intraocular pressure of glaucomatous patients. *European Journal of Applied Physiology and Occupational Physiology, 52*(1), 136-138.

Sit, A. J. (2014). Intraocular pressure variations: causes and clinical significance. *Canadian Journal of Ophthalmology*, *49*(6), 484-488. doi: 10.1016/j.jcjo.2014.07.008.

Sollanek, K. J., Kenefick, R. W., Walsh, N. P., Fortes, M. B., Esmaeelpour, M., & Cheuvront, S. N. (2012). Assessment of thermal dehydration using the human eye: What is the potential? *Journal of Thermal Biology, 37*(2), 111–117. doi:10.1016/j.jtherbio.2011.12.006.

Swain, D., Abernathy, K. S., Smith, C. S., Lee, S. J., & Bunn, S. A. (1994). Target heart rates for the development of cardiorespiratory fitness. *Medicine & Science in Sports & Exercise*, *26*(1), 112-116.

Tonnu, P. A., Ho, T., Sharma, K., White, E., Bunce, C., & Garway-Heath, D. (2005). A comparison of four methods of tonometry: method agreement and interobserver variability. *British Journal of Opthalmology, 89*(7), 847-850. doi: 10.1136/bjo.2004.056614.

Vermeire, E., Hearnshaw, H., Van Royen, P., & Denekens, J. (2001). Patient adherence to treatment: three decades of research. A comprehensive review. *Journal of Clinical Pharmacy and Therapeutics*, *26*(5), 331-342.

Vieira, G. M., Oliveira, H. B., de Andrade, D. T., Bottaro, M., & Ritch, R. (2009). Intraocular pressure variation during weight lifting. *Archives of Ophthalmology*, *124*(9), 1251–1254. doi:10.1001/archopht.124.9.1251.

Vuori, I. (2004). Physical Inactivity as a Disease Risk and Health Benefits of Increased Physical Activity. In: Oja P, Borms J, (Eds.), Perspectives-The multidisciplinary series of physical education and sport science: Health enhancing physical activity (pp., 29-73).

Wang, Y. L., Hayashi, M., Yablonski, M. E. & Toris, C. B. (2002). Effects of multiple dosing of epinephrine on aqueous humour dynamics in human eyes. *Journal of Ocular Pharmacology and Therapeutics*, *18*(1), 53–63. doi: 10.1089/108076802317233216.

Wannamethee, S. G., Shaper, A. G., & Alberti, K. G. (2000). Physical activity, metabolic factors, and the incidence of coronary heart disease and type 2 diabetes. *Archives of Internal Medicine*, *160*, 2108–2116. doi:10.1001/archinte.160.14.2108.

Whitacre, M. M. & Stein, R. A. (1993). Sources of error with use of Goldmann-type tonometers. *Survey of Ophthalmology*, *38*, 1-30. doi: 10.1016/0039-6257(93)90053-A.

Wilson, M. R. (1997). The Myth of "21". *Journal of Glaucoma*, *6*(2), 75–77.

Williams, P. T. (2009). Relationship of incident glaucoma versus physical activity and fitness in male runners. Medicine & Science in Sports & Exercise, *41*(8), 1566-1572. doi: 10.1249/MSS.0b013e31819e420f.

Wimpissinger, B., Resch, H., Berisha, F., Weigert, G., Polak, K., Schmetterer, L. (2003). Effects of Isometric Exercise on Subfoveal Choroidal Blood Flow in Smokers and Nonsmokers. *Investigative Ophthalmology & Visual Science, 44*(11), 4859-4863.

Winters, J. E., & Pihos, A. M. (2008). Sight for seniors: A summary of findings and

challenges to providing community-based eye care to low-income seniors. *Optometry*, *79*(12), 718-723.

World Health Report [WHO] (2010). Physical activity for health. In: The World Health Report. (pp. 9-11), *Global Recommendations on Physical Activity for Health*. Geneva, World Health Organization.