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The effect of Trendelenburg positioning in laparoscopic colorectal surgery on intraocular pressure and cognitive function

By

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Declaration:

Except where acknowledged, I declare that this Thesis is the result of my own work which has been mainly undertaken during my period of registration for this degree at The University of Nottingham.

Parveen Vitish-Sharma

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Publications arising from this thesis:

The following peer reviewed publications (to date) are based on work documented within Chapters of this thesis:

Chapter 3:

Can the SENSIMED Triggerfish® lens data be used as an accurate measure of intraocular pressure?

Vitish-Sharma P, Acheson AG, Stead R, Sharp J, Abbas A, Hovan M, Maxwell-Armstrong C, Guo B, King AJ.

Acta Ophthalmol. 2017 Apr 9. doi: 10.1111/aos.13456.

Chapter 4:

The effect of acetazolamide on intraocular pressure after Trendelenburg positioning.

Parveen Vitish-Sharma, Anthony J. King, Ali Abbas, Charles Maxwell-Armstrong, Boliang Guo, Austin G. Acheson

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Dedicated to my Mum,

who was the inspiration behind this research.

ABSTRACT

Trendelenburg positioning is frequently used during laparoscopic surgery particularly when access to the pelvis is required. With improvements in laparoscopic skills, high risk patients and more complex procedures are now frequently being performed laparoscopically. (Improvement, 2016) The aim of this thesis is to investigate the effect of Trendelenburg positioning on intraocular pressure (IOP) and cognitive function.

Chapters 2 and 4 look at the effect of Trendelenburg positioning on IOP. Perioperative vision loss occurs rarely but it is a life changing complication. A rise in IOP is a recognised risk factor for POVL. The incidence of POVL following laparoscopic colorectal surgery has been quoted as 1.24 in 10,000 cases. (Pinkney *et al*., 2012) Chapter 2 is an observational study during which IOP was monitored during laparoscopic colorectal surgery. This was correlated with the degree of Trendelenburg tilt used during surgery. This study revealed an increase in IOP occurred which was dependent on the degree of Trendelenburg tilt as well as the time spent in this position (Pearson's correlation coefficient was 0.78). Patients undergoing left-sided colonic resections had a mean maximum IOP rise of 15.2mmHg. Chapter 4 is a follow-on study which looked at acetazolamide as a method of reducing the IOP rise that occurred whilst in the Trendelenburg position. This was a randomised placebo controlled cross-over healthy volunteer study. After

4 hours of Trendelenburg, the mean IOP increase was 3.17mmHg in the placebo group compared to 0.02mmHg in the acetazolamide group ($P<0.05$). This suggests acetazolamide has a role in reducing the IOP rise that occurs from Trendelenburg positioning.

The second half of this thesis focuses on the effect of Trendelenburg positioning on cognitive function. Post-operative cognitive decline (POCD) is defined as cognitive impairment following surgical intervention. It is associated with increased hospital stay, longer return to work/normal functioning, and in patients with existing cognitive impairment a further decline can result in loss of ability to carry out activities of daily living. (Moller *et al*., 1998) Chapter 5 is an observational study that explores the incidence of short- or long-term POCD following laparoscopic colorectal surgery. Post-resectional surgery, 55.4% of patients had evidence of POCD on Day 1 and 31.6% at long-term follow-up. On Day 2, 11.6% had POCD following right-sided resection compared to 16.3% in the left-sided resection group. Chapter 6 and 7 look at the effect of Trendelenburg positioning on cognitive function in healthy volunteers.

Chapter 6 assessed changes in brain function using magnetoencephalography and n-back testing as well as looking at MRI structural changes after 2 hours in Trendelenburg position. Although the difference was not statistically significant, there was an increase in brain

volume after 2 hours in Trendelenburg compared to pre-Trendelenburg MRI scan suggesting an element of cerebral oedema. Chapter 7 was a volunteer study designed to assess the effect of time spent in Trendelenburg position on cognitive function using cognitive tests (n back, stroop and lexical decision making tasks). This was carried out at regular intervals whilst in the Trendelenburg position and again once the volunteer was placed supine. After 3 hours in the Trendelenburg position, 40% had cognitive decline compared to 26.7% after 30 minutes.

Chapter 1：Introduction

1.1 Laparoscopic Surgery

1.1.1 History of Laparoscopic Surgery

The technological advances made in laparoscopic surgery during the 1990's is hailed as a technological break-through in modern day medicine (Kaiser, 2014). It is one of the largest technical revolutions in medicine since the solid organ transplant in 1954 (Kaiser, 2014). George Kelling, a surgeon from Dresdon in 1901 and Dimitri Ott, a gynaecologist from St. Petersburg, were the first to perform a 'true' laparoscopic procedure (Kaiser, 2014, Kaiser and Corman, 2001). George Kelling performed laparoscopy on a dog by inserting a cystoscope through a small abdominal incision and injecting air to create a pneumoperitoneum; and Dimitri Ott inspected the pelvic organs by making an incision through the posterior vaginal wall and inserting a ventroscope. Hans Christian Jacobaeus was a Swedish surgeon who further developed these techniques and named it laparoscopy. Following the publication of Hans and Kelling's work, diagnostic laparoscopy became an accepted diagnostic technique (Kaiser, 2014, Kaiser and Corman, 2001). During 1912 to 1924, the indications for laparoscopy increased and the Trendelenburg position was adopted to facilitate pelvic procedures (Vitish-Sharma, 2009 1997, Lau et al., 1997). The next significant development in laparoscopy occurred in 1982 when Kurtt Semm, performed the first laparoscopic appendicectomy followed by the first laparoscopic cholecystectomy performed in 1985 by Erich Muehe (Kaiser and Corman, 2001).

The next major breakthrough occurred with the invention of video laparoscopy (Jette *et al*., 2012). Developments in the computer industry introduced the use of a computer chip television camera. In 1986, it was attached to the laparoscope, giving rise to the era of video-guided surgery in which laparoscopic surgical techniques could be used for more complicated gastrointestinal procedures. It also facilitated the education of trainees with the use of videotapes. Rapid developments in imaging have resulted in higher resolution video monitors, affording greater clarity and definition. Also, improved magnification of the operative field, made fine dissection of the tissue plane easier (Vitish-Sharma, 2009 2009, Lau *et al*., 1997). Close collaboration further developed between industry and surgeons which allowed the development of further instruments such as sealing devices and staplers (Kaiser, 2014, Kaiser and Corman, 2001).

1.1.2 Laparoscopic Colorectal Surgery

The first reported laparoscopic assisted colectomy was performed in 1991 by Jacob *et al*. This proved to be a more challenging compared to previous laparoscopic procedure given the involvement of more than one area of the abdomen; the need to correctly identify the section of bowel to remove; correct identification of the blood supply with safe transection; removal of the specimen and performing an anastomosis (Kaiser, 2014). The COLOR Trial compared open to laparoscopic colorectal surgery. They found the laparoscopic approach had many advantages including reduced need for post-operative opiates, reduced hospital stay and earlier return of bowel function. They also found a

reduced inflammatory response compared to open surgery (COLOR, 2000). Randomised controlled trials comparing the oncological effectiveness of laparoscopic versus open surgery demonstrated little or no difference in oncological outcomes (Pascual *et al*., 2016, Nonaka *et al*., 2016).

As a result of these studies and advances in instruments available to perform such procedures, there has been a steady rise in the proportion of cases being carried out laparoscopically. The uptake of colorectal procedures performed laparoscopically in England in 2009 was 22% compared to 8.8% in 2007 (Pascual *et al*., 2016). National Bowel Cancer Audit report for 2016 showed 52.3% of cases were attempted laparoscopically (Improvement, 2016). The NICE guidelines in 2006 recommended laparoscopic approach should be recommended as an alternative to open surgery in whom both laparoscopic and open approaches are considered suitable (NICE, 2011). This led to the development of Lapco in 2007, a national training programme in laparoscopic colorectal surgery funded by cancer action team at the Department of Health (Coleman, 2015).

Year of report	**2012**	**2014**	**2016**
Laparoscopic	36.7%	44.8%	52.3%

Laparoscopic converted to open	13.0%	10.1%	8.5%
Age:			
≤ 64 years	31.8%	46.5%	52.8%
65-74 years	32.5%	46%	55.1%
75-84 years	28.7%	42.9%	44%
85+ years	7%	39.2%	28.1%
Co-morbidities:			
0	65.8%	47.8%	55.4%
1	26.1%	44.1%	51.8%
2+	8.2%	39.2%	49.9%
ASA grade			
1	16.8%	54.3%	58.4%
2	59.3%	48.7%	56.7%
3	22.3%	38.2%	44%
4 or 5	1.6%	17.1%	28.1%
Cancer site			
Rectosigmoid	7.9%	50.5%	57.8%
Rectal	23.7%	45.5%	55.5%

TABLE 1 COMPARISON OF LAPAROSCOPIC SURGERY RATES AS PER THE NATIONAL BOWEL CANCER AUDIT DATA. (IMPROVEMENT, 2016, IMPROVEMENT, 2014, IMPROVEMENT, 2012)

The National Bowel cancer audit reports show an increase in colorectal cancer cases being performed laparoscopically. There is also an increase in laparoscopic surgery being carried out in older patients; in patients with higher ASA grades; and more comorbidities. This change in patients now routinely offered a laparoscopic approach for colorectal surgery increases the potential complications that can arise. The incidence of Perioperative Vision Loss (POVL) following laparoscopic colorectal surgery in the USA was 1.24 per 10,000 in 2009 (Pinkney *et al*., 2012). When rectal surgery is carried out, patients are routinely placed in the Trendelenburg position which can lead to a rise in intraocular pressure (IOP) which is a known risk factor for POVL (Nuzzi and Tridico, 2016). With the increase in rectal and rectosigmoid cancers now being carried out laparoscopically, this number is likely to increase. The incidence of post-operative cognitive decline (POCD) following laparoscopic colorectal surgery has not been documented, but studies have suggested Trendelenburg positioning is a potential risk factor due to the increase in central venous pressure. With increased laparoscopic rectal surgery in patients who are older, we are likely to see an increase in the incidence of POCD.

1.2 Eye Anatomy

1.2.1 Structures involved in Vision

The retina is composed of an outer layer of pigmented cells, pars pigmentosa, and an inner transparent layer known as the pars nervosa which is important for vision (Figure 1). The pars nervosa is arranged in distinct layers including neurons essential for carrying light signals to the

brain. The photoreceptor layer containing rods and cones are responsible for responding to visual stimuli by photochemical reactions and is connected to the ganglion cell layer by bipolar cells. The axons of the ganglion cells bundle together to form the optic nerve which carries the light-induced impulses to the brain. Within the retina the lens, aqueous humor and vitreous humor are responsible for the refractive aspect of vision (Shahidullah M., 2011).

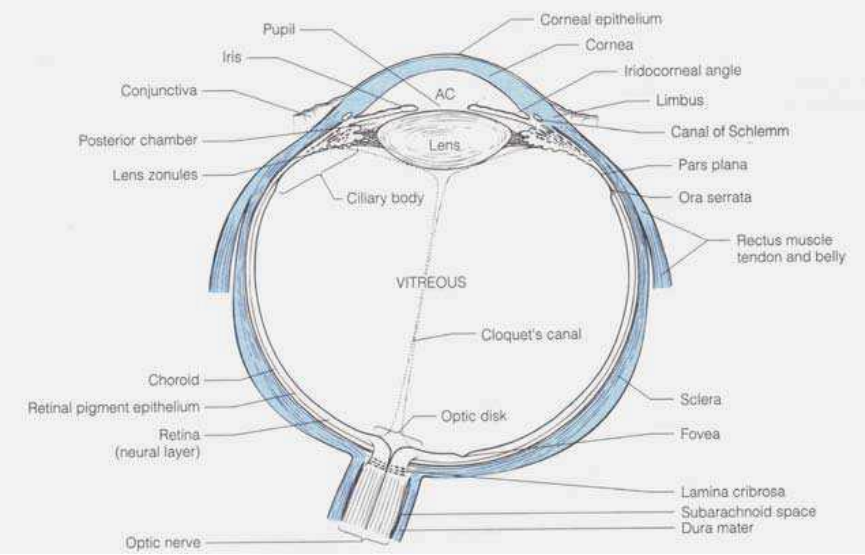


FIGURE 1 (REPRODUCED) HORIZONTAL SECTION OF HUMAN EYE. (AC = ANTERIOR CHAMBER) (SHAHIDULLAH M., 2011)

1.2.2 Anatomy of Ciliary body

Aqueous humor is produced by the ciliary body which is located between the iris and the choroid (Figure 2). The ciliary body is composed of ciliary processes, ciliary ring, ciliary muscle, and basal lamina (Shahidullah M., 2011). It attaches to the scleral spur creating a space between it and the sclera. The ciliary muscles are responsible for accommodation

(relaxation/contraction of lens) and forms most of the ciliary body. The inner surface of the ciliary body is continuous with the choroid and is in contact with the vitreous surface. The outer surface forms the anterior insertion of the uveal tract. (Figure 3)

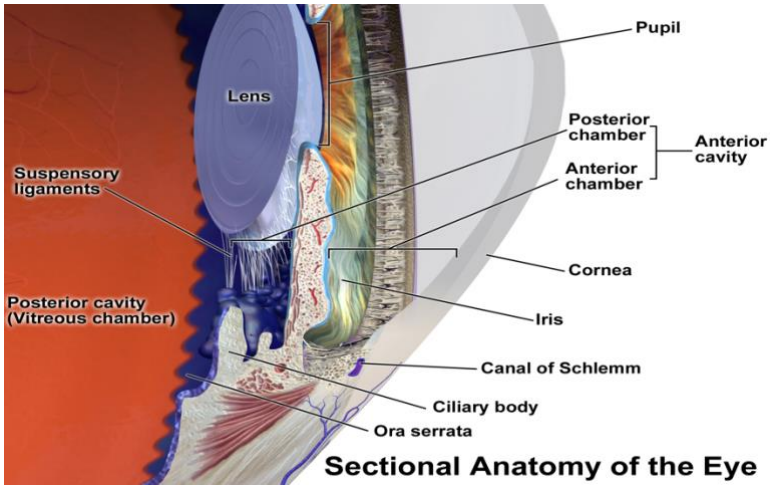


FIGURE 2 (REPRODUCED) ANATOMY OF HUMAN EYE (WIKIPEDIA, 2016A)

The inner aspect of the ciliary body is divided anatomically into two parts: anterior portion (pars plicata) and the posterior portion (pars plana). The pars plicata is characterised by ciliary processes which are a continuation of the posterior surface of the iris (Figure 3). The ciliary processes have increased basal and lateral interdigitations, mitochondria and rough endoplasmic reticulum in the non-pigmented epithelium. It is here that aqueous humor production occurs (B'Ann Gabelt, 2006, Borges- Giampani A. S., 2013). The pars plana has a relatively flat, pigmented inner surface, and is continuous with the choroid at the ora serrata (terminating point of the retina at the ciliary body) (Borges- Giampani A. S., 2013, B'Ann Gabelt, 2006). The choroid

extends from the ora serrata to the optic nerve and supplies blood to the retina. Nerves and arteries supplying the anterior structures of the eye also pass through the choroid (Shahidullah M., 2011). The ciliary body is supplied by both sympathetic and parasympathetic fibres. The oculomotor nerve (third cranial nerve) forms the parasympathetic plexus and the sympathetic nerve supply originates from the superior cervical ganglion (Borges- Giampani A. S., 2013).

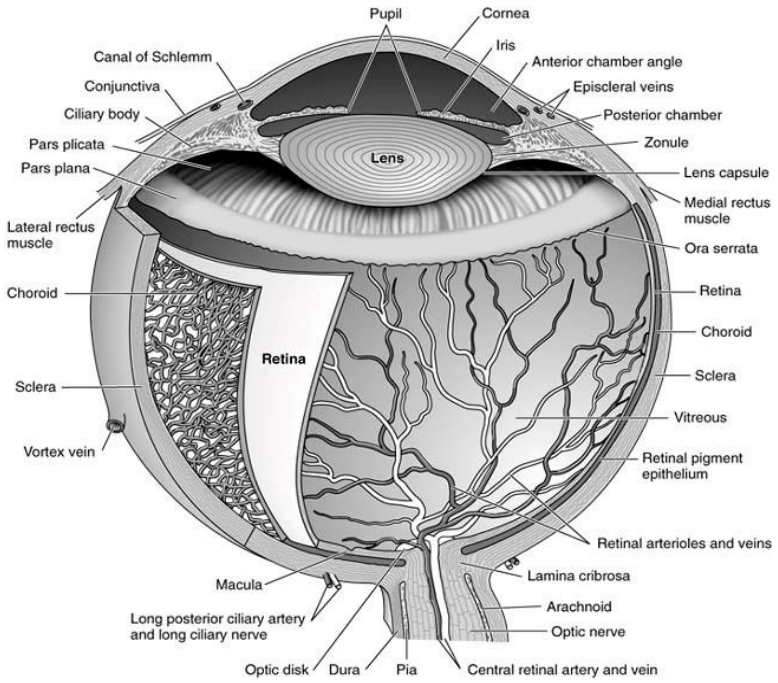


FIGURE 3 (REPRODUCED) INTERNAL STRUCTURES OF THE EYE (PAUL RIORDAN-EVA, 2011)

1.2.3 Anatomy of Schlemm's canal

The limbus is a transitional zone from the cornea to the sclera and the scleral sulcus is a small indentation on its inner surface. The trabecular

meshwork covers the top of the scleral sulcus creating a circular channel known as the Schlemm's canal.

The inner side of the canal is formed by three layers of the trabecular meshwork. First layer is the uveal meshwork, extension of ciliary muscle inserting into the cornea. The second layer is several sheets of connective tissue between the scleral spur and the peripheral cornea. The third layer is the juxtacanalicular tissue (also known as cribiform plexus), which forms the inner wall of Schlemm's canal.

Within the Schlemm's canal are internal collector channels connected to episcleral and conjunctival veins by external collector channels, the intrascleral venous plexus, deep scleral plexus and the aqueous veins (Figure 4).

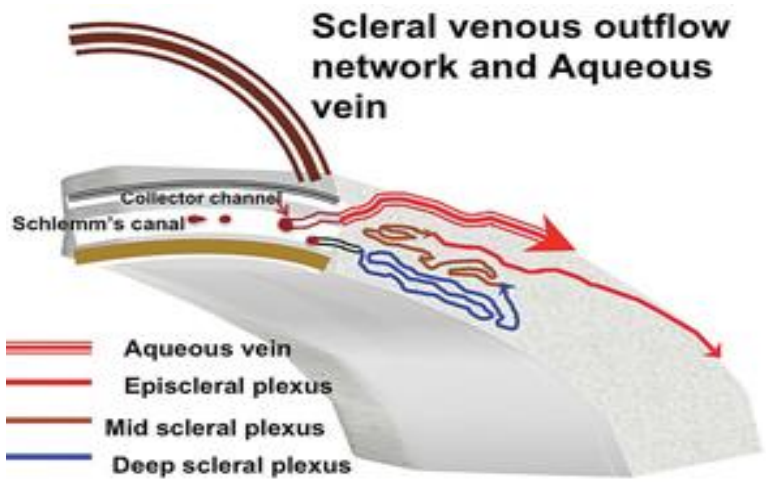


FIGURE 4 (REPRODUCED) AQUEOUS HUMOR ROUTE ONCE IT LEAVES SCHLEMM'S CANAL (OPHTHALMOLOGY, 2014)

1.2.4 Blood supply to Ciliary body

The iris is supplied mainly by medial and lateral long posterior ciliary arteries which form a major arterial circle near the root of the iris (Figure 5). These form branches that supply the iris, ciliary body and the anterior choroid. They penetrate the sclera posteriorly and travel anteriorly in the suprachoroid. The seven anterior ciliary arteries also contribute to this major arterial circle (Figure 6). They supply the extraocular rectus muscles and then enter via the sclera anteriorly to the outer and posterior areas of the ciliary muscle, and the peripheral area of the choroid (Borges- Giampani A. S., 2013).

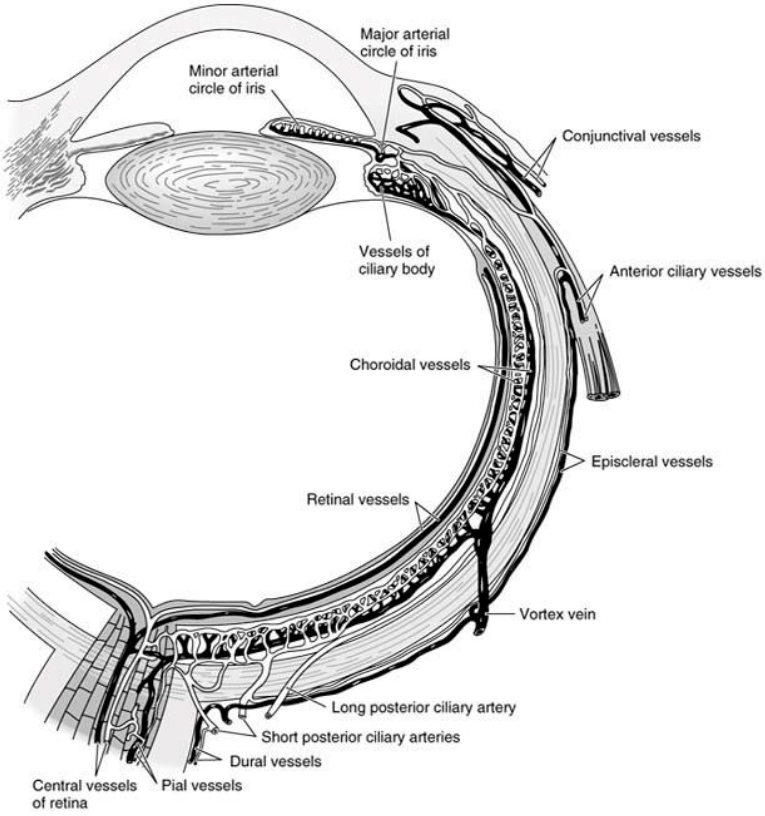


FIGURE 5 (REPRODUCED) BLOOD SUPPLY TO THE EYE (PAUL RIORDAN-EVA, 2011)

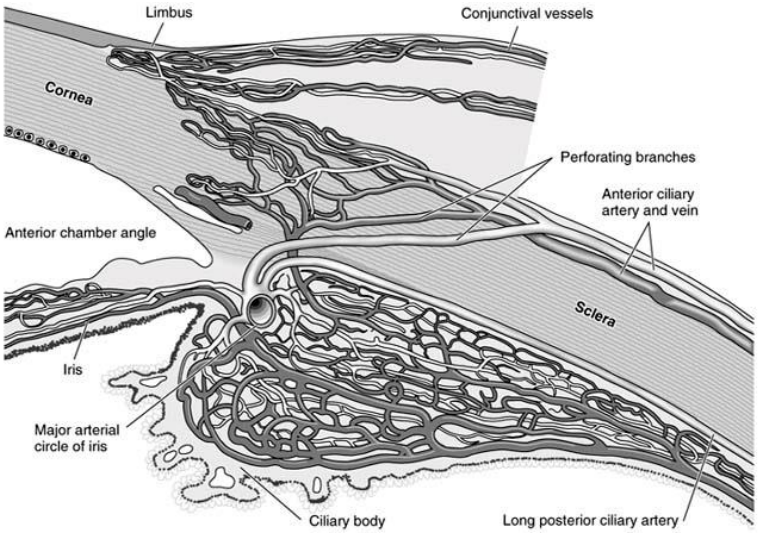


FIGURE 6 (REPRODUCED) VASCULAR SUPPLY TO ANTERIOR SEGMENT (PAUL RIORDAN-EVA, 2011)

The microvasculature of ciliary process arises from the short radial ciliary arteries. The ciliary arteries originate from the ophthalmic artery which is a branch of the internal carotid artery. The anterior aspect of the ciliary processes drains via venules passing through the ciliary body. The major and minor ciliary processes are drained posteriorly by venules located at the margin of the ciliary processes. The venules then drain through the vortex system of the choroid. Branches from each short radial ciliary artery allows an extensive capillary network to form. They are highly fenestrated and thin walled which provides a large surface area for aqueous formation to occur (Figure 7) (B'Ann Gabelt, 2006, Borges-Giampani A. S., 2013).

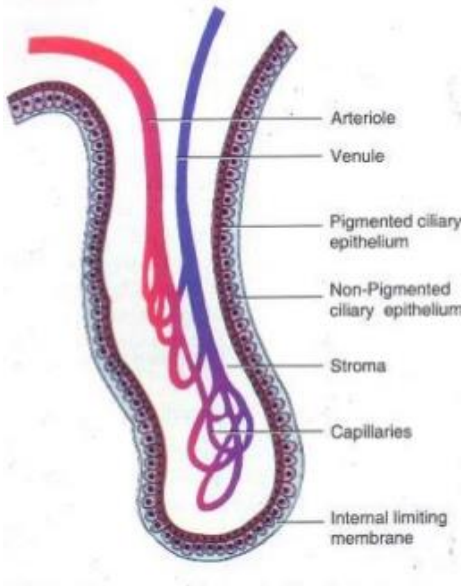


FIGURE 7 (REPRODUCED) MICROSCOPIC STRUCTURE OF CILIARY PROCESS (CHALLA, 2014)

1.2.5 Optic Nerve Anatomy

The optic nerve arises from ganglion cells in the retina's nerve fibre layer. It enters the globe via the posterior scleral foramen about 1mm below and 3mm nasal to the posterior aspect of the globe. The nerve myelination begins once it has left the eye so its width is 1.5mm within the sclera, and it increases to 3mm in the orbit. Once in the orbit, the optic nerve travels within the optic muscle cone, via the bony optic canal, and then enters the cranial cavity. It then joins the opposite optic nerve to form the optic chiasm. The ganglion cells forming the optic nerve do not regenerate if damaged (Paul Riordan-Eva, 2011).

1.2.5.1 Optic nerve blood supply

The intraocular portion of the optic nerve is also known as the optic head. The optic head includes the optic disc and the part of the nerve that travels through the scleral canal. The main blood supply to the optic head

comes from the ophthalmic artery and is delivered to the optic nerve head via the central retinal artery and the posterior ciliary arteries (Figure 8). The circle of Zinn-Haller is formed by posterior ciliary arteries and is the main blood supply to the optic nerve head. Choroidal arterioles and recurrent pial arterioles also partly provide arterial supply to the optic nerve however, there is significant variation in this blood supply. Various factors, including the watershed areas between the areas of distribution of the short posterior ciliary arteries, may lead to ischemia in susceptible individuals (Fraser and Bugnyar, 2011, Grant *et al*., 2010).

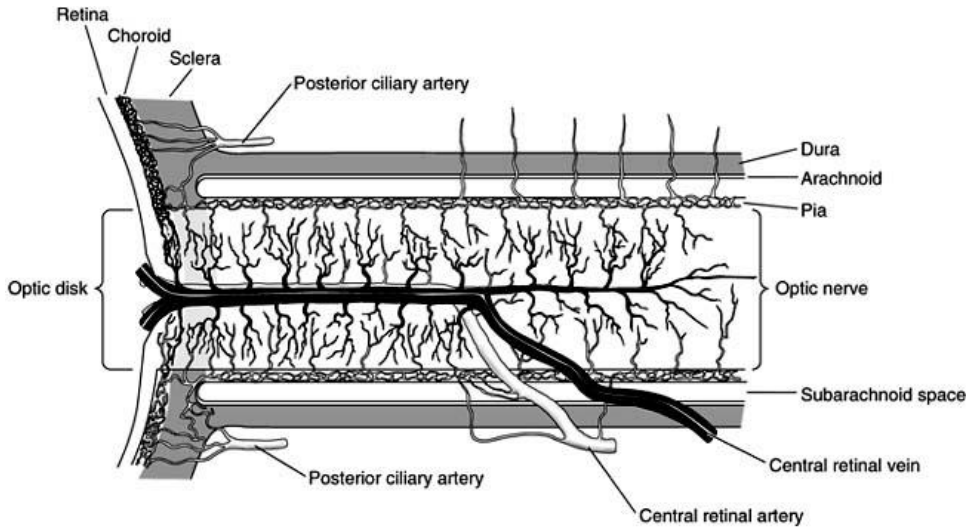


FIGURE 8 (REPRODUCED) BLOOD SUPPLY TO THE OPTIC NERVE (PAUL RIORDAN-EVA, 2011)

1.2.6 Aqueous Humor

Aqueous humor is a transparent solution formed continuously from plasma. Its main functions include: (B'Ann Gabelt, 2006)

1. Oxygen and nutrient delivery and removal of waste products to and from avascular structures. These include blood, macrophages, inflammatory products, or other debris from avascular structures such as posterior cornea, lens and iris.
2. Maintenance of IOP with continuous production and drainage.
3. Transparent colourless properties allow a lower refractive index between the posterior lens and cornea.
4. Facilitates cellular and humoral responses in the eye to infection or inflammation.
5. High ascorbate levels protect against ultraviolet induced oxidative products such as free radicals.

Aqueous humor is found within the anterior and posterior chambers. The anterior chamber contains most of the aqueous humor and is found between the anterior surface of the iris and the internal surface of the cornea. The posterior chamber is smaller and is surrounded by the lens, the iris and the ciliary body (Figure 1) (Shahidullah M., 2011).

1.2.6.1 Production of aqueous humor

Aqueous humor production involves diffusion, ultrafiltration, active secretion and selective transfer of solutes and water from blood plasma by complex ciliary epithelium. This fluid then accumulates in the anterior and posterior compartments of the eye.

1.2.6.1.1 Diffusion

Diffusion occurs as a passive process of solutes and lipid soluble substances passing down a concentration gradient through capillaries

and the posterior chamber membrane. The rate of diffusion depends on the concentration gradient as per Fick's law:

Rate of diffusion = K(C1-C2)

K= Constant dependent on nature and permeability of membrane, temperature, concentration of solutes; C_1 = Concentration on side with higher concentration; C_2 = concentration on side with lower concentration.

1.2.6.1.2 Ultrafiltration

Ultrafiltration of plasma also passively occurs through fenestrated capillaries in the vascular plexus of the ciliary processes into the interstitial space between the vessels and the ciliary epithelia. Due to the protein content within the capillaries of the ciliary process, it has an oncotic pressure of approximately 14mmHg. In healthy eyes, the IOP is usually maintained at around 15mmHg, so a capillary hydrostatic pressure of at least 29mmHg would be required to allow ultrafiltration to occur. Within the ciliary stroma, the capillary hydrostatic pressure has been estimated to be 25 to 33mmHg. For ultrafiltration to be the major form of fluid movement, it would require a capillary pressure greater that 50mmHg. As the pressure in healthy eye is estimated between 25 – 33mmHg, it only partly contributes to aqueous humor production (B'Ann Gabelt, 2006).

1.2.6.1.3 Active secretion

Up to 80% of aqueous humor production is from active secretion. Active transport in non-pigmented epithelial cells takes place through selective trans-cellular movement of anions, cations, and other molecules across a concentration gradient between the blood-aqueous barrier. Aquaporins are molecular water channels which transport fluids against an osmotic pressure gap. Na^+ and K^+ transport is mainly carried out by membrane-bound Na^+/K^+ ATPase, which is present along the lateral cellular interdigitations of the non-pigmented ciliary epithelium. The transmembrane Na^+/K^+ transport protein is energised by the Gibbs free energy of hydrolysis of ATP (adenosine triphosphate), mediated by ATPase. The ATP required for this process is derived predominantly from oxidative metabolism of glucose via the Krebs' citric acid cycle. Na^+/K^+ ATPase can be inhibited by many different molecules, including cardiac glycosides, dinitrophenol, vanadate, and possibly acetazolamide through pH changes. Thus, Na^+/K^+ ATPase is of particular interest in pharmacological studies of aqueous humor dynamics (Kristina Irsch, Arthur C. Guyton, 2006).

Carbonic anhydrase, found in the non-pigmented and pigmented ciliary epithelia mediates the transport of bicarbonate across the ciliary epithelium by the reversible hydration of CO_2 to form HCO_3^- and protons through the following reaction:

$$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$$

Bicarbonate ion formation affects fluid transport by affecting Na^+, possibly by regulating the pH for optimal active ion transport.

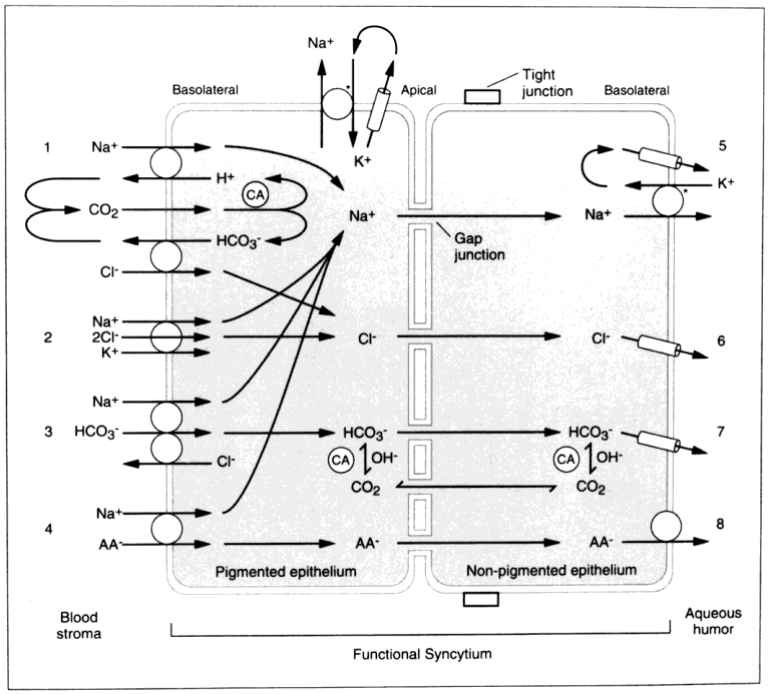


FIGURE 9 (REPRODUCED) SECRETORY PATHWAYS IN CILIARY PROCESSES. AA, ASCORBIC ACID, CA, CARBONIC ANHYDRASE. (B'ANN GABELT, 2006)

Electrochemical gradients regulate the movement of electrolytes across the ciliary epithelium which leads to secretion, and the hydrostatic and oncotic forces lead to resorption of aqueous humor. Chloride ion is the major anion transported across the epithelium through Cl^- channels, ascorbic acid is secreted against a concentration gradient by sodium-dependent vitamin C transporter 2, and certain amino acids are secreted by different solute carriers. These active transports lead to an osmotic

gradient allowing ultrafiltration and diffusion to occur across the ciliary epithelium. Aqueous humor is composed mainly of organic and inorganic ions, carbohydrates, glutathione, urea, amino acids and proteins, oxygen, carbon dioxide, and water. Aqueous humor is slightly hypertonic to plasma with no difference found between aqueous humor in the anterior chamber and posterior chamber (B'Ann Gabelt, 2006, J. Cameron Millar, 2006).

Carbonic anhydrase enzyme creates an osmotic gradient for water to then pass into the posterior chamber (Quaranta *et al*., 2013, Murgatroyd and Bembridge, 2008). This occurs independently to IOP as aqueous humor has the role of supplying oxygen and glucose to the avascular lens and cornea (Quaranta *et al*., 2013).

1.2.6.2 Resorption of Aqueous humor

Aqueous humor enters the posterior chamber by the ciliary processes and flows around the lens and then goes through the pupil into the anterior chamber. Once in the anterior chamber, it re-enters the venous circulation by different exit routes (Figure 10).

1.2.6.2.1 Trabecular meshwork route

The trabecular meshwork route involves the trabecular meshwork on the inner aspect of Schlemm's canal and is how the majority of aqueous humor is reabsorbed.

The trabecular meshwork consists of collagen and elastic fibres, several layers of endothelium enmeshed into sheets of glycosaminoglycans, proteoglycans and various other macromolecules. The cribiform plexus is thought to cause the majority of resistance to outflow (Shahidullah M., 2011, B'Ann Gabelt, 2006).

1.2.6.2.2 Posterior uveoscleral route

The posterior uveoscleral route accounts for approximately 5-20% of the total absorption of aqueous humor. Aqueous humor flows from the chamber angle across the iris and anterior part of the ciliary muscle through the connective tissue spaces between the ciliary muscles. Fluid passes through these spaces into the suprachoroid and then into the sclera into the episcleral tissue into the venous circulation. As pressure in the suprachoroid space is lower than the anterior chamber, it allows aqueous humor to take this route (Shahidullah M., 2011). The rate of flow can be explained using Poiseuille's law:

$$F = C\,(P-P_e)$$

F - aqueous flow, C - facility of outflow, P - IOP, P_e, - episcleral venous pressure.

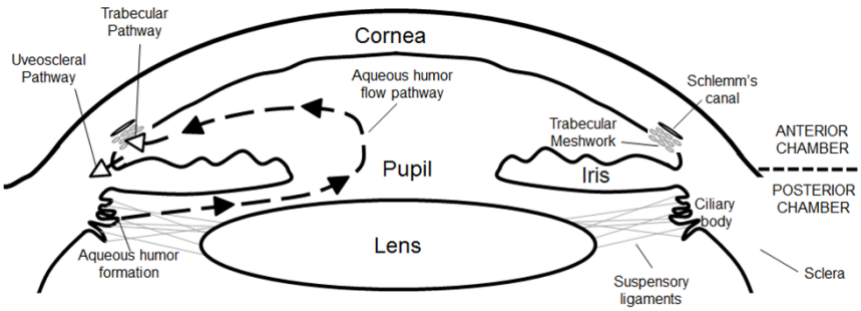


FIGURE 10 (REPRODUCED) SHOWING THE AQUEOUS HUMOR FLOW PATHWAY (SHAHIDULLAH M., 2011)

A small amount of aqueous humor passes into the vitreous humor and is absorbed into the posterior part off the eye.

1.2.6.3 Intraocular Pressure and Aqueous humor

Any imbalance in absorption or production of aqueous humor can affect intraocular pressure (IOP). If there is insufficient drainage of aqueous humor, it will cause an excessive build up within the globe leading to an increase in IOP. Abnormally high IOP can lead to death or degeneration of light sensitive and signal transmitting tissues within the eye leading to partial or complete vision loss (Molloy, 2011).

IOP is thought to affect aqueous humor resorption via Schlemm's canal by affecting the structure of the endothelial layer lining Schlemm's canal. Variation in IOP brings about changes in the structure of the endothelial lining of Schlemm's canal. Elevated IOP leads to an increase in the number and size of vacuoles, and a decrease in IOP decreases the number and size of vacuoles (Goel *et al*., 2010).

Under normal conditions, aqueous humor formation and outflow remains almost equal. It has two components: a hydrostatic component and secretary component.

1.3 IOP Physiology

IOP is defined as the pressure exerted from the contents of the eye against its containing wall (Murphy, 1985) and is normally within the range of 11 to 21 mmHg. A value above 25 mmHg is considered pathological (Cunningham and Barry, 1986).

There are three factors that affect intraocular pressure:

1. Aqueous humor dynamics: to include production and drainage.
2. Choroidal blood volume: Controlled by autoregulation, central venous pressure, chemical $PaCO_2$ and PaO_2, and metabolic pH.
3. Vitreous volume: which is controlled by osmotic pressure, extraocular muscle tone and neurogenic control.

1.3.1 Epinephrine and IOP

Aqueous humor is exchanged at a rate of 2.4 ± 0.6µl/min (mean ± SD, daytime measurements in adults aged 20–83 years). Circadian rhythm of aqueous humor flow has been observed in humans. Aqueous humor flow is highest in the morning at 3.0µl/min, 2.4µl/min in the afternoon and 1.5µl/min at night (B'Ann Gabelt, 2006).

Studies have been carried out looking at the effect of epinephrine and acetazolamide on the rate of aqueous humor flow through the anterior chamber. Epinephrine increased the rate of aqueous flow in sleeping subjects to a greater extent than in awake subjects and acetazolamide reduced the rate of flow in both awake and epinephrine stimulated subjects. Norepinephrine has also been shown to stimulate aqueous flow, but not as effectively as epinephrine. Another hypothesis supporting epinephrine influence on circadian rhythm could be a ciliary production of this hormone. However, epinephrine concentration in human aqueous humor appears to be very low, ranging from 0 to 0.1ng/ml. Moreover, in patients with surgical adrenalectomy or Horner syndrome (reduced or absent sympathetic innervation on one side), the circadian flow pattern was observed to be normal (B'Ann Gabelt, 2006, Quaranta *et al*., 2013).

1.3.2 Ocular perfusion pressure

Ocular perfusion pressure (OPP) is defined as the difference between mean arterial pressure (MAP) and IOP.

$$OPP = MAP – IOP$$

Given the above equation, an increase in IOP can reduce OPP (even if MAP is maintained).

1.3.3 Systemic arterial pressure and IOP

Intraocular blood volume is another factor that may affect IOP. Within the eye, the choroid contains the majority of the intraocular blood volume mainly within the venules. Filling of the venules is dependent on pressure within the orbital veins (Ozcan *et al*., 2004). As the orbital venous system is a valveless system, changes in CVP directly affects orbital venous pressure. Body positioning also affects CVP. Trendelenburg or prone positioning both increase CVP, which in turn increases orbital venous pressure leading to congestion in the choroid which ultimately increases IOP by increasing intraocular blood volume. Conversely, positions which reduce CVP such as reverse Trendelenburg, can lead to a decrease in IOP (Ozcan *et al*., 2004, Kiel, 1994, Grant *et al*., 2010).

1.3.4 Venous Pressure and IOP

Episcleral venous pressure is important factor in regulation of IOP and is influenced by body position, venous drainage pressure in both the superior and inferior ophthalmic veins, cavernous and petrosal sinuses, internal and external jugular veins (Figure 11). Any increase in venous pressure in the venous drainage system of the eye can result in a rise in IOP. Problems in venous drainage can also reduce the arterial blood supply. This could reduce the oxygen delivery to the eye, which can result in ischaemia and neovascularisation (Craven, 2004). Medications which reduce aqueous humor formation are more effective than drugs that increase trabecular aqueous outflow or Prostaglandin analogues (Ophthalmology, 2016).

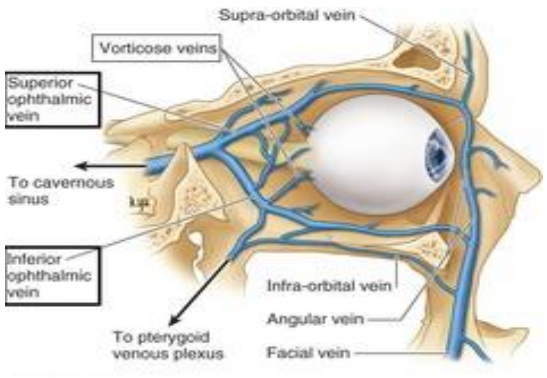


FIGURE 11 (REPRODUCED) VENOUS DRAINAGE OF EPISCLERAL VEINS (SHAHIDULLAH M., 2011)

Redistribution of venous blood and pressure within the venous system draining the eye are important factors in determining IOP. The absence of venous valves means venous pressure is directly correlated to changes in CVP. Therefore, any changes in CVP translate into changes of ocular venous pressures and therefore affect IOP (Grant *et al*., 2010).

Macri *et al* studied the relationship between venous pressure and IOP. They studied both intact and enucleated eyes and increased venous pressure. Increasing venous pressure showed a similar increase in anterior chamber pressure. Decreasing venous pressure also decreased IOP to a similar degree. Based on their findings, Macri *et al* suggested that the diameter of intraocular blood vessels is either the cause or effect of changes of the venous pressure. The changes in vessel diameter results in changing IOP by their effects on intraocular volume (Murphy, 1985).

Episcleral venous pressure (EVP) is normally between 8-12mmHg, but obstruction to venous outflow can increase this. If external pressure is increased by 7mmHg, it can cause the vein to collapse completely (Rachel Peck, 2006).

1.3.5 PCO_2 and IOP

Vascular tone alters capacitance of vessels. Intraocular vascular tone is essentially affected by arterial PCO_2 and central controlling areas in the diencephalon. Samuel and Beugie studied the effect of end tidal CO_2 on IOP. They found a significant positive correlation between end tidal CO_2 and IOP with CO_2 concentrations at 3, 5 and 8%. They also found that at these CO_2 concentrations, CVP remained unchanged. They hypothesised that the decrease in IOP was a result of vasoconstriction of the choroidal blood vessels, decrease in aqueous humor formation which is controlled by carbonic anhydrase and is under the influence of PCO_2 (Samuel and Beaugié, 1974).

Hvidberg *et al*. studied the effect of changes in PCO_2 and body positions on IOP during general anaesthesia and found a similar correlation between PCO_2 and IOP as Samuel and Beugie. Hvidberg *et al* hypothesised that changes in IOP due to PCO_2 were too rapid to be due to changes in aqueous formation. They found that PCO_2 changes were followed by changes in CVP and concluded that the increase in IOP after PCO_2 increase was due to choroidal vasodilation or CVP elevation or, more likely a combination of both. Petounis *et al* found that the increase

in IOP from PCO_2 increase was not prevented by acetazolamide (inhibitor of aqueous formation) use. They therefore concluded that the rise in IOP was due to the increase in CVP and choroidal vasodilatation after hypoventilation. They also concluded that intraocular vasodilatation must be the cause (Hvidberg *et al*., 1981). Studies where retinal vessels were photographed different levels of PCO_2 and found this to be true (Hvidberg *et al*., 1981). With the use of radioactive krypton desaturation technique, choroidal vascular resistance was also shown to vary with the concentration of inhaled CO_2 (Murphy, 1985).

1.3.6 Effect of change in Aqueous Drainage on IOP

Schlemm's canal is the major outflow route for aqueous humor into the episcleral veins (Craven, 2004). As this outflow process is passive, it relies upon a pressure gradient between IOP and episcleral venous pressure (Ozcan *et al*., 2004). Therefore, any change in episcleral venous pressure can also affect IOP by changing the volume of aqueous humor. The rate of aqueous humor exchange is relatively fast. A complete exchange of aqueous humor can occur within 2 hours. As the eye has limited distensibility, it only requires a small change in aqueous humor volume for IOP to change significantly. Along with IOP affecting the outflow of aqueous humor, if IOP is very high, it can also affect the rate of production of aqueous humor (Ozcan *et al*., 2004). Resistance to outflow of aqueous humor was studied extensively by Grant in enucleated eyes. When the trabecular meshwork between the anterior chamber and Schlemm's canal was disrupted, there was a 75% reduction in outflow. Contraction of the ciliary muscle opens the

trabecular meshwork, which also decreases resistance to outflow (Grant, 1955).

Adrenergic stimulation also affects resistance to outflow of aqueous humor. Langham *et al* studied the effects of topical adrenaline, noradrenaline, and isoproterenol (β-adrenergic agonist) on aqueous humor dynamics, IOP, and pupillary size. He found that α-stimulation induced dilation of the pupil, decrease in IOP, increased aqueous humor outflow, and ß-stimulation decreased IOP without affecting pupillary size or aqueous humor outflow (Langham *et al*., 1971).

In low doses, adrenaline causes ß-stimulation and at higher doses it leads to α-stimulation. The effect these stimulations have on the blood flow in ciliary processes are thought to be the cause for IOP and aqueous outflow changes (Murphy, 1985).

1.3.7 Positioning and IOP

IOP has been shown to be reduced when in the supine position after general anaesthetic. The balance between the increase in IOP that may occur when in the Trendelenburg position and the reduction in IOP that occurs following general anaesthetic, is likely to play an important role in the net ocular perfusion pressure. Resting IOP has been shown to be determined by episcleral venous pressure with IOP varying directly with episcleral venous pressure. Vascular congestion leading to episcleral

venous congestion may also be a significant factor in the rise in IOP when in the Trendelenburg position (Grant *et al*., 2010). (Section 1.3.4 Venous Pressure and IOP)

Grosso *et al* compared 3 groups of patients, those undergoing laparoscopic surgery supine, laparoscopic surgery in Trendelenburg position and open surgery in supine position. They found the mean IOP increase following 45 minutes after the start of surgery in the Trendelenburg group was 5.05 mmHg versus 4.23 mmHg in the laparoscopic group not placed in Trendelenburg (Grosso *et al*., 2013).

1.3.8 Pneumoperitoneum and IOP

Grosso *et al* compared 3 groups of patients, those undergoing laparoscopic surgery supine, laparoscopic surgery in Trendelenburg position and open surgery in supine position. They looked at the effect of pneumoperitoneum (12-14mmHg) on IOP, and found a mean rise of 4mmHg (range 0-11.2 mmHg).

1.3.9 General anaesthesia and IOP management

There are various drugs and pathways that can be used during anaesthesia to reduce IOP (Samuel and Beaugié, 1974).

Vasoconstriction to reduce blood flow into the eye and reduce IOP can be achieved with adrenergic drugs such as topical adrenaline or by

inducing hypocarbia with hyperventilation (Section 1.3.6 Effect of change in Aqueous Drainage on IOP).

Relaxation of ocular muscles can be achieved with volatile agents such as halothane or trichloroethylene. Use of non-depolarizing relaxants including curare, gallamine, and pancuronium. Also, the use of a facial and retrobulbar nerve block.

Reduction of CVP with a general anaesthetic that avoids coughing, straining, and vomiting or even the use of reverse Trendelenburg positioning.

Arterial hypotension can also be induced with the use of halothane or ganglion blockade, but it also occurs at anaesthetic induction.

Aqueous humor production can be reduced by inhibition of active transport mechanism with acetazolamide or cardiac glycosides. Spontaneous and induced hypothermia can also reduce aqueous humor production. Aqueous humor drainage can be increased with the use of cholinergic drugs including eserine or pilocarpine. Increasing plasma hypertonicity with mannitol, urea, sucrose or glycerol, and the use of digital orbital pressure can also reduce IOP.

1.4 Measuring IOP

1.4.1 Goldmann applanation tonometry

Goldmann applanation Tonometry is known to be the gold standard non-invasive measure of IOP. It requires the patient to be seated and a prism and slit lamp to perform this test. The need for the slit lamp limits where this examination can be carried out. As the Goldmann tonometer needs to make contact with the front of the eye (Stevens *et al*., 2007).

FIGURE 12 GOLDMANN TONOMETER

Local anaesthetic eye drops are administered along with fluorescein drops. The slit lamp beam is directed onto the Goldmann tonometer from the same side as the eye in which IOP is being measured, i.e. from the left-hand side for left eye. The blue light filter and wide beam is used as it makes visualising the fluorescein rings easier. The patient looks straight ahead with a fixed gaze and keeps both eyes open. The

tonometer is kept perpendicular to the eye and the blue light is directed onto the prism head. The tonometer is moved closer to the patients' eye until it rests gently on the surface of the eye (Stevens *et al*., 2007, Optometry, 2015).

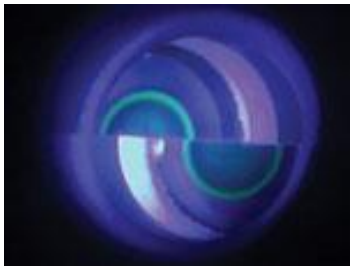


FIGURE 13 (REPRODUCED) ACTUAL VIEW THROUGH GOLDMANN TONOMETER (OPTOMETRY 2015)

The dial on the calibrated Goldmann tonometer is turned until the two fluorescein semi-circles in the prism head are seen to meet in an 'S' shape (Figure 14) reading on the Goldmann tonometer is the IOP.

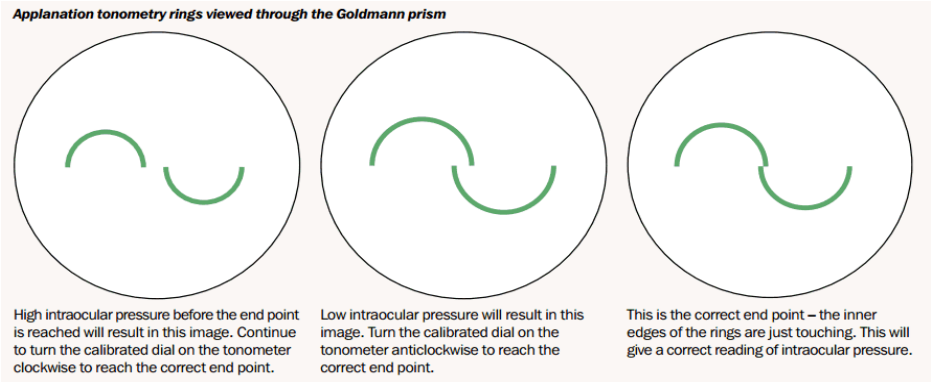


FIGURE 14 (REPRODUCED) GOLDMANN APPLANATION TONOMETRY (STEVENS ET AL., 2007)

1.4.2 Tonopen XL® applanation tonometer

FIGURE 15 TONO-PEN® XL APPLANATION TONOMETER

The Tono-pen® XL applanation tonometer is a portable device used to measure IOP. The tonometer uses the Imbert-Fick law:

$$P = F/A$$

P = IOP, F= the amount of force exerted by the tonometer to flatten a specific area of the eye, and A= the area flattened.

The Tono-pen® XL averages four successful readings and then displays the mean and standard deviation (Molloy, 2012). The percentage markers seen below the screen are where the standard error of the 4 readings is indicated. To further improve the accuracy of the Tono-pen XL® Tonometer readings, it is recommended to take the average of 3 readings with standard error of less than 5%.

1.4.2.1 Tono-pen XL® versus other handheld tonometers

There are other available handheld tonometers. Lasseck *et al* compared the accuracy of the Tono-pen® XL, the Perkins tonometer and Schiötz tonometer (indentation tonometry) against invasive IOP measurements. All measurements were taken whilst under general anaesthetic. Ten minutes after inducing deep anaesthesia, one author used the Tono-pen® XL, the Perkins tonometer and Schiötz tonometer in a random order to measure IOP. Following this, a 26-guage cannula attached to a calibrated pressure monitor was placed into the anterior chamber for 10 seconds until the reading on the monitor was stable. Of the three non-invasive methods, the Tono-pen® XL most closely reflected IOP (Lasseck *et al*., 2008).

1.4.2.2 Goldmann versus Tonopen

The accuracy of the Tono-pen® XL applanation tonometer has also been compared to the Goldmann applanation measurement of IOP. Horowitz *et al* looked at 138 patients who had IOP measured using the Goldmann tonometer and the Tono-pen® XL applanation tonometer by 2 different clinicians. The sequence in which each instrument was used to measure IOP was randomised and the investigators were blinded to any measurements taken before them. This study showed that by averaging a minimum of 2 Tono-pen® XL applanation tonometer readings, its accuracy was comparable to the gold-standard Goldmann tonometer measurements. When the IOP measurements taken were between 0-30mmHg, there was no significant difference in the 2 methods of

measuring IOP. When pressures were greater than 30mmHg, the Tono-pen® XL applanation tonometer tended to underestimate the IOP with a mean difference of 2.2mmHg (Horowitz *et al*., 2004).

1.4.3 Central corneal thickness

A 'normal' central corneal thickness (CCT) has been looked at by a meta-analysis carried out by Doughty *et al*. Of 300 'normal' eyes examined revealed an average CCT of 0.534mm (Doughty and Zaman, 2000). They also looked at the correlation between CCT and IOP. They found the two were significantly correlated with a 10% difference in CCT resulted in a 3.4 ± 0.9mmHg difference in IOP ($P \leq 0.001$, $r = 0.419$) (Doughty and Zaman, 2000). CCT is known to affect accurate measure of IOP measurements. A thicker cornea requires a greater force to applanate whereas a thinner one is more easily flattened (Tonnu *et al*., 2005). So patients with a lower CCT will have 'lower' IOP readings compared to higher IOP readings with higher CCT.

1.5 Perioperative vision loss (POVL)

Perioperative vision loss (POVL) is commonly associated with prone positioning, long duration surgery, more common following spinal surgery and in surgery with hypotension or considerable blood loss (Heitz and Audu, 2008, Molloy, 2011, Molloy and Cong, 2014, Roth, 2009, Song *et al*., 2014, Baig *et al*., 2007, Pinkney *et al*., 2012). Elevated CVP causing reduced drainage from ophthalmic veins and prolonged Trendelenburg positioning leading to decreased venous outflow are thought to increase the risk of POVL (Molloy, 2011, Roth, 2009).

This risk of POVL has been shown to be reduced with reverse Trendelenburg positioning, maintaining pre-operative haematocrit by transfusion of blood products, normothermia, normoglycaemia and maintaining urinary output with a minimum 0.5mL/kg/hr (Roth, 2009).

Peri-operatively, patients' blood pressure is initially maintained with the use of crystalloid over packed red blood cells. Lee *et al* studied the effect of anaemia and hypotension on optic nerve blood flow in porcine model. They found in these conditions optic nerve compensatory mechanisms failed leading to reduced oxygen delivery (Lee *et al*., 2016).

Raised IOP without change in systemic arterial pressure reduces perfusion pressure to the anterior optic nerve. Therefore, the proposed theory is that an increase in IOP is a risk factor for anterior ischaemic optic neuropathy and perioperative visual loss (POVL) (Roth, 2009).

The blood supply to the anterior optic nerve is maintained by endocrine and metabolic factors to a certain degree within a critical range. Co-morbidities that affect arterial system such as hypertension, diabetes mellitus, and atherosclerosis can affect the autoregulation and therefore increase the critical perfusion pressure below which the autoregulation

of the anterior optic nerve fails. Although the anterior optic nerve blood supply is autoregulated to a certain degree, it may not look after the entire anterior optic nerve and it also varies between individuals (Ozcan *et al*., 2004, Harris *et al*., 1998).

Ocular perfusion pressure (OPP) = MAP – IOP

Macri *et al* carried out a study to assess this in cats. The femoral, ophthalmic, and long posterior ciliary arteries, and the anterior chamber of the eye were cannulated after administering an anaesthetic. Pressure changes in each component were plotted against changes in systemic arterial (femoral) pressure. The systemic and ophthalmic artery pressures showed significant positive correlation, but the ophthalmic and long posterior ciliary arteries pressures showed no correlation. The long posterior ciliary artery pressures and IOP did however show a significant positive correlation. Macri concluded there was a dissociation that occurred between the long posterior ciliary arteries and the ophthalmic artery causing systemic arterial pressure changes being poorly transmitted to the eye (Murphy, 1985). Friedman found that, in general, choroidal blood flow was directly related to perfusion pressure, with IOP up to 30mmHg (Kiel, 1994).

Posterior ischaemic optic neuropathy (PION) is rare event that follows ischaemia of the posterior part of the optic nerve. Ischaemia leads to swelling of the nerve, so when it passes through the scleral canal and is

confined by bony structures, there is axonal nerve compression which can lead to optic nerve damage (Dunker *et al*., 2002).

Ischaemic visual loss is classified into 3 groups based on site of injury: ischaemic injury to optic nerve which is further divided into anterior and posterior ischaemic optic neuropathy; cortical blindness resulting from emboli, shock or cardiac arrest; and central retinal arterial occlusion (Frost, 2010, Warner, 2006, Roth, 2009).

Studies have shown that CVP correlates with IOP. Decrease in venous outflow leads to reduced flow from the ocular arterial system. All of these factors cause an increase in IOP (Friberg *et al*., 1987, Ozcan *et al*., 2004). Ozcan *et al* studied the effect of the level of body inclination during the prone position on IOP in awake patients. They found moving the volunteers from supine to prone increased IOP by 32% (Ozcan *et al*., 2004). Studies looking at the same movement in anaesthetised patients found the IOP more than doubled (Cheng *et al*., 2001). This is thought to be due to the general anaesthesia impairing the autoregulatory mechanism of the choroidal circulation which leads to larger increases in IOP (Ozcan *et al*., 2004).

Prone position may also affect circulation of aqueous humor. If excess IV fluids are administered as it further increases CVP and therefore

increases episcleral venous pressure and IOP (Ozcan *et al*., 2004, Murphy, 1985). When patients are operated on in the prone position, MAP may be maintained at a lower level to help reduce blood loss during surgery. As ocular perfusion pressure is defined as the difference between MAP and IOP, a decrease in MAP leads to a decrease in the perfusion pressure of the anterior optic nerve. If there is blood loss during surgery, the resulting decreased MAP and haematocrit also affects perfusion to the anterior optic nerve. In this case, the IOP becomes an even more critical factor in maintenance of blood supply to the anterior optic nerve (Murphy, 1985, Cheng *et al*., 2001, Ozcan *et al*., 2004).

Awad *et al* also looked at the effect of steep Trendelenburg positioning on IOP during robotic prostatectomy (Awad *et al*., 2009). Their analysis revealed Peak airway pressure, duration of surgery, end tidal CO_2 levels and mean arterial pressure were all significant predictors of IOP change during surgery.

1.6 Cerebral Physiology

The brain is a semisolid structure and weighs approximately 1400g, cerebrospinal fluid is approximately 100-150 mL and is produced primarily by the choroid plexus at a rate of approximately 20mL/hour and is resorbed by arachnoid granulations in the venous system, intravascular blood forms 100-150mL and is determined by cerebral blood flow (Arthur C. Guyton, 2006).

1.6.1 Cerebral metabolic rate

Cerebral metabolic rate is defined as the rate at which the brain uses metabolic substrates such as oxygen and glucose. The brain has the highest metabolic requirement and consumes 20% of basal oxygen consumption at rest. Cerebral blood flow adjusts to meet metabolic demand to deliver oxygen and energy substrates as required. The grey matter consumes 5 times more oxygen than white matter (Arthur C. Guyton, 2006).

Glucose is the main energy substrate for the brain and is also a precursor for neurotransmitters such as: γ-aminobutyric acid, glutamate, and acetylcholine. Of the energy produced by oxidative phosphorylation, 60% is used for functioning neurons and the rest is used to maintain homeostasis of the neuronal cells. The brain has limited capacity to carry out anaerobic metabolism (Arthur C. Guyton, 2006, Tameem and Krovvidi, 2013).

Where neuronal activity is higher, there is higher cerebral blood flow to that region to deliver the required oxygen and glucose. The change in blood flow occurs within seconds of increased functional cerebral activity.

1.6.2 Cerebral Perfusion Pressure

Cerebral perfusion pressure (CPP) is dependent upon mean arterial pressure (MAP), intracerebral pressure (ICP) or central venous pressure (CVP). CPP is defined as:

$$CPP = MAP – (ICP \text{ or } CVP)$$

ICP and CVP can be interchanged in patients with normal physiology and provide a reasonable approximation of effective CPP. In this case the CVP that is referred to is CVP of the upper half of the body. However, if significant cerebral perivascular oedema develops, the effective CPP may deviate from this significantly (Tameem and Krovvidi, 2013).

Cerebral vasoconstriction decreases cerebral blood flow, and cerebral vasodilation increases cerebral blood flow:

$$\text{Perfusion Pressure} = \text{Flow X Resistance}$$

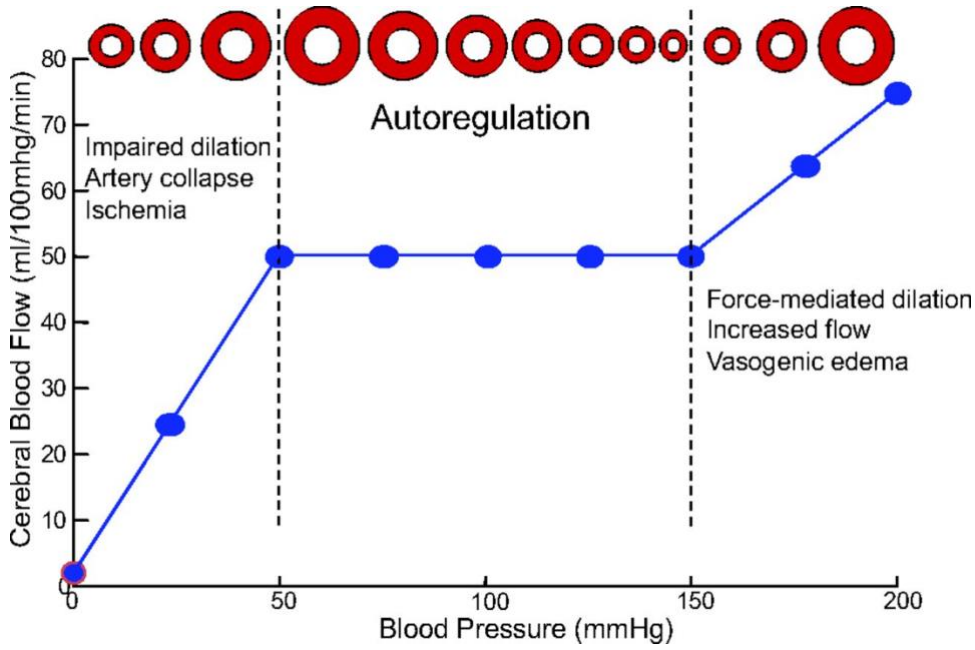


FIGURE 16 (REPRODUCED) CEREBRAL BLOOD FLOW IN RELATION TO ARTERY LUMEN DIAMETER. DOTTED LINES REPRESENT THE LOWER AND UPPER LIMITS OF CEREBRAL BLOOD FLOW AUTOREGULATION. RED CIRCLES REPRESENT THE CEREBRAL ARTERIES, AND BLUE LINE REPRESENTS THE CEREBRAL BLOOD FLOW. (PIRES ET AL., 2013)

Loss of consciousness occurs within seconds of ischaemia secondary to a reduction in cerebral blood flow. If the insufficient blood supply lasts for 3 – 8 minutes, permanent brain damage can occur (Tameem and Krovvidi, 2013).

1.6.2.1 Autoregulation

The brain requires the largest proportion of blood flow and receives 12-15% of the resting cardiac output, despite the brain only forming 2% of body mass. Cerebral blood flow relies on the relationship between flow, cerebral perfusion pressure and the calibre of cerebral vessels. This

means cerebral blood flow will improve with an increase in CPP and vasodilation of the cerebral vasculature (Tameem and Krovvidi, 2013).

Cerebral autoregulation is a physiological process that maintains constant cerebral blood flow despite variation in systemic blood pressure or cerebral perfusion pressure:

$$\text{Cerebral Blood Flow} = \frac{\text{Cerebral Perfusion Pressure}}{\text{Cerebrovascular resistance}}$$

Autoregulation of cerebral blood flow is believed to occur due to a myogenic mechanism. When MAP increases, the transmural vessel tension increase leads to depolarisation of the vascular smooth muscle. This leads to constriction of the precapillary resistance vessels. The opposite happens if MAP and transmural tension decreases. This regulation occurs between a MAP of 50–150 mmHg, (Figure 17). The response is almost instantaneous as it occurs within minutes of the pressure change. Nitric oxide and endothelium derived relaxing factors are responsible for the autoregulation. Outside of this range, cerebral blood flow becomes pressure-dependent and directly changes with changes in MAP (Tameem and Krovvidi, 2013).

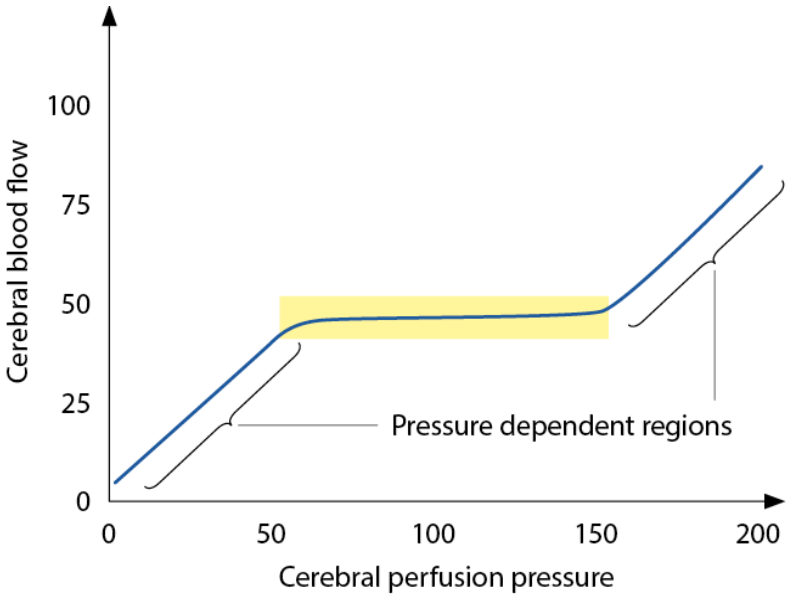


FIGURE 17 (REPRODUCED) CEREBRAL BLOOD FLOW IN RESPONSE TO CEREBRAL PERFUSION PRESSURE (D ROYTOWSKI, 2013)

1.6.2.2 Arterial carbon dioxide tension

The relationship between arterial carbon dioxide pressure and cerebral blood flow remains linear between $PaCO_2$ 2.7 – 10.5kPa with cerebral blood flow changing by approximately 11 – 15ml per 100g of tissue per minute for each 1kPa change in $PaCO_2$. (Figure 18) Once the upper plateau is reached with a $PaCO_2$ of 10.5kPa, the cerebral arterioles are at maximum vasodilation and cerebral blood flow is doubled. Beyond this point there is no further increase in cerebral blood flow. On the lower limit of the curve when $PaCO_2$ is 2.7kPa, cerebral blood flow is halved due to vasoconstriction and can lead to cerebral ischaemia. It essentially forms a sigmoid curve (*Figure 18*) (Tameem and Krovvidi, 2013).

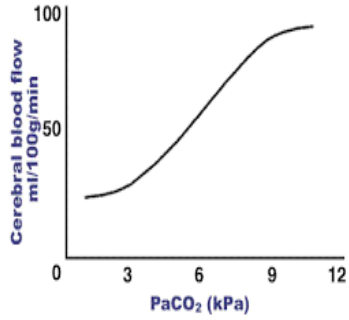


FIGURE 18 (REPRODUCED) CEREBRAL BLOOD FLOW IN RESPONSE TO $PaCO_2$ (2007)

The changes that occur with changes to cerebral arterial CO_2 tension are more pronounced within the grey matter due to the change in interstitial H^+ concentration. The blood brain barrier allows carbon dioxide to readily diffuse across, which reduces extracellular pH which leads to vascular smooth muscle dilatation (Tameem and Krovvidi, 2013).

1.6.2.2.1 $PaCO_2$ and intracranial pressure

The change that occurs to cerebral blood flow and therefore cerebral blood volume to altering levels of arterial CO_2 occurs within 1 minute and plateaus at 12 minutes. A decrease in $PaCO_2$ from 5.3 to 2.7kPa can decrease the cerebral blood volume by 10 – 14 ml almost immediately. This rapid response to change in blood volume is an important way in controlling ICP, which is why hyperventilation can reduce $PaCO_2$ to reduce acute rises in ICP. Prolonged hypocapnia however, can lead to cerebral ischaemia and has been shown to have limited benefit in reducing ICP as cerebral blood flow returns to baseline after 6-8 hours as the brain adapts (Tameem and Krovvidi, 2013).

1.6.2.3 Cerebral arterial oxygen tension

Cerebral blood flow can also be increased by hypoxia which leads to cerebral vasodilatation. As long as PaO_2 is maintained above 6.7kPa, the effect of $PaCO_2$ on cerebral blood flow is limited. Below PaO_2 of 6.7kPa, ion channels in the vascular smooth muscle are activated and vasoactive substances including: nitric oxide, adenosine, prostacyclin, angiotensin, vasopressin and opioids are released. The release of all these leads to vasodilatation which increases cerebral blood flow in response to the hypoxia. Increasing level of oxygen has the reverse effect and leads to vasoconstriction (Tameem and Krovvidi, 2013).

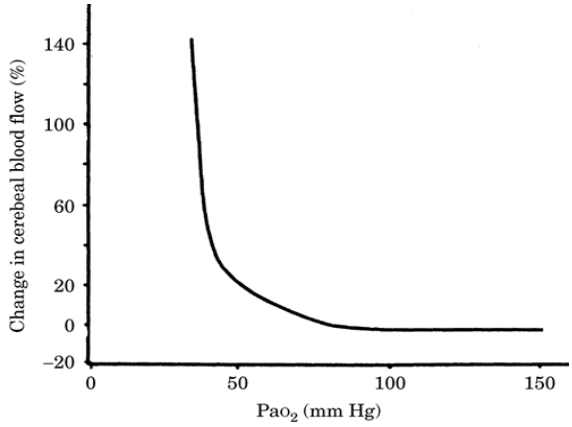


FIGURE 19 (REPRODUCED) EFFECT OF PaO_2 ON CEREBRAL BLOOD FLOW (SHAWASH, 2010)

1.6.2.4 Neurogenic control

Cerebral vessels are supplied by postganglionic sympathetic nerve supply from the superior cervical ganglion and is activated by noradrenaline and neuropeptide Y (Arthur C. Guyton, 2006). Sympathetic activation leads to vasoconstriction and can shift the

autoregulation curve to the right. This response is protective in times of acute increases in blood pressure which can disrupt the blood brain barrier. The parasympathetic supply arises from the sphenopalatine and the otic ganglia and uses acetylcholine and vasoactive intestinal peptide. Activation of parasympathetic supply leads to cerebral vasodilatation which is protective in hypotensive states. There are also fibres that originate from the trigeminal ganglion which have vasodilators such as substance P and calcitonin gene-related peptide. Activation of this in response to hypertension leads to vasodilation (Tameem and Krovvidi, 2013).

The three various nervous supplies to the cerebral vasculature are responsible for the immediate increase in cerebral blood flow that needs to occur in response to increased metabolism.

1.6.2.5 Temperature

When body temperature is reduced, cerebral metabolism is also reduced. A 7% decrease in cerebral metabolic rate occurs with every 1^{o}C decrease in body temperature which decreases cerebral blood flow. At 27^{o}C cerebral blood flow is halved. Mild hypothermia also causes vasoconstriction which decreases cerebral blood flow and ICP (Tameem and Krovvidi, 2013).

1.6.2.6 Intracranial Pressure

The concept of ICP is best described by Monro-Kellie doctrine which states the volume of the brain and its constituents inside the skull is fixed and cannot be compressed.

The contents of the brain can be divided into:

1. Brain volume - approximately 85%
2. Cerebrospinal fluid - approximately 10 % (150 ml) and
3. Blood - approximately 5 % (50-75 ml).

ICP is normally within the range of 5-15 mmHg when supine, but changes depending on posture. If ICP rises too high, it decreases CPP and if it increases significantly it can lead to local compression of brain tissue and ultimately can lead to herniation. Therefore, maintenance of ICP is important and is controlled by maintaining the pressure-volume relationship (Tameem and Krovvidi, 2013). When a patient is in the sitting position, even when not anaesthetised, CPP decreases by 15%. When a patient is sitting and anaesthetised, vasodilation and myocardial depression can further decrease CPP. This is due to the fact, that whilst in the sitting position ICP and CVP are negative at the level of the head. This means the CPP in the sitting position is roughly equivalent to MAP (Tameem and Krovvidi, 2013, Lynn Fitzgerald Macksey, 2012).

Raised ICP can lead to cerebral ischaemia. Blood and cerebrospinal fluid respond first if ICP increases. Though blood only forms 5% of the skull contents, it plays the most significant role in compensating for acute changes in ICP. It does so by increasing venous drainage. Venodilation, reduced venous drainage, and increased CBF all increase ICP. Reduced venous drainage can also occur due to increased CVP (Tameem and Krovvidi, 2013).

The cerebrospinal fluid is mainly produced by the choroid plexus at a rate of 0.3-0.4 ml/min and is resorbed by the arachnoid granulations into the venous circulation. Though the production of cerebrospinal fluid remains constant, it can be displaced from the cranium into the spinal cord. Though there is a level of compensation, this is limited in the acute change of intracranial pressure (Tameem and Krovvidi, 2013).

1.7 Post-operative cognitive decline

Post-operative cognitive decline (POCD) is increasingly recognised after major surgery. The incidence of POCD is likely to rise as the age of surgical patients continues to increase (Tsai *et al*., 2010). POCD is characterised by a measurable decline in cognitive function such as memory concentration information processing (executive function). The patient remains orientated in time and space, but elicits signs of decline from their baseline cognitive function (Hanning, 2005).

In contrast to delirium where a patient displays signs of acute confusion with disturbance of attention and decreased awareness which can fluctuate during the day; a patient with POCD is orientated however exhibits significant decline from their baseline level in one or more neuropsychological domains. Contrary to post-operative delirium (POD), POCD often takes several days to weeks to be identified due to the lack of obvious clinical symptoms (Hudetz *et al*., 2010).

Long-term cognitive dysfunction is defined as POCD lasting more than 3 months. Patients affected by POCD may experience delayed transfer from the intensive care unit, prolonged hospitalisation and a longer recovery before returning to their normal level of functioning (Hudetz *et al*., 2010). Cardiac and major orthopaedic surgery are associated with persistent POCD in 50% of patients. Along with this, other non-modifiable risk factors include age, pre-existing dementia, and genetic risk factors that overlap with neurodegenerative disorders (e.g. Alzheimer's disease) to include the apolipoprotein E gene. A higher education status has been shown to have a protective effect against cognitive decline at 1 week (Nadelson *et al*., 2014, Pratico *et al*., 2005).

ISPOCD1 trial defined POCD as a binary definition. A decline of more than 2 control group standard deviations or a z score of 1.96 or greater was taken to mean POCD (Moller *et al*., 1998).

1.7.1 Delirium

Delirium is a non-specific cerebral syndrome with reduced awareness of the environment and disturbance of consciousness, attention and sleep-wake cycle (Deiner and Silverstein, 2009, Steinmetz and Rasmussen, 2016). It may also be accompanied with disturbance of perception, thinking, memory and psychomotor behaviour.

The delirious state is transient and of fluctuating intensity most cases recover within 4 weeks or less (World Health, 1993). The DSM Diagnostic criteria for Delirium includes (American Psychiatric Association, 2013):

A. Disturbance in attention and awareness of their environment.
B. This change in attention and awareness from baseline develops over a short period of time, usually hours to days and fluctuates during the course of the day.
C. Additional disturbance in cognition to include: memory, disorientation, language, visuospatial ability, or perception.
D. The disturbances mentioned in A&C are not explained by another established disorder or reduced consciousness (e.g. a patient in a coma)
E. Evidence from history, examination and laboratory findings that the disturbance is a direct consequence of another medical condition substance intoxication or withdrawal or exposure to a toxin or due to multiple causes.

POD is a known consequence of major surgery. Most patients present with hypoactive delirium which consists of fatigue, and lack of activity which is commonly mistaken for post-operative drowsiness by staff (American Psychiatric Association, 2013, Steinmetz and Rasmussen, 2016). The remaining patients present with hyperactive delirium which is easily recognised by staff due to the lack of co-operation and the high risk of falls (Steinmetz and Rasmussen, 2016). It is more common in the elderly and usually occurs within 72 hours after surgery (Hudetz *et al*., 2010, Biedler *et al*., 2000). Predictors of POD include: age over 50 years, alcohol abuse, poor cognitive and functional status, pre-existing dementia, electrolyte and glucose abnormalities, and the type of surgery. The incidence of POD following major general surgery is approximately 10% (Pratico *et al*., 2005). Patients who suffer with POD are at higher risk of future cognitive decline or dementia (Nadelson *et al*., 2014).

1.7.2 Pathophysiology of POCD

1.7.2.1 Pain

Wang *et al* looked at the effect of post-operative pain on POCD. They found patients who took post-operative analgesia orally were less likely to experience POCD. Studies have shown 36% of patients with delirium had a resting pain score of 5 or greater. In patients with POCD, only 14% of patients had a resting pain score of 5 or more. Wang *et al* found that patients who received intravenous opioids (patient controlled analgesia (PCA)) were more likely to develop POCD than those who only received oral analgesia. This may be due to the first pass effect resulting in lower blood levels of the drug compared to intravenously administered opioids

which cross the blood brain barrier. As this difference could have been attributed to the higher level of post-operative pain experienced by patients using a PCA, they adjusted for the level of pain. However, even after adjusting for the pain level, the difference remained significant (Wang *et al*., 2002).

Chronic pain has also been shown to decrease grey matter in areas that are involved in anticipation of pain including the anterior cingulate cortex, insula and dorsolateral prefrontal cortex. It is therefore thought that acute pain in the immediate post-operative period also contributes to delirium and early POCD. In patients with chronic pain, once the pain is under control, cognitive function does return to normal (Nadelson *et al*., 2014, Pratico *et al*., 2005).

1.7.2.2 Systemic inflammatory response

The trauma of surgery initiates a systemic inflammatory response. The release of pro-inflammatory cytokines disrupts the hippocampal long-term potentiation that allows learning and memory formation. Inflammation in this area initiates lethargy, anorexia, fever and cognitive dysfunction. These are protective responses to encourage rest and allow healing. This initial inflammatory immune response is curbed and healing then begins. This initial immune response is thought to contribute to POD and early POCD.

1.7.2.3 General anaesthesia

General anaesthesia affects brain function on many levels including neuronal membranes, receptors, ion channels, neurotransmitters, cerebral blood flow and metabolism. This effect is increased in the elderly as brain morphology changes with reduction in brain weight, loss of dendrite tree and synapses, physiology changes with a decrease in cerebral blood flow, and neuronal function changes include altered neurotransmitter systems and reduced oxidative metabolism. Therefore, the effect of anaesthetic agents is altered (Tameem and Krovvidi, 2013).

The dopaminergic tract is involved in initiation procedures; serotoninergic tract is involved in repletion of behaviours; noradrenergic tracts are involved in maintenance of consciousness and behaviour; cholinergic tracts is involved in learning and memory (Tameem and Krovvidi, 2013).

The neurotransmitter hypothesis suggests reduced cholinergic function may be a cause of POCD. The cholinergic function includes mood, memory, motor function and behavioural changes. Another theory suggests cytokines interact with the neurotransmitter system initiating a stressful inflammatory response precipitating POD (Pratico *et al*., 2005, Steinmetz and Rasmussen, 2016).

Propofol is a short acting intravenous anaesthetic agent which can quickly cross the blood brain barrier resulting in fast onset and quick patient recovery. Propofol blocks the sympathetic nervous system and inhibits the vasomotor centre which inhibits the effects of norephinephrine and stress response mediators. It can however, cause anterograde and retrograde amnesia and this effect is usually dose dependent. Propofol also effects blood glucose levels and modulates the supply and demand of cerebral oxygen balance. These effects are what make propofol exert cerebral protection as it decreases the generation of oxygen free radicles and facilitates patients' recovery from cerebral injury (Zhi *et al*., 2016).

Qiao *et al* looked at the effect of inhalational anaesthesia versus propofol infusion. They included patients aged 65-75 undergoing oesophageal resection for carcinoma. They were then randomised to 1 of 3 groups: preoperative methylprednisolone and sevoflurane anaesthesia; sevoflurane anaesthesia; and propofol infusion. Methylprednisolone suppressed postoperative increases in the plasma IL-6 and TNF-α which are found in significantly higher concentrations in the first week following sevoflurane anaesthesia versus propofol infusion. Qiao *et al* found a higher incidence of POCD in patients following sevoflurane anaesthesia after major surgery compared to those who received propofol infusion and was even lower in patients who received the preoperative methylprednisolone (Qiao *et al*., 2015).

Inhalational anaesthetic drugs have been shown to promote neuronal apoptosis in animal models resulting in a decline in learning ability and memory. Propofol is reported to inhibit the activation and release of inflammatory factors such as IL-6 and TNF-α by astrocytes in the central nervous system. Despite its potential protective effects, propofol has an excessive sedative effect which can adversely affect patients' recovery and therefore is not used alone.

Remifentanil is a μ-opioid-receptor agonist with a rapid onset of action and strong analgesic effect. It is often used in conjunction with propofol. Remifentanil has a very short effect time and is easily cleared with its metabolism being unaffected by liver or renal function and therefore it does not have a cumulative effect. Zhi *et al* concluded that a combination of remifentanil and propofol induce cognitive decline after anaesthesia. This is associated with Tau phosphorylation and modulation of biochemical parameters within the brain (Zhi *et al*., 2016). Tau is an axonal microtubule associated protein which binds to microtubules, stabilising them and promoting their polymerisation. Phosphorylation through kinases decrease the affinity of tau to microtubules, whereas phosphatase activity dephosphorylates and therefore increases affinity which results in tubulin binding and microtubule stabilisation. In Alzheimer disease, tau becomes abnormally hyperphosphorylated and self assembles into a number of higher order structures. How the hyperphosphorylated tau, paired helical filaments, or neurofibrillary tangles contribute to cellular and synaptic dysfunction is unclear.

However, the correlation between cognitive deficits is better than other lesions such as amyloid plaques (Eckenhoff and Planel, 2012).

There have been various animal studies which have shown an increase in tau concentrations within the brains. A study on mice given sevoflurane anaesthesia without surgery once a month for 5 months showed an immediate rise in tau concentrations in the brain within 24 hours of exposure of the first anaesthetic. With repeated exposures to sevoflurane, the increase in tau became less transient, and after the 5th (and final) exposure, tau levels within the hippocampus remained high 1 month after surgery (Le Freche *et al*., 2012). This was of interest as anaesthetics may directly bind to and alter tubulin which promotes both tau release and microtubule dysfunction. This was also found in patient studies, where following propofol/remifentanil or sevoflurane anaesthesia, tau concentrations within cerebrospinal fluid remained high 48 hours postoperatively (Tang *et al*). However, the link between phosphorylated tau and memory remains weak in human studies and further studies are needed (Eckenhoff and Planel, 2012).

Brain function monitoring during general anaesthesia such as bispectral index (BIS) facilitates the titration of general anaesthetic agents to reduce the anaesthetic exposure. Chan *et al* looked at how BIS monitoring affected the dose of anaesthesia and POD and POCD. They found use of BIS-guided anaesthesia reduced the propofol delivery by

21% and volatile anaesthetic by 30%. This reduced the risk of POD by 35% and POCD at 3 months following surgery by 31% (Chan *et al*., 2013).

1.7.2.4 Surgery

Surgery results in complex systemic responses including neuroinflammation. Animal studies have suggested inflammation is a possible mechanism along with the possibility of cytokines such as interleukin-1β, however translational studies have yet to be carried out. In theory, cytokines lead the inflammatory response to infection or aseptic traumatic injury and are essential in restoring homeostasis and are shown to affect behaviour especially memory and cognition. The hippocampus is largely responsible for learning and memory processes, which also expresses the highest density of IL-1 receptors making it vulnerable to neuroinflammation. Although IL-1β is essential for normal learning and memory processes, exogenous administration or excessive endogenous levels have detrimental effects on cognition. IL-1β can translocate through the intact blood brain barrier and within the brain, the cytokines interact with microglia cells. Upon activation, microglia cells secrete cytokines and neurotoxins such as amyloid β. Activated microglia also inhibit neurogenesis in the hippocampus following endotoxaemia, further exacerbating the extent of injury on memory processes. Terrando *et al* showed hippocampal-dependent memory impairment after 3 days (Terrando *et al*., 2010, Steinmetz and Rasmussen, 2016). Rosczyk *et al* showed aged mice had increased

levels of proinflammatory cytokine IL-1β in the hippocampus following minor surgery. The degree of postoperative inflammation was proportional to the size of surgical incision (Rosczyk *et al*., 2008). IL-6 is an important regulator of synapse formation, with high local concentrations of IL-6 resulting in inhibition of synaptic function. Rat studies have shown hippocampal neurogenesis in the dentate gyrus was decreased by 63% in adult rats that overexpressed IL-6 from their astrocytes (Qiao *et al*., 2015).

1.7.2.5 Cerebral Blood flow

The rate of cerebral blood flow changes in proportion to $PaCO_2$ levels when in the range of 2.7-8 kPa. If regional oxygen saturations were less than 80% of baseline or less than 50%, there has been shown to be a higher risk of post-operative cognitive decline. A reduction in regional O_2 saturation has been shown in patients undergoing abdominal surgery and in patients with raised ICP (Moller *et al*., 1998), (Park *et al*., 2009a).

1.7.2.6 Trendelenburg positioning

Trendelenburg positioning increases ICP and cerebral oedema resulting in increased cerebrovascular resistance and reduced cerebral blood flow resulting in impaired tissue oxygenation and therefore may cause mild cognitive dysfunction (Choi *et al*., 2008). *(See section* 1.9.3 Cerebral Function*)*

1.7.3 Effects of POCD

Long term effects of POCD include: increased mortality, impairment of daily functioning, premature departure from labour market and

dependency on government economic assistance post discharge from hospital (Tsai *et al*., 2010).

It can affect patients at any age, but was shown to have a longer and more significant effect on daily life activities and return to work in patients over 60 years (Tsai *et al*., 2010).

1.8 Cognitive Testing

1.8.1 Mini Mental State Examination (MMSE)

The Mini Mental state is a helpful tool for quick assessment of a patient's global cognitive function. It is a 5-10 minutes examination that assesses orientation, attention, memory recall and registration, and language (Hodges, 2007).

The examination produces a mark out of 30, and it is widely accepted that a score of less than 23 though not diagnostic of dementia, it does provide supporting evidence. MMSE score of 26-29 implies a degree of cognitive deficit (Hodges, 2007).

Scores of 28 or less are associated with a two-fold increase in the risk of POD compared to those who scored 29 or 30 (Fines and Severn, 2006). It is useful as a serial measure for cognitive decline and is used in Alzheimer's disease to monitor disease progression. Although it is a useful tool for highlighting significant declines in cognitive function, it is

not as effective at picking up minor changes in cognition (Di Nino *et al*., 2010).

Various other tests are now used to assess various aspects of cognition and are more accurate at picking up minor changes. These tasks are computer based and monitor accuracy of the test as well as reaction time of the subject.

1.8.2 N back

The N-back task is used as a measure of working memory and executive function. It was introduced as a visuo-spatial task by Kirchner in 1958 (Kirchner, 1958). A continuous stream of stimuli (one image at a time) is presented to the volunteer and they must decide if the image shown on the screen is the same as that shown 'N' images back. *Figure 20* is an example of a one-back task.

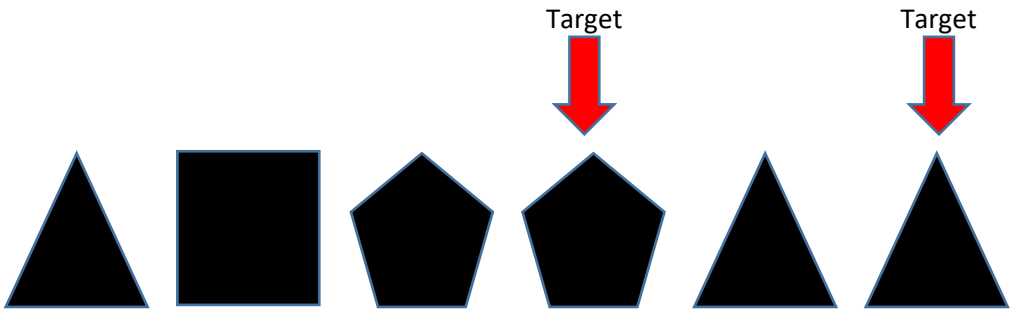


FIGURE 20 EXAMPLE OF ONE BACK TASK WITH TARGETS IDENTIFIED

The N-back task is currently the most popular means of assessing working memory (Conway *et al*., 2005). It is favoured as the ability to change the value of "N" gives researchers a reliable way of altering the processing load of the task. The changes in processing load are

reflected by changes in the accuracy and average speed of responses (Jonides *et al*., 1997).

Many cognitive processes are required for the N-back test. The task requires monitoring, updating, manipulation of information within short-term working memory (Owen *et al*., 2005). Due to the consecutive nature of the task, participants must simultaneously retain multiple items (the number depends on the value of N), whilst also updating the contents of their working memory. With each new stimulus, old or irrelevant information must be discarded, and new information stored (Jaeggi *et al*., 2010, Jonides *et al*., 1997). The zero back task only requires recognition and does not involve manipulation within working memory (Owen *et al*., 2005).

1.8.3 Stroop

The Stroop test provides a paradigm case of attention and inhibition. Participants must differentiate between the meaning of a colour word and the colour that it appears in. For example, when given the word GREEN printed in RED ink, subjects must answer RED. The Stroop effect is recognised as the inclination to say the word presented, rather than the colour that it appears in. A delay in response is usually seen when the colour of the word does not match the meaning of the word (an "incongruent stimulus"). The delay is due to the conflict of the volunteers' inclination to read the word, and the requirement of the task to identify the colour (Bench *et al*., 1993, Pardo *et al*., 1991, Miller and Cohen,

2001). The key mental function that the Stroop test measures is inhibition of competing responses. Selective attention is a crucial component of this as successful performance requires focusing attention of the task-relevant process and inhibiting the task-irrelevant one. In other words, the executive process of attention and inhibition is recruited whenever an incongruent stimulus is presented (Smith and Jonides, 1999, Miller and Cohen, 2001).

1.8.4 Lexical Decision Making Task

In the Lexical Decision task, subjects are presented with various letter combinations. The subject must decide whether the string of letters is a word (e.g. D-O-G), or a non-word (e.g. K-U-G). The task is time limited as each letter string is only displayed for 1.5 seconds. This is to allow automatic rather than studied response making the process of word identification used similar to the process that occurs in reading (Katz *et al*., 2012). Lexical decision task primarily tests the language aspect of cognitive function. Executive functions (decision-making) are also tested in this task, as a quick decision must be made as to whether the letters form a word or not.

1.8.5 Assessment of POCD

The agreed definition of POCD includes a decline in neuropsychological tests from baseline in learning and memory, attention, executive function and language. Most studies of POCD have studied changes in performance from baseline of executive function, attention, learning, language, visuospatial skills or motor function (Tsai *et al*., 2010). The

choice of tests used to look for these changes has varied greatly between studies.

The most important issues that need to be addressed when choosing which test to use include:

1. A choice of difficulty level that does not have a floor or ceiling effect to improve the sensitivity of the tests in picking up a change from baseline.
2. Choosing tests whose content can be varied between each test period to avoid recall from previous tests which can increase bias.

When the tests are administered, they should be done so in a standardised manor with consensus recommendations including ‘the same suitably qualified and trained individual should conduct the tests’ and the tests should be performed in the same standardised manor.

Despite a variety of scoring methods used to date, all authors agree on the following:

1. Baseline performance prior to surgery (preferably not on the day of surgery as this may result in increased anxiety levels.
2. Take into account practice - ‘learning effect’. This is done by carrying out the tests in a control group and assessing the learning effect in this group.

3. A change in one or more tests.

The timing of tests is also important. Early POCD assessment is likely to be accompanied with issues such as pain, use of drugs, nausea, limited mobility and fatigue. Previous studies had suggested a minimum of 1 week prior to the first POCD test, however, recent evidence suggests this delay is unnecessary as POCD detected in patients within 1 week after surgery was usually associated with negative outcomes (Tsai *et al*., 2010). Monk *et al* were the first to report an association with POCD and increased mortality. They found patients found to have POCD at hospital discharge were less likely to be alive for the 3-month testing time (Monk *et al*., 2008).

1.9 Trendelenburg Positioning Physiology

Trendelenburg position is when the patient is supine and the head of the bed is lower than the foot end. It Is named after a German surgeon Friedrich Trendelenburg as he used this position to improve surgical access to pelvic organs. He first used this position when carrying out a vesicovaginal repair.

Trendelenburg positioning is commonly used during laparoscopic colorectal surgery to allow the use of gravity to move the small bowel out of the pelvis and provide the surgeon with adequate views. The degree of tilt and time spent in these positions varies depending on the type of resection and complexity of the case.

The gravitational effect of Trendelenburg positioning is thought to divert blood away from lower extremities and increase central blood volume. This is thought to increase cardiac preload and therefore cardiac output (Zorko *et al*., 2011).

1.9.1 Pulmonary Function

Trendelenburg positioning has significant effect on pulmonary function. It reduces functional residual volume by 20% and decreases vital capacity and pulmonary compliance. Pulmonary engorgement occurs and is worsened the steeper the head-down position. In extreme Trendelenburg position, most of the lung may fall below the left atrium leaving it susceptible to pulmonary interstitial oedema. The shift of abdominal contents towards the diaphragm reduces diaphragmatic movement which also reduces pulmonary function (Lynn Fitzgerald Macksey, 2012).

Park *et al* looked at the effect of Trendelenburg position and pneumoperitoneum in patients undergoing robot-assisted laparoscopic prostatectomy. They found PaO_2 and $PaCO_2$ increased significantly after the induction of the pneumoperitoneum, and 30, 60, 120 minutes after Trendelenburg position compared to baseline levels (Park *et al*., 2009a).

1.9.2 Haemodynamic changes

Trendelenburg position activates baroreceptors with compensatory vasodilation. The baroreceptor reflex which results from an increase in hydrostatic pressure leads to a decrease in vasoconstriction which leads

to a decrease in blood pressure. The blood pressure decrease is counteracted by an increase in heart rate. Overall, Trendelenburg position leads to an increase in MAP, left arterial pressure and pulmonary artery wedge pressure but also a decrease in stroke volume. Possible complications include congestive heart failure, pulmonary oedema and facial engorgement.

Terai *et al* studied the effect of a 10 degrees Trendelenburg position on flow through the internal jugular vein (IJV) in 10 healthy volunteers. Echocardiography was used to measure left ventricular end diastolic volume (LVEDV) and cardiac output (CO), and pulsed doppler to examine the IJV after 1 minute and 10 minutes of being in the Trendelenburg position. They found a significant increase in CO and LVEDV which returned to normal after 10 minutes. They found a decrease in IJV velocity and an increase in the cross-sectional area after one minute, but both returned to normal after ten minutes. The authors therefore concluded that Trendelenburg effect in normotensive patients is transient and produces no adverse effect to cerebral circulation (Ostrow *et al*., 1994, Terai *et al*., 1995).

A study carried out by Zorko *et al* compared the effects of 20 degrees Trendelenburg position on patients whilst under general anaesthetic (GA), and on healthy volunteers whilst they were awake. The patients in the GA group were anaesthetised to undergo a coronary artery bypass

graft. All measurements in Trendelenburg were compared to supine values. In the GA group, Trendelenburg position caused a non-significant decrease in heart rate (HR) and a significant increase in MAP and CO. In the non-GA group, Trendelenburg lead to a significant increase in HR, but a non-significant increase in MAP and decrease in CO. When they were returned to supine, in the GA group there was a significant decrease in CO and a non-significant decrease in MAP and HR increase. In the non-GA group, there was a non-significant decrease in MAP and HR, along with an increase in CO. The authors believe the non-GA group had a limited response due to baroreceptor reflex, which is blunted in the anaesthetised group (Zorko *et al*., 2009).

Park *et al* looked at the effect of Trendelenburg and pneumoperitoneum in patients undergoing a robot assisted laparoscopic prostatectomy. Of the thirty-two patients included in their study, they found MAP and CVP increased significantly after induction of pneumoperitoneum, and 30, 60 and 120 minutes in the Trendelenburg position compared to the baseline (Park *et al*., 2009a).

A study looking at the haemodynamic effect of Trendelenburg on critically ill patients found in normotensive patients, Trendelenburg positioning increased preload, slightly increased cardiac output (CO), decreased systemic vascular resistance (SVR) and did not change MAP.

In hypotensive patients there was a decrease in CO, with no change to preload, but a slight increase in afterload (Richard L. Summers, 2009).

Ostrow *et al* also looked at the effect of Trendelenburg on normotensive cardiac patients looking at cardiac index, CO, MAP, SVR and oxygenation. They placed patients in 10 degrees Trendelenburg and then 30 degree modified Trendelenburg for 10 minutes each in a cross over design study. The measurements in these positions was compared to the same measurements taken whilst supine. Of the 18 patients who completed the study, they found no statistically significant changes to CO, MAP, SVR or tissue oxygenation (Ostrow *et al*., 1994).

1.9.3 Cerebral Function

Trendelenburg position increases cerebral blood flow and intracranial pressure. In patients with normal physiology, CVP can be interchanged with ICP. However, after being in steep Trendelenburg for a prolonged period of time, significant cerebral perivascular oedema can develop.

Trendelenburg position increases arterial pressure and CVP which can impair venous outflow from the brain increasing hydrostatic pressure within the cerebral vasculature. As microvascular fluid exchange is governed by hydrostatic pressure and osmotic pressures, a change in hydrostatic pressures changes the balance of Starling forces, which causes an increase in extracellular water content in dependent tissues. Within the brain this could eventually lead to an increase in ICP and

cerebral oedema which would eventually result in increased cerebrovascular resistance and reduced cerebral blood flow. All of these can cause impaired perfusion and diffusion (Gisolf *et al*., 2004). If, however, the increase in arterial pressure is higher than the CVP rise, there will be an increase in CPP. If all other factors remain stable such as CO_2 levels, cerebral blood flow will be maintained by vasoconstriction (Kalmar *et al*., 2012).

Cerebral oedema can affect vascular tone at the pre-capillary arteriolar level and cerebral veins that are affected by ICP and CVP. CPP is determined by the pre-capillary arteriolar level vascular tone, and the cerebral venous pressure which is affected by ICP and CVP. The pre-capillary arteriolar pressure determines the downstream arteriolar pressure as long as ICP does not exceed the critical collapsing pressure of the arteriolar pressure (Kalmar *et al*., 2012). Many studies have shown Trendelenburg position leads to an increase in ICP. This increase in ICP is thought to be due to an increase in venous pressure which reduces cerebral venous drainage leading to an increase in cerebral blood volume and cerebrospinal fluid.

Kalmer *et al* looked at the effect of Trendelenburg positioning on cerebral perfusion in 14 patients undergoing robotic prostatectomy. They found that prolonged steep Trendelenburg position has a significant effect on cerebral perfusion pressure. The theory being, whilst in steep

Trendelenburg, CVP should increase over time. Kalmer showed that although an increase did occur, it was not significant, even after 3 hours in steep Trendelenburg. They concluded that although cerebral perivascular oedema may occur, it doesn't significantly affect cerebral perfusion. Cerebral vascular resistance was assessed by estimating CPP (eCPP). The eCPP is slightly lower than the CPP, but the gradient between the CPP and the eCPP did not change over the course of the operation. There are multiple factors that affect CPP including positive end expiratory pressure (PEEP), muscle tone, CO_2 reactivity and positioning, the maintenance of eCPP suggests that cerebral autoregulation is preserved during prolonged steep Trendelenburg (Kalmar *et al*., 2012).

1.10 Pneumoperitoneum Physiology

To perform laparoscopic surgery, a pneumoperitoneum is required. Insufflation is carried out using carbon dioxide and intra-abdominal pressure is maintained at 11-15mmHg.

1.10.1 Cardiovascular Effects

Increase in intra-abdominal pressure affects the cardiovascular system in a variety of ways. The rise in intra-abdominal pressure causes an increase in CVP which leads to reduced vascular resistance and reduced preload. All of which leads to decreased stroke volume. The increase in intra-abdominal pressure also leads to an increase in pulmonary capillary wedge pressure which leads to reduced left ventricular diastolic volume and a decrease in preload. The higher the intra-abdominal pressure the greater the effect.

Increase in intra-abdominal pressure also leads to an increase in SVR and MAP. These lead to an increase in afterload and a decrease in stroke volume. Pneumoperitoneum also leads to a peritoneal stretch which stimulates a vasovagal response resulting in a decrease in HR. Cardiac output is determined by stroke volume multiplied by HR. The resulting reduced HR, and increase in CVP, pulmonary capillary wedge pressure, SVR and MAP all lead to a decrease in stroke volume. All of these lead to a decrease in cardiac output. The obstruction of venous return causes an increase in CVP which is thought to reduce cerebral venous outflow which in turn increases cerebral blood volume and cerebral spinal fluid volume. An increase in these can cause an increase in ICP (Park *et al*., 2009a).

Halverson *et al* carried out a study to evaluate the mechanism of increased ICP with insufflation. They found if rapid insufflation was carried out, there is a transient increase in CVP. This is thought to be due to blood being forced out of the splanchnic circulation and inferior vena cava. If insufflation was reduced to 1.5 l/min, there was less of a mechanical effect (Halverson *et al*., 1998).

Kastan *et al* looked at the different effect of hypo/normo/hypervolaemia on venous return to the heart after increased intra-abdominal pressure. Hypovolaemic and normovolaemic conditions, lead to increased venous resistance therefore decreasing venous return to the heart. With

hypervolaemia, the increase in mean systemic pressure overrides the increase in resistance, resulting in increased blood return to the heart (Halverson *et al*., 1998).

If CO_2 is used to inflate the abdomen, an increase in CO_2 (to $PaCO_2$ of 55-70 mmHg) from absorption causes an increase in vasopressin and catecholamines. Elevated CO_2 levels also leads to myocardial depression. These effects are countered by sympathetic stimulation that increase HR and systematic vasoconstriction. The catecholamine release can counter the effects of moderate hypercarbia including an increase in HR, MAP, CVP, pulmonary artery pressure, CO and stroke volume.

1.10.2 Cerebral Effects

Intra-abdominal insufflation obstructs drainage from the lumbar venous plexus resulting in an increase in the vascular compartment of the sacral space therefore leading to increased ICP.

If CO_2 is used for insufflation, the resulting catecholamine release and CO_2 absorption leads to increased cerebral blood flow (Park *et al*., 2009b). *(See section 1.6.2.2.1 PaCO2 and intracranial pressure)*

Pneumoperitoneum also directly affects mechanical ventilation as diaphragmatic movement is impaired resulting in decreased functional

residual capacity and increased alveolar dead space and peak airway pressures. The resulting hypercarbia, results in vasodilation and increased CBF. Though this should mean an increase in CPP, the increased arterial pressure and increase in central venous pressure also affect CBF. The result of the combination of these is variable. The increased CBF and absorption of CO_2 leads to vasodilation and increased cerebral arterial blood flow (Park *et al*., 2009a).

Park *et al* looked at 32 patients undergoing robot-assisted laparoscopic prostatectomy. They found a significant increase in regional O_2 saturation after induction of the pneumoperitoneum whilst in the Trendelenburg position (Park *et al*., 2009a).

1.10.3 Intracranial Pressure

Intracranial pressure has been shown to increase with induction of pneumoperitoneum. This increase has been shown to be due to the pressure increase and not due to the CO_2 absorption. Rosenthal *et al* demonstrated a rise in ICP even with abdominal pressures as low as 8mmHg. The effect of the raised ICP is worsened when in the Trendelenburg position (Rosenthal *et al*., 1997).

The cause for the ICP rise is thought to be based on the Monroe-Kellie doctrine. The initial management of ICP rise includes increased venous drainage, reduced CBF. The next step in managing raised ICP is displacement of cerebrospinal fluid into the spinal cord.

1.10.4 Acid-Base balance

Carbon dioxide is the most commonly used gas for induction of pneumoperitoneum. Elimination of CO_2 is efficient as it is a natural product of cellular metabolism, a small amount is eliminated from the lungs, the rest combines with water:

$$CO_2 + H_2) \Leftrightarrow H_2CO_3 \Leftrightarrow H^+ + HCO_3$$

The hydrogen ions combine with haemoglobin and bicarbonate diffuses into the plasma. The majority of CO_2 absorbed by the peritoneum is eliminated in this way. Elimination of CO_2 can be facilitated by increasing minute ventilation therefore increasing CO_2 elimination by the lungs to maintain eucapnia. If there is an increase in CO_2 levels, the body can adapt by use of intracellular and plasma buffering systems and increasing the rate of CO_2 transport. In patients with decreased pulmonary function, reduced CO, or a high metabolic and cellular respiratory rate, the ability to eliminate the extra CO_2 is reduced (Park *et al*., 2009a).

1.10.5 Renal

Increase in intra-abdominal pressure affects renal blood flow and glomerular filtration rate. This is an effect of the reduced cardiac output but mostly due to raised intra-abdominal pressure. Studies have shown external pressure on the abdomen of 20mmHg, reduced renal blood flow and glomerular filtration rate by 25%. When CO was returned to baseline using a volume expander, the renal effects remained. This has been looked at in various other studies which also confirmed these findings.

(Grabowski and Talamini, 2009) Kirsch *et al* examined the effect of abdominal insufflation on renal function in rats. They found that though urine output was reduced and creatinine increased, 2 hours after the pressure was released serum creatinine returned to normal and after 22 hours, urine output also returned to normal (Kirsch *et al*., 1994).

The renal effects are thought to be due to multiple reasons including the effect of vascular and parenchymal compression, and the release of vasopressin. The decrease in right atrial preload due to the intra-abdominal pressure effects induce the release of vasopressin. Vasopressin promotes reabsorption of water by acting on vasopressin receptors on the distal tubule and collecting ducts in the kidney. The increased intra-abdominal pressure also reduces renal blood flow, which is not thought to have any long-term effects in healthy individuals (Grabowski and Talamini, 2009).

1.11 Summary

Trendelenburg positioning results in an increase in upper body CVP. As discussed above, IOP is governed by many various factors. By increasing upper body CVP, there is also an increase in episcleral venous pressure which increases IOP.

CPP is defined as MAP minus ICP or CVP, therefore an increase in CVP reduces CPP. Trendelenburg positioning can also reduce the venous outflow from the brain and result in cerebral oedema which may affect cognitive function.

Chapter 2 : Evaluation of intraocular pressure (IOP) variation during colorectal laparoscopic surgery

Abstract

Background

The incidence of perioperative visual loss following colorectal surgery is quoted as 1.24 per 10,000 in USA. This is thought to be due to raised IOP during extreme Trendelenburg positioning leading to reduced optic nerve head perfusion.

Aim

To assess the effect of the degree of Trendelenburg tilt and time spent in this position on IOP during laparoscopic colorectal surgery.

Method

Area under the curve (AUC) was calculated for each patient where a cumulative value for the degree of head-down position and the time spent (minutes) in this position are considered. Patients with AUC $\leq$ 500 degrees x mins were compared to those with AUC > 500 degrees x mins as Group 1 and Group 2 respectively. Baseline IOP measurements using a Tonopen® XL applanation tonometer were carried out, and then every hour during surgery and each time when the operating table was tilted.

Results

Group 1 (n=24) had a mean (± SD) age of 66.92 (± 16.36) years and Group 2 (n=26) 64.39 (± 14.62) years, ($p > 0.05$). The mean (± SD) length of surgery for Group 1 was 156.92 (± 69.92) minutes and Group 2 was 248.73 (± 104.86) minutes with ($p \leq 0.05$). The median IOP rise from

baseline during surgery was 8.84 mmHg (IQR = 8.84) in Group 1 and 14.17 mmHg (IQR = 14.17) in Group 2 ($p \leq 0.05$). The median maximum degree of head down tilt during surgery in Group 1 was 9.75^{o} (IQR: 4.5 - 13.76) and Group 2 was 18.25^{o} (IQR: 15.33 - 22.85), ($p \leq 0.05$).

Conclusion

A rise in IOP occurs during laparoscopic colorectal surgery and appears to be more pronounced in those with a greater degree of Trendelenburg tilt for a prolonged time. This may have important implications for those patients undergoing prolonged surgery and especially those with a history of glaucoma.

2.1 Introduction

Post-operative vision loss (POVL) is a serious complication which significantly affects quality of life. The incidence of POVL has gradually been increasing, the cause of which is thought to be multifactorial (Frost, 2010, Warner, 2006). There is an increase in more complex surgeries being performed, and operating on patients with multiple co-morbidities who are at higher risk of post-operative complications. In cases where the cause is not identified (e.g. foreign body in eye), the most common explanation is optic nerve ischaemia (Frost, 2010, Molloy, 2011). Ischaemia may be the result of anaemia, hypotension, blood loss or raised IOP leading to optic nerve ischaemia (Dunker *et al*., 2002, Frost, 2010).

Glaucoma affects 2% of the population over the age of 40 years and this increases with age. (NICE, 2009) In addition about another 3-5% of the population over this age suffer from ocular hypertension which is a risk factor for the development of glaucoma (King *et al*., 2013). Therefore, potentially 1 in 50 patients undergoing a laparoscopic colorectal resection could have glaucoma.

2.2 Aim

To assess the effect of the degree of Trendelenburg tilt and time spent in this position on IOP during laparoscopic colorectal surgery.

2.3 Methods

This was a prospective clinically based observational study. The study was reviewed and approved by the Northampton Research Ethics Committee (protocol number: 11GA019) and undertaken in accordance with the tenets of the Council of Helsinki.

2.3.1 Patient Population

All patients undergoing planned laparoscopic colorectal resection under the colorectal surgery service at Nottingham University Hospital were invited to participate in the study. Those expressing an interest to participate were given a patient information leaflet and patients who were willing to participate signed a consent form prior to any study interventions.

2.3.1.1 Inclusion Criteria

- Patients undergoing laparoscopic colorectal surgery
- Aged 18 years and over

2.3.1.2 Exclusion Criteria

- Patients with a history of significant ocular disease or ocular surgery other than glaucoma
- Allergy to Tetracycline or Latex

2.3.2 Baseline Tests

For each patient included in the study, demographic data including gender, age, smoking history, co-morbidities and medication history was collected. Baseline eye examination was carried out on all patients that

agreed to take part including: best corrected visual acuity, Gonioscopy, central corneal thickness, Goldmann Applanation Tonometry and Tono-pen® XL applanation tonometer, Tono-pen® XL applanation tonometer measurements were repeated after lying the patient supine for 5 minutes. All Tono-pen® XL applanation tonometer readings during this study were taken after administering 1% tetracaine eye drops and repeated to obtain an average of 3 readings at 5% accuracy.

2.3.3 Day of Surgery

On the day of surgery, baseline IOP was taken in the right eye using the Tono-pen® XL applanation tonometer. IOP measurements were repeated in the right eye at the following points during surgery: after induction of general anaesthetic, at the start of surgery, after pneumoperitoneum created, every hour after the start of surgery, any time the table was tilted, and at the end of surgery. The timings of these readings were documented along with the angle of the table tilt, positive end expiration pressure, CO_2 level, MAP and pulse rate.

For part of the analysis, we divided the patients into two groups: Group 1 included patients with an AUC $\leq$ 500 degree x min, and Group 2 included patients with AUC > 500 degree x mins. This was done to directly compare the effect of AUC on maximum IOP increase. The value of 500 was chosen as it provided almost equal numbers in each group for analysis.

The following anaesthetic protocol was followed: if a spinal was required, intrathecal diamorphine and bupivacaine was given. Induction included midazolam, Remifentanil 0.5-1 mcg/kg, fentanyl (2-20 mcgs/kg), propofol (if <55 years 2-2.5mgs/kg, max dose 250mgs; if >55 years or ASA III/IV 1-1.5mgs/kg, max dose 200mgs). Intra-operatively remifentanyl infusion at 0.2-0.5 mcg/kg/min) and neuromuscular blockade with either Rocuronium or atracurium was given.

2.3.4 Statistical analysis

To incorporate the length of time spent at various degrees of Trendelenburg tilt, area under the curve (AUC) was calculated by plotting the time since start of surgery against the degree of Trendelenburg tilt. Trendelenburg tilt was recorded as a positive tilt and reverse Trendelenburg as negative (positive and negative y-axis portion of graph respectively Figure 21). Therefore, the tilt AUC considers time spent head-down and the effects of being supine or head-up that also affect IOP. At each time point IOP was measured, the change from baseline IOP was calculated to give a ‘change in IOP’. A ‘change in IOP AUC’ was calculated by plotting the time from start of surgery against the change in IOP at each time point.

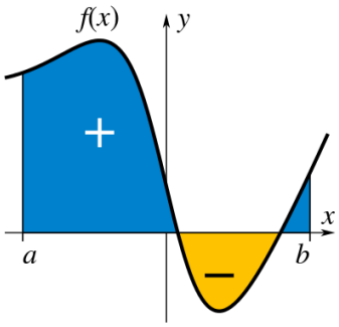


FIGURE 21: TILT AUC CALCULATION METHOD= START OF SURGERY, B= END OF SURGERY, Y-AXIS= DEGREE OF HEAD DOWN TILT, X-AXIS= TIME IN MINUTES. FOR 'CHANGE IN IOP' AUC: Y-AXIS= CHANGE IN IOP IN MMHG, X-AXIS = TIME IN MINUTES.

A multilevel mixed analysis was carried out comparing the following variables to the 'change in IOP AUC' that occurred at each time point in each patient. The variables analysed included: Time from start of surgery (minutes); AUC; Pneumopressure (mmHg); positive end expiration pressure (PEEP); expired CO_2 level (CO_2); mean arterial pressure (MAP).

I divided the data into two groups: Group 1 AUC $\leq$ 500 and Group 2 AUC > 500. The max IOP increase was compared in both groups using the Mann Whitney U test.

IOP five minutes following induction of pneumoperitoneum was also compared to maximum IOP increase during surgery using a t-test.

A Pearson's Correlation co-efficient between IOP measured by the Tono-pen® XL applanation Tonometer and degree of Trendelenburg tilt was calculated for each patient. The individual correlation coefficients were then pooled using a meta-analytic approach by considering the different number of readings and potential heterogeneity between patients. Stata metan code was used to perform meta-analysis modelling. All correlation coefficients were transferred into Fisher's Z-value for meta-analysis modelling, the pooled Fisher Z score (95% CI) was then transformed back to a correlation coefficient with 95% CI using z to r transformation equation.

2.4 Results

55 patients were enrolled in this study of which 5 withdrew consent. Of the 50 patients included, 26 were male and 24 females with a mean (± SD) age of 66 ± 16.46 years. Three of the patients were graded as ASA 1, 43 were ASA 2 and 4 were ASA 3. Average (± SD) BMI 27.24 (± 5.18) kg/m^2. Table 2 summarises the demographics of the 50 patients included in our study. Table 3 shows the average baseline IOP measurements and the average maximum IOP rise that occurred peri-operatively for all 50 patients.

Gender		
Male	n = 26	
Female	n = 24	
Age (years)	66.0	

	+/-16.64 years	
BMI	27.2 +/-5.18	
ASA Grade		
ASA I	n = 3	
ASA II	n = 43	
ASA III	n = 4	
Operation		
Laparoscopic Right Hemicolectomy	24	
Laparoscopic Anterior Resection	15	1 converted to open
Laparoscopic Hartmann's	3	2 converted to open
Laparoscopic Subtotal colectomy	4	1 converted to open
Laparoscopic panproctocolectomy	1	
Laparoscopic completion proctectomy and ileoanal pouch	1	Converted to open
Extralevator abdominoperineal resection	1	
Laparoscopic colotomy	1	

Operative Time (minutes)		
<100	n = 5	
100-199	n =22	
200-299	n = 14	
300-399	n = 3	
400-499	n = 4	
>500	n = 2	
Length of Stay (days)		
< 3	n = 2	
3-5	n = 24	
6-10	n = 15	
>10	n = 8	
RIP	n = 1	(Day 2 from chest infection)
Trendelenburg Tilt		
< 14^0	n = 22	
14-20^o	n = 20	
>20^0	n = 8	
Blood loss		
<100mls	n = 32	
100-500mls	n = 10	
>500mls	n = 8	

TABLE 2 DEMOGRAPHIC DATA FOR ALL 50 PATIENTS INCLUDED IN STUDY

Mean Baseline IOP	16.57 mmHg ± 3.84
Mean maximum change from baseline IOP peri-operatively	11.55 mmHg ± 6.65

TABLE 3 OVERALL MEAN BASELINE IOP AND MEAN RISE IN IOP PERI-OPERATIVELY

A multilevel mixed analysis carried out comparing the 'change in IOP AUC' at each time point with each variable measured to include: Time from start of surgery; Tilt AUC; pneumopressure; PEEP; CO_2 level; MAP. For this analysis, all patients were included. The output from this analysis is detailed in Table 4.

Change in IOP AUC	**Coefficient**	**Std. Err.**	**z**	**P>z**	**Co-Efficient (95% CI)**	**P-Value**
Time from Start of Surgery	**4.327806**	**0.488**	**8.88**	**0**	**4.33 (3.37, 5.28)**	**0.00**
Tilt AUC	**0.4831947**	**0.038**	**12.66**	**0**	**0.48 (0.41, 0.56)**	**0.00**
Pneumo pressure	-2.462214	4.160	-0.59	0.55	-2.46 (-10.62, 5.69)	0.55

PEEP	25.04822	26.540	0.94	0.35	25.05 (-26.97, 77.07)	0.35
CO_2	**121.6906**	**47.061**	**2.59**	**0.01**	**121.69 (29.45, 213.93)**	**0.01**
MAP	1.459559	1.845	0.79	0.43	1.46 (-2.16, 5.07)	0.43

TABLE 4 REGRESSION ANALYSIS OUTCOME FOR ALL PATIENTS

The statistical analysis carried out showed the important factors that affected IOP rise was the length of surgery, Tilt AUC, expired CO_2.

2.4.1 Tilt AUC comparative analysis

Further analysis to look at the combined effect of the head-down tilt and time spent in Trendelenburg was carried out by dividing patients into 2 groups: Group 1 tilt AUC $\leq$ 500 degrees x mins and Group 2 tilt AUC > 500 degrees x mins. A Mann Whitney U test was carried out to compare the 2 groups. Group 2 had a significantly higher maximum IOP rise that group 1, and the maximum degree of Trendelenburg tilt was also significantly higher in Group 2 (Figure 22, Table 5).

	Group 1 Median (LQR, UQR)	**Group 2 Median (LQR, UQR)**	**z-value**	**P-value**
AUC	$\leq$ 500 degrees x mins	> 500 degrees x mins		

Number	24	26		
Max IOP increase (mmHg)	9.64 (6.50, 11.75)	14.60 (11.66, 18.00)	3.039	P=0.00236
Maximum Tilt	9.75 (4.5, 13.76)	18.75 (15.33, 22.85)	4.6119	$P \leq 0.05$

TABLE 5 MANN WHITNEY U TEST TO COMPARE THE MAXIMUM IOP INCREASE IN GROUP 1 WHERE AUC < 500, GROUP 2 AUC > 500.

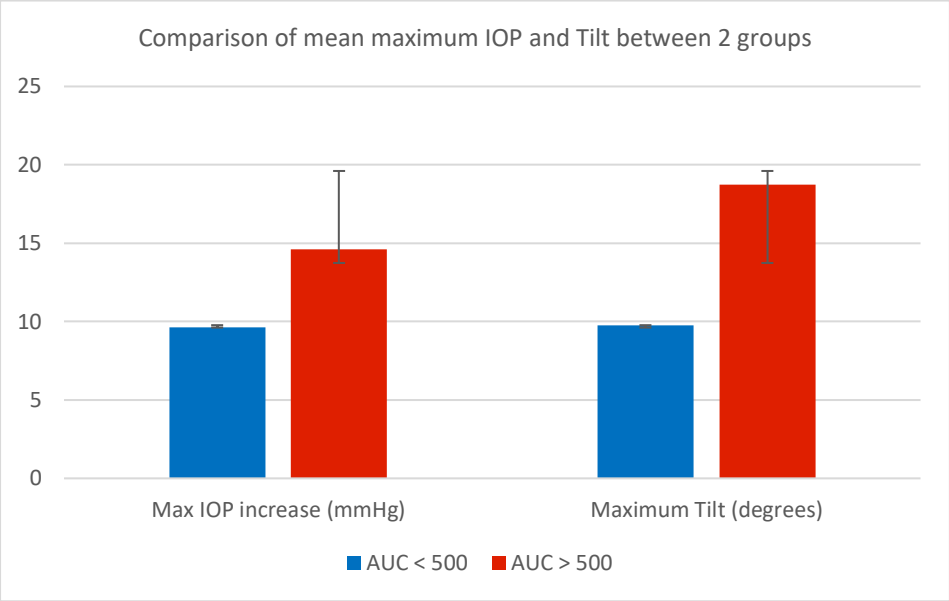


FIGURE 22: MEAN MAXIMUM IOP RISE PERI-OPERATIVELY AND MEAN MAXIMUM TRENDELENBURG TILT BETWEEN GROUP 1 (AUC < 500) AND GROUP 2 (AUC > 500)

2.4.2 Pneumoperitoneum and IOP

To assess the effect of the pneumoperitoneum on IOP, we compared the IOP measured 5 minutes after the induction of the

pneumoperitoneum to the maximum IOP rise that occurred peri-operatively. Figure 23 Two tailed t test was carried out. t = 7.786, P ≤ 0.0001 95% CI (6.1969, 9.3751). Table 6 In one patient we were unable to measure IOP after the induction of pneumoperitoneum as a central line was being placed.

	Maximum IOP increase	**IOP rise following pneumoperitoneum**
Mean	12.22	4.43
SD	5.98	5.96
N	50	49

TABLE 6 COMPARATIVE DATA FOR MAXIMUM IOP INCREASE AND IOP INCREASE FOLLOWING PNEUMOPERITONEUM INDUCTION

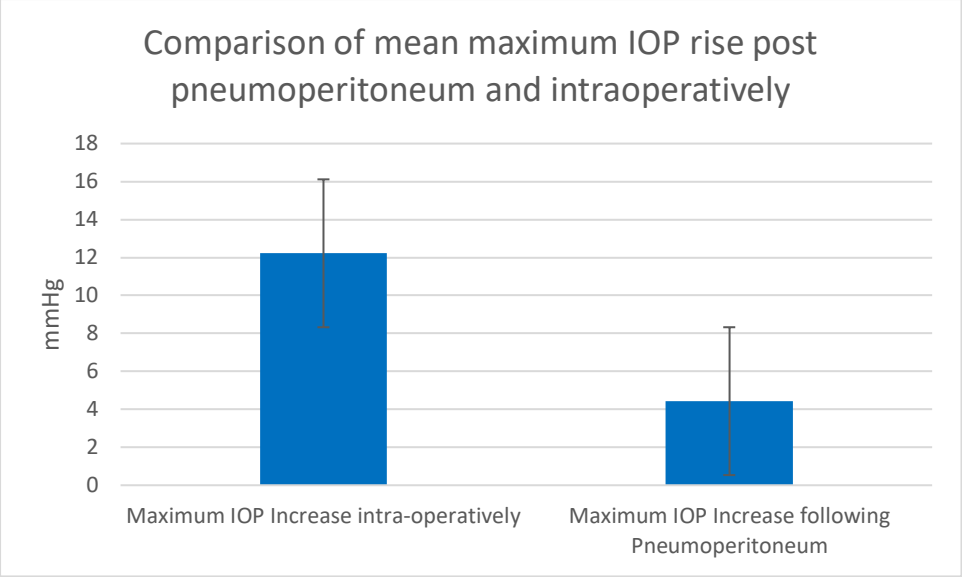


FIGURE 23: COMPARISON OF MEAN IOP RISE AFTER PNEUMOPERITONEUM AND MAXIMUM IOP RISE PERI-OPERATIVELY

2.4.3 Comparison between left and right sided laparoscopic colorectal surgery

Patients undergoing right-sided colon resections are hypothesised to spend less time in the Trendelenburg position compared to those undergoing left-sided resections. Therefore, a further analysis dividing the patients into Group A (right-sided laparoscopic colorectal surgery) and Group B (left-sided laparoscopic colorectal surgery) was carried out.

Figure 24 and Figure 25 show the maximum Trendelenburg tilt and IOP for each patient in Group A and B respectively.

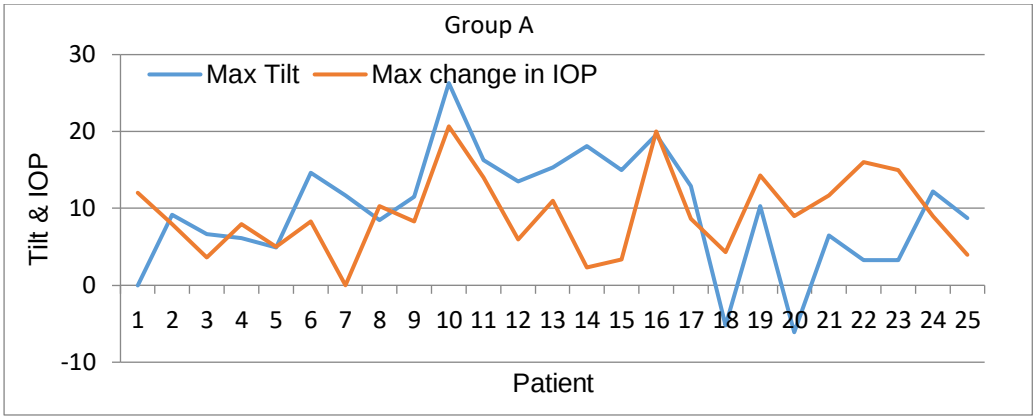


FIGURE 24 COMPARISON GRAPH OF MAXIMUM TRENDELENBURG TILT AND MAXIMUM CHANGE IN IOP IN GROUP A

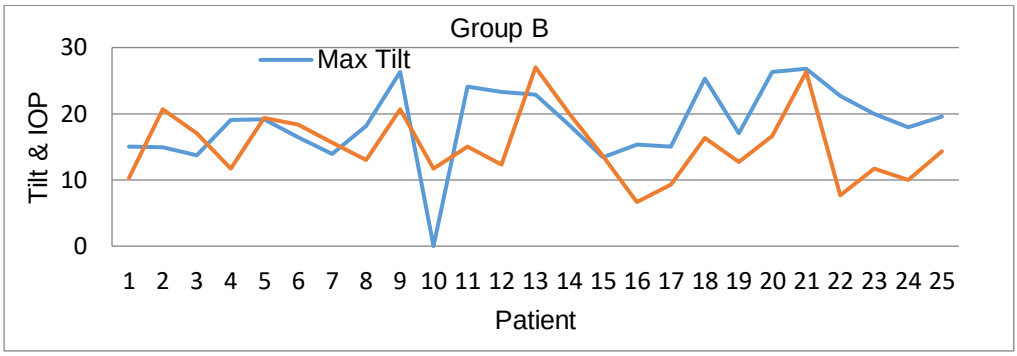


FIGURE 25: COMPARISON GRAPH OF MAXIMUM TRENDELENBURG TILT AND MAXIMUM CHANGE IN IOP IN GROUP B

An unpaired t test was performed of the maximum IOP increase and maximum head-down tilt between Group A and Group B. For the maximum IOP increase from baseline t = 3.89 with p = 0.0003 (95% confidence interval -8.79 to -2.81). For the maximum head-down tilt a t score of 4.719 with a p-value of <0.0001 (95% confidence interval -12.64 to -5.09). (Table 7).

	Group 1	Group 2	P value
Age (years)	68.7 (SD=13.9)	62.5 (SD=16.4)	P=0.153
Mean Baseline IOP	16.1 mmHg (SD=4.4)	16.6 mmHg (SD=2.9)	P = 0.639
Mean length of Surgery	141.6 minutes (SD=49.3)	267.7 minutes (SD=99.0)	P <0.001
Mean maximum Trendelenburg Tilt	9.7^0 (SD=5.3)	15.1^0 (SD=5.2)	P <0.0001
Mean maximum increase from baseline IOP intra-operatively	9.3 mmHg (SD=5.3)	15.1 mmHg (SD=5.2)	P = 0.0003

TABLE 7 OVERALL MEAN LENGTH OF SURGERY, BASELINE IOP AND MEAN RISE IN IOP INTRA-OPERATIVELY BETWEEN GROUP 1 AND GROUP 2.

2.4.4 Correlation between Tilt and IOP analysis

The correlation between the degree of tilt and IOP was analysed. Meta-analysis of Pearson's correlation coefficient between degree of tilt and IOP was 0.78 (Heterogeneity chi-squared = 72.86 (df = 47) p = 0.009) (Figure 26). Indicating there is a significant strong positive correlation between the IOP and degree of Trendelenburg tilt. Two patients were excluded from this analysis as they remained supine (at 0^0) which did not allow a Pearson's correlation calculation.

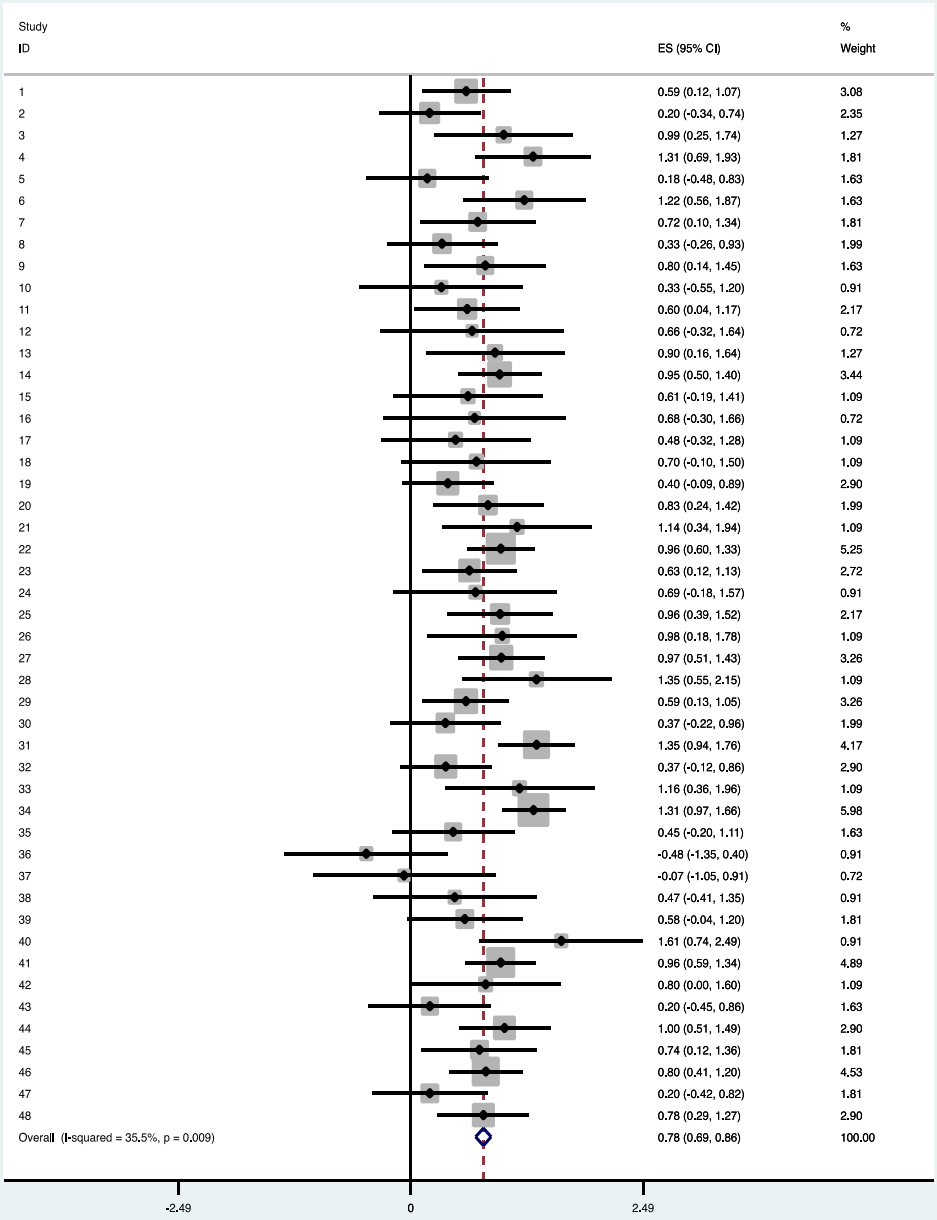


FIGURE 26 META-ANALYSIS GRAPH OF IOP MEASUREMENTS AND THE CORRELATING DEGREE OF TILT FOR EACH PATIENT.

Figure 26 shows a strong correlation between the degree of tilt and the IOP measurements taken using the Tono-Pen® XL.

2.5 Discussion

Laparoscopic surgery is the preferred approach for most colorectal resections. Advantages include smaller incisions; reduced blood loss; less post-operative pain, and reduced recovery time (Group, 2000). Trendelenburg positioning is used during laparoscopic colorectal surgery and other specialities including urology and gynaecology to utilise gravity as a form of retraction. Trendelenburg position allows the small bowel to fall out of the pelvis away from the operative field during left sided resections. During a right hemicolectomy, Trendelenburg position is sometimes used to help move the small bowel away during the caecal dissection.

Our study found the degree of tilt used and the time spent in Trendelenburg is significantly lower compared to left-sided resections. Our study found often a reverse Trendelenburg position is used during dissection of the hepatic flexure. This was why we used AUC as a measure to also take into account the time spent in the reverse Trendelenburg. As head-up tilt was measured as a negative tilt, the amount of time spent in the head up position reduced the overall AUC value.

An IOP value above 25 mm Hg is considered pathological (Cunningham and Barry, 1986). Chauhan *et al* looked at the effect of raised IOP in rats. They increased the IOP in one eye and used the other eye as a control.

They monitored the IOP change from baseline in both eyes and looked at the effect on the optic disc and the optic nerve. Their data suggested changes were dependent on the peak increase in IOP. They found a peak increase of 15mmHg in IOP resulted in extensive axonal loss (mean loss of 69.2%), and a peak increase of 20mmHg in IOP resulted in profound axonal structural loss (mean reduction of 76.7%). They concluded that optic nerve axonal damage was related to the peak increase in IOP as opposed to the length of time the IOP was raised (Chauhan *et al*., 2002).

Chauhan concluded a change in IOP of 10 mmHg or more can lead to damage of the optic nerve (Chauhan *et al*., 2002). Along with the degree of increase in IOP, the length of time IOP is raised has an additional cumulative effect (Grosso *et al*., 2013, Sultan *et al*.). Similar findings were also made by Morrison *et al* (Morrison *et al*., 1997). The use of tilt AUC allowed assessment of this possible cumulative effect. Our results showed a significant difference in the maximum change in IOP with a mean IOP rise of 9.64 mmHg, versus 14.60 mmHg in patients with a tilt AUC $\leq$ 500 degrees x mins compared to AUC > 500 degrees x mins respectively. The maximum Trendelenburg tilt was also compared between patients with an AUC $\leq$ 500 mean maximum tilt of 9.75^{o}, compared to 18.75^{o} in those with an AUC > 500. This difference was also statistically significant.

Grosso *et al* compared 3 groups of patients, those undergoing laparoscopic surgery supine, laparoscopic surgery in Trendelenburg position and open surgery in supine position. They looked at the effect of pneumoperitoneum (12-14mmHg) on IOP, and found a mean rise of 4mmHg (range 0-11.2 mmHg) which was comparable to our 4.43 mmHg rise following pneumoperitoneum. They found the mean IOP increase following 45 minutes after the start of surgery was 5.05 mmHg in the Trendelenburg group versus 4.23 mmHg in the laparoscopic group not placed in Trendelenburg (Grosso *et al*., 2013). In our study, we compared the IOP rise that was measured 5 minutes following induction of pneumoperitoneum to the overall maximum IOP rise that occurred during surgery. This gave a mean rise of 4.43 mmHg following pneumoperitoneum induction compared to an overall rise of 12.22 mmHg. This too was statistically significant suggesting the creation of pneumoperitoneum alone (at 11-14 mmHg) that was used on our patients does not cause a significant increase in IOP.

Awad *et al* also looked at the effect of steep Trendelenburg positioning on IOP during robotic prostatectomy (Awad *et al*., 2009). Their analysis revealed Peak airway pressure, duration of surgery, end tidal CO_2 levels and mean arterial pressure were all significant predictors of IOP change during surgery. Gosso and Awad studies data set varied from our study as their patients were placed in Trendelenburg position at the same degree of tilt and IOP measurement were taken at specific time points (Awad *et al*., 2009, Grosso *et al*., 2013). In our study, the degree of

Trendelenburg varied as did the time spent in Trendelenburg. This allowed us to assess what affect the steepness of head-down position and time spent in Trendelenburg had on IOP. Our analysis also showed length of surgery; time spent in Trendelenburg position and the degree of Tilt; and $ETCO_2$ as significant factors for change in IOP during surgery.

Our study also showed the degree of Trendelenburg tilt was strongly correlated with IOP, with a co-efficient value of 0.78 ($p=0.009$). During the study, we observed that by reducing the tilt even by a few degrees, the IOP would reduce almost immediately. This is of great clinical significance, as by reducing the degree of tilt by even a few degrees can reduce the IOP almost immediately. This may be a useful mechanism to prevent sustained IOP elevation during surgery when prolonged surgery is being undertaken or in patients in whom there is concerns that optic nerve ischemia of prolonged IOP elevation may be risky such as patients known to have glaucoma.

2.5.1 Limitations

There are limitations in this study including the use of Tonopen instead of the gold standard Goldmann's tonometer for IOP measurement (Okafor and Brandt, 2015). Studies have shown by taking an average of 2 readings, the accuracy of the Tonopen is greatly increased and is comparable with Goldmann. For this study, I took 3 measurements and used the average. Studies have shown this improves the accuracy of Tonopen measurements to the same as Goldmann's tonometer (De Smedt, 2015, Okafor and Brandt,

2015, Lasseck *et al*., 2008). Measuring IOP in only one of the eyes can also be a potential limitation. However, Grosso *et al* measured IOP in both eyes at each time point and found minimal difference between the left and right eye (Sit *et al*., 2006, Grosso *et al*., 2013).

2.6 Conclusion

In conclusion, this study showed along with the degree of Trendelenburg tilt, the time spent in this position also affects IOP during laparoscopic colorectal surgery. I identified significant and prolonged IOP elevation in a significant proportion of patients. This should be considered especially in patients known to have glaucoma.

Vision loss is an important potential complication of steep Trendelenburg positioning, however even where catastrophic vision loss does not occur sustained IOP elevation may result in some subclinical optic nerve damage which may increase the risk of later vision loss (Chauhan *et al*., 2002), particularly in those patients who have pre-existing optic nerve damage or develop optic nerve pathology later in life.

Chapter 3 : Can the SENSIMED Triggerfish® lens data be used as an accurate measure of intraocular pressure (IOP)?

Abstract

Introduction

The SENSIMED Triggerfish® Contact Lens Sensor (CLS) is a soft disposable silicone contact lens with an embedded micro-sensor that captures spontaneous circumferential changes at the corneoscleral junction. These readings are taken every 5 minutes and are transmitted via an antenna to a device where these measurements are stored. It is currently used to monitor “IOP fluctuations” in patients with glaucoma. During laparoscopic colorectal surgery, patients are placed in Trendelenburg and reverse Trendelenburg positions to expose the surgical site and allow adequate views for the surgeon. Trendelenburg positioning and pneumoperitoneum have been shown to effect IOP, therefore IOP can vary significantly (Awad *et al*., 2009).

Aim

To assess if the circumferential changes in the corneoscleral area can be correlated to the dynamic IOP changes measured using Tono-pen® XL applanation tonometer during laparoscopic colorectal surgery.

Method

Patients undergoing laparoscopic colorectal resections were included in this study. On the day of surgery, baseline IOP was taken and the SENSIMED Triggerfish® CLS was then set up in one eye of the patient. During surgery (whilst under general anaesthetic), IOP measurements were taken in the contralateral eye every hour and any time the table

was moved to record the fluctuations of IOP during surgery and any association with position change. The timings of these readings were documented. All contralateral IOP measurements were taken with a Tono-pen® XL applanation tonometer.

Results

Twenty patients were included in this study (6 males, 14 females). Average age (± SD) was 64.6 ± 16.3 years. The fluctuation in IOP measured in the reference eye ranged between 6.33 to 46.67 mmHg. The mean correlation co-efficient between CLS output measurements and these IOP measurements was r=0.29 (95%CI).

Conclusion

My results showed a weak correlation between the SENSIMED Triggerfish® CLS data output and IOP measurements taken using the Tono-pen® XL applanation tonometer.

3.1 SENSIMED Triggerfish® contact lens sensor

SENSIMED Triggerfish® is a non-invasive wireless soft CLS which was designed to take automated recordings of IOP-related patterns for up to 24 hours (medGadget, 2013). The CLS is a soft disposable contact lens containing a sensor which sits on the front of the eye like an ordinary contact lens. The lens itself is made from pure silicone with an oxygen plasma surface treatment to avoid it drying out allowing it to be worn for 24 hours. The sensor is 585µm thick in the centre and 260µm thick at the periphery with a diameter of 14.1mm.

FIGURE 27: (REPRODUCED) SENSIMED TRIGGERFISH® CONTACT LENS SENSOR (SENSIMED, 2014).

The CLS has an oxygen transmissibility of 119 Dk/t units, which exceeds the levels recommended for normal contact lenses to avoid hypoxia of the cornea.

3.1.1 Setting up of SENSIMED Triggerfish® CLS

After the lens is fitted, a self-adhesive, flexible, disposable antenna is placed on the peri-orbital region for a single 24-hour period. A data cable connects the antenna to the recorder which is worn around the person's neck in the pouch (NICE, 2014).

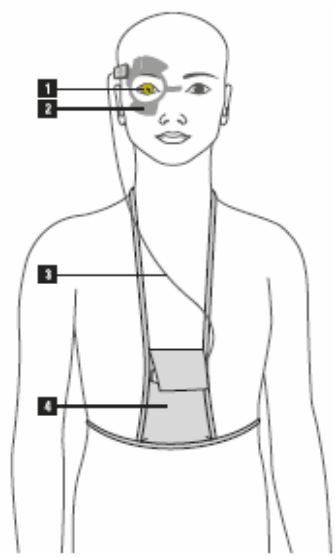


FIGURE 28: (REPRODUCED) SHOWING CLS, ANTENNA, AND RECORDER SET UP. 1-CONTACT LENS SENSOR; 2-ANTENNA; 3-DATA CABLE CONNECTING ANTENNA TO RECORDER; 4-POUCH HOLDING THE RECORDER (SENSIMED, 2014).

3.1.2 Data collected by SENSIMED Triggerfish® CLS

The CLS measures spontaneous dimensional changes of the eye at the corneoscleral junction to record the IOP-related profile for 24 hours. The CLS takes 300 data points during the 30 seconds recording period at 5 minute intervals over the 24 hours. The median value from these reading intervals is recorded and transmitted wirelessly from the sensor to the antenna, and then transferred via the wire from the antenna to the

recorder. Over a 24-hour period, 288 data points are recorded in mV equivalents (mVeq) (Mansouri *et al*., 2015a).

As the lens relies on changes in the corneoscleral junction, it requires a decent fit on the eye, and is therefore available in 3 curvature radius sizes: 8.4mm (steep), 8.7mm (medium) and 9.0mm (flat). The size of lens is decided based on measurements taken using Keratometry. The CLS measures even minor changes in ocular dimensions through a strain gauge in the contact lens. The assumption behind this technology is that variations in IOP lead to changes in ocular volume and dimensions (Mansouri *et al*., 2015b, NICE, 2014).

Hjortdal *et al* carried out an in vivo study (Hjortdal and Jensen, 1995) and Lam *et al* an in vitro study (Douthwaite and Lam, 1997) looking at correlation between IOP and corneal curvature in humans. They showed an IOP change of 1mmHg causes a change of central corneal radius of curvature of approximately 3μm (over a typical radius of 7.8mm) (Leonardi *et al*., 2004).

Leonardi *et al* described five major physical forces that act on a contact lens when in the eye (Figure 29) (Leonardi *et al*., 2004).

1. Atmospheric pressure (P_0) surrounds the anterior and peripheral surfaces of the lens tears;

2. Hydrostatic pressure (P_1) from the pre-corneal tear film which acts against the lens;
3. Force of gravity (p) from the weight of the lens;
4. Eye lid force (F_{lid}) which is the force created by the lid during a blink;
5. Surface tension forces ($F\sigma$) between the molecules of tears at the interfaces between air and tears and between tears and lens.

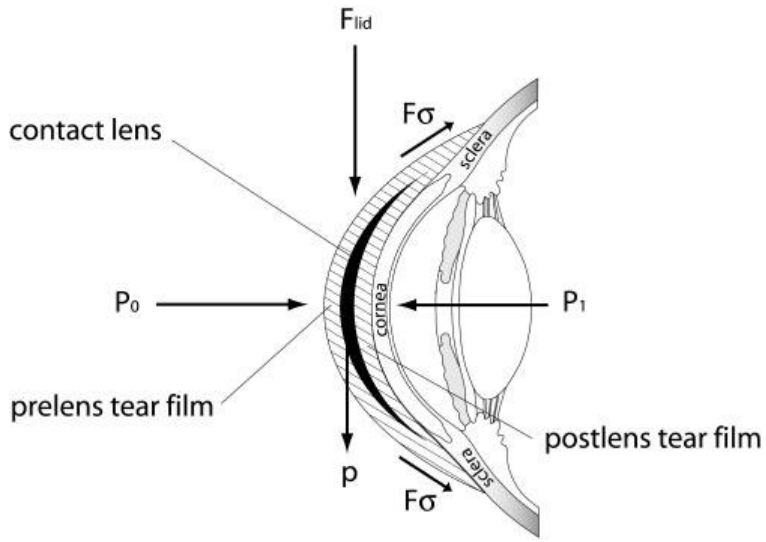


FIGURE 29: (REPRODUCED) THE FIVE MAJOR PHYSICAL FORCES ACTING ON A CONTACT LENS: P0- ATMOSPHERIC PRESSURE; P1- HYDROSTATIC PRESSURE OF THE POSTLENS TEAR FILM; Fσ- SURFACE TENSION OF THE PRELENS TEAR FILM; P- LENS WEIGHT; AND FLID- LID FORCE (LEONARDI ET AL., 2004).

The interactions of these forces at different points in the eye and lens with the various conditions all determine the fit of the lens. When the lens fits properly, the lens has both pre- and post-tear films, which allow the contact lens slide on the corneal surface and find its natural position after each blink. With this proper fit, the CLS adapts to follow any corneal deformations by bending as required, and has only circumferential strain.

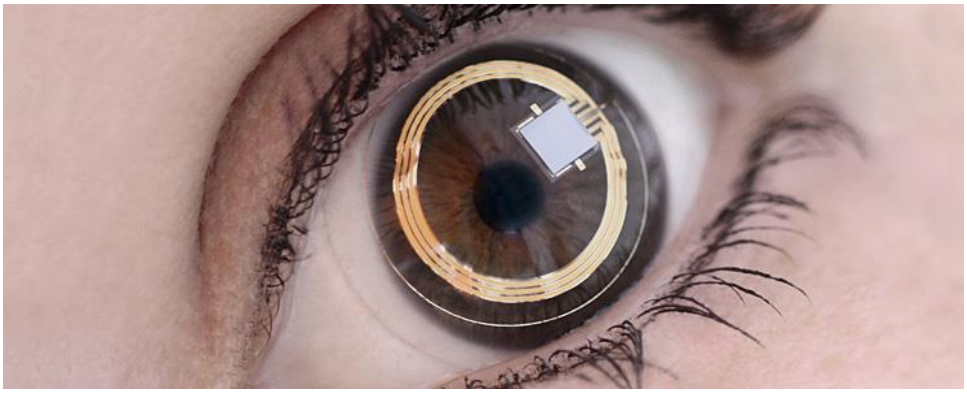


FIGURE 30: (REPRODUCED) GOOD FITTING CLS (SENSIMED, 2014).

The resistive gauges in the device are designed to have a circular arc shape around the centre, and are placed over a circumference of 11.5mm diameter, which is the average position of the corneoscleral junction. Studies on distensibility of the cornea and sclera have shown that the corneoscleral junction has the maximum variation following IOP changes. It is here where the changes in IOP are believed to induce the most corneal deformation. The compensation-resistive gauges, used only for thermal compensation, are placed radially, where they do not interfere with the readings. The CLS is stimulated by a typical DC current

(I_0) of 100 μA, and it gives an output voltage proportional to strain on the lens and theoretically to the IOP variations (Leonardi *et al*., 2004). The initial reading taken when the lens is first inserted is recorded as 0mVeq. All subsequent readings are recorded in proportion to this. For example, if the distension of the corneoscleral region is less than when the lens was first inserted, it is recorded as a negative reading.

NICE have suggested the SENSIMED Triggerfish® CSL produces a qualitative profile of relative IOP peaks and patterns over 24 hours, whereas GAT gives definitive IOP values at a fixed time point (NICE, 2014). As the data from the sensor are measured in electrical units referenced against a starting value of 0 at each recording session, data from the SENSIMED Triggerfish® cannot be directly compared with results from currently used IOP measurement devices such as Goldmann Applanation Tonometry or Tono-pen® XL tonometer, which measure pressure in millimetres of mercury (mmHg) (Mansouri *et al*., 2015a).

3.2 Right versus left eye IOP

The contralateral eye had to be used as a control in this study as with the CLS in place, the Tono-pen® XL applanation tonometer cannot accurately measure IOP. There have been various studies that have shown similar 24-hour IOP profiles in the right and left eye. Though the absolute IOP measurements may not be the same, the variation was similar in both eyes. So, if IOP increased in the right eye, it also

increases a similar amount in the left eye (Liu *et al*., 2005, Sit *et al*., 2006).

3.3 Aim

To assess if the circumferential changes in the corneoscleral area measured using the SENSIMED Triggerfish® CLS can be correlated to IOP measurements taken using Tono-pen® XL applanation tonometer during laparoscopic colorectal surgery.

3.4 Methods

The study was reviewed and approved by the Northampton Research Ethics Committee (protocol number: 11GA019) and undertaken in accordance with the tenets of the Council of Helsinki.

3.4.1 Patient Population

All patients undergoing planned laparoscopic left-sided colorectal resection under the colorectal surgery service at Nottingham University Hospital were invited to participate in the study. Those expressing an interest to participate were given a patient information leaflet. Patients who were willing to participate signed a consent form prior to any study interventions.

3.4.1.1 Inclusion Criteria

- Patients undergoing laparoscopic left-sided colorectal surgery
- Aged 18 years and over

3.4.1.2 Exclusion criteria

- Patients with a history of significant ocular disease or ocular surgery other than glaucoma
- Allergy to Tetracycline or Latex

3.4.2 Baseline Tests

Baseline eye examination was carried out on all patients that agreed to take part including: best corrected visual acuity; Gonioscopy; central corneal thickness; Goldmann Applanation Tonometry and Tono-pen® XL applanation tonometer; Tono-pen® XL applanation tonometer measurements were repeated after lying the patient supine for 5 minutes. All Tono-pen® XL applanation tonometer readings during this study were taken after administering 1% tetracaine eye drops and repeated to obtain 3 readings at 5% accuracy and averaged. Keratometry was also carried out so the correct CLS size was used.

3.4.3 Day of Surgery

On the day of surgery, baseline IOP was taken (reference IOP) as the initial CLS reading when placed is a calibration reading and is recorded at 0 mVeq. The SENSIMED Triggerfish® CLS was then set up in one eye of the patient. The left eye was used unless the patient preferred the right eye. During surgery (whilst under general anaesthetic), IOP measurements were taken in the fellow (control) eye at every hour following anaesthetic induction and any time the table was tilted. These recordings acted as the reference IOP values against which fluctuation recorded by the SENSIMED device were compared. It also allowed

profiling of IOP and determination of maximum fluctuation of IOP. The timings of these readings were documented to allow direct comparison with the SENSIMED tracing. All contralateral eye IOP measurements were taken with a Tono-pen® XL applanation tonometer. The CLS automatically stopped recording after 24 hours and was removed. The data was then downloaded using SENSIMED software, extracted and analysed.

3.4.4 Statistical Analysis

As each lens is calibrated to the individual patient, we could not simply pool all the data from our patients. A Pearson's Correlation co-efficient between SENSIMED Triggerfish® CLS measurements and IOP measured by the Tono-pen® XL applanation Tonometer was calculated for each patient. The individual correlation coefficients were then pooled using a meta-analytic approach by considering the different number of readings and potential heterogeneity between patients. Stata metan code was used to perform meta-analysis modelling. All correlation coefficients were transferred into Fisher's Z-value for meta-analysis modelling, the pooled Fisher Z score (95% CI) was then transformed back to a correlation coefficient with 95% CI using z to r transformation equation. A two-tailed student t-test was carried out to compare the baseline IOP between both eyes. $P<0.05$ was considered significant.

3.5 Results

Twenty-five patients agreed to take part in this study. However, five patients were excluded as three patients did not tolerate the lens, and

with two patients we had CLS equipment issues. The final analysis consisted of the 20 patients that completed the study, (6 males and 14 female). All patients underwent scheduled routine colorectal surgery. They had a mean (± SD) age of 64.6 ± 16.3 years (range: 18 to 78 years old). (Table 8)

Baseline IOP measurements using Goldman tonometry were taken in both eyes and did not show a statistically significant difference. The eye in which CLS was placed had a mean (± SD) IOP of 15.45 (± 2.54) mmHg, compared to the control eye (in which the Tonopen measurements were taken) with a mean IOP baseline of 15.5 (± 2.16) mmHg, t-value = 0.33, df = 19; p=0.7481. There was no significant difference between central corneal thickness in fellow eyes, mean CLS group thickness was 547.35 (± 26.36) µm; control group mean thickness of 547.5 (± 27.66) µm; t-value = 0.0752, df = 19; p=0.9409.

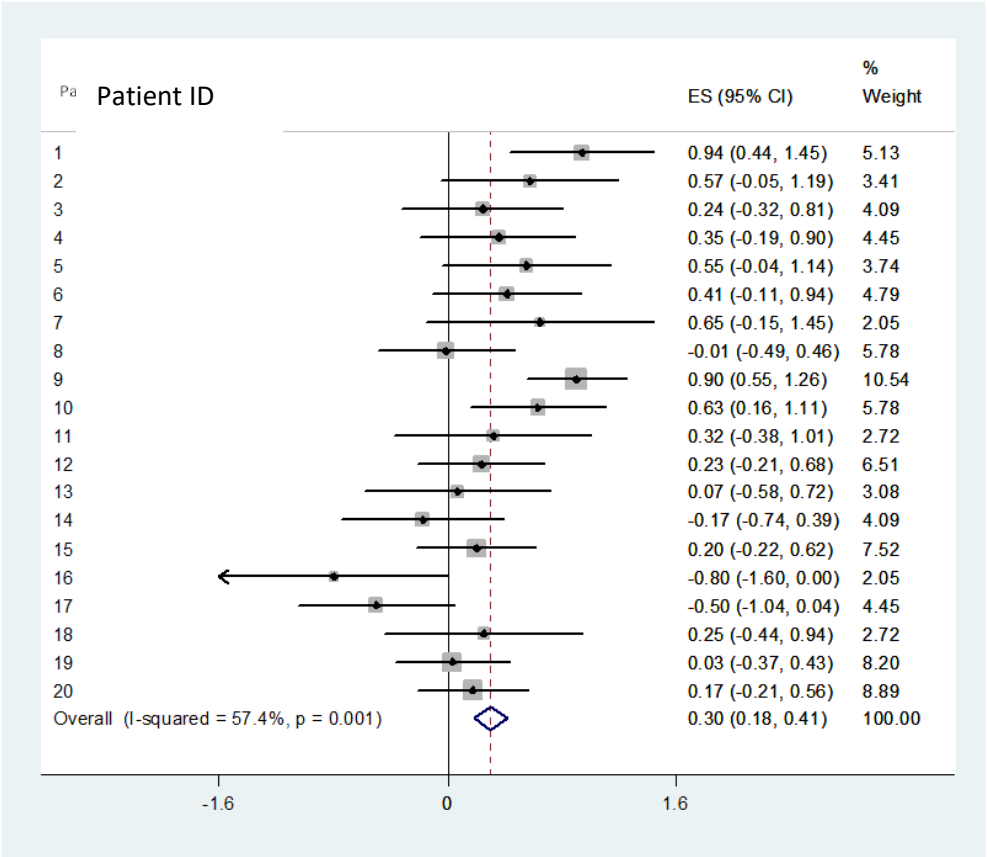
Pt ID	Age	M / F	Laparoscopic operation	No of readings	R-correlation coefficient	Z value	Standard Error (Z value)
1	75	F	Anterior Resection	18	0.737	0.943	0.258
2	77	F	Anterior Resection	13	0.518	0.573	0.316
3	72	F	Anterior Resection	15	0.239	0.244	0.289

4	63	F	subtotal colectomy (converted to open)	16	0.340	0.354	0.277
5	60	M	Anterior Resection (converted to open)	14	0.499	0.548	0.302
6	62	M	Anterior Resection	17	0.390	0.412	0.267
7	66	F	Anterior Resection	9	0.570	0.648	0.408
8	57	F	Anterior Resection	20	-0.013	-0.013	0.243
9	78	M	Panproctocol ectomy	34	0.718	0.904	0.180
10	76	M	Anterior Resection	20	0.559	0.632	0.243
11	76	F	Anterior Resection	11	0.308	0.318	0.354
12	26	F	subtotal colectomy	22	0.231	0.235	0.229
13	71	F	Anterior resection	12	0.069	0.069	0.333
14	68	F	Hartman’s procedure	15	-0.172	-0.174	0.289
15	52	F	extended right	25	0.199	0.202	0.213

			hemicolectomy				
16	74	F	right hemicolectomy	9	-0.662	-0.796	0.408
17	75	M	Extralevator abdominoperineal excision	16	-0.462	-0.500	0.277
18	70	F	Anterior Resection	11	0.245	0.250	0.354
19	75	F	subtotal colectomy	27	0.034	0.034	0.204
20	18	M	subtotal colectomy	29	0.171	0.173	0.196

TABLE 8 – PATIENT DEMOGRAPHICS AND PEARSON'S CORRELATION CO-EFFICIENT FOR TONOPEN IOP AND SENSIMED TRIGGERFISH® CLS OUTPUT

Fisher's Z transformation was carried out on the Pearson's correlation coefficients. Table 8 shows the individual correlation coefficients for each patient with the standard error and the z values obtained after the Fisher's r to z transformation was carried out.



GRAPH 1- FOREST PLOT OF META-ANALYSIS OF CORRELATION FISCHER Z-VALUES FROM SENSIMED TRIGGERFISH® STUDY DATA

A fixed-effect meta-analysis showed there is significant between patient heterogeneity among correlation fisher z score (Chi squared=44.56, df =19, p=0.001), therefore random effect model was performed to integrate the 20 patients' Z-values. The pooled Z-value of 0.30 (0.18, 0.41, p<0.05) as shown in Graph 1 using a random effect model plot.

This Z-value was then converted using Fisher's r to Z-value transformation giving an r correlation coefficient of 0.291 There was

significant heterogeneity; I^2 was 57.4% and chi-squared was 44.56 (df = 19) with p = 0.001.

Pearson's correlation coefficient between CLS output data and the Tono-pen® measurements was 0.291 (95% CI, using same p value as for pooled Fisher Z). Indicating there is a weak positive correlation between the readings taken by the Tono-pen® and CLS.

3.6 Discussion

SENSIMED Triggerfish® CLS is based on the assumption that variations in IOP lead to proportional changes in ocular volume and dimensions, which the CLS captures through embedded strain gauges. Although this assumption has been validated in vitro by Lam *et al* (Douthwaite and Lam, 1997), the practical use of CLS data needs to be further validated (Mansouri *et al*., 2015b). At present the CLS output signal is delivered in arbitrary units for which no conversion into IOP values exists. This makes individual lens readings difficult to interpret.

This study was designed to look at the accuracy of the SENSIMED Triggerfish® CLS IOP fluctuations in comparison to the accepted method of IOP measurements taken using the Tono-pen® XL applanation tonometer. Tonopen® XL has been shown by Horowitz *et al* to be comparable to the gold standard technique of Goldman tonometry when measuring IOP and therefore is a valid technique to assess IOP

especially in environments where slit lamp examination is not possible (Horowitz *et al*., 2004).

The Tono-pen® XL tonometer has been shown to provide comparable IOP measurements to the current gold-standard method of non-invasive IOP measurements taken using the Goldmann tonometer. Though the Tono-pen® XL tonometer is portable, it still requires a trained operator to carry out the measurements and is cumbersome and disruptive in an operating theatre environment The SENSIMED Triggerfish® CLS would overcome these issues and allow IOP measurements to be carried out without disruption or the need for an operator to be available to take measurements throughout the procedure. Availability of IOP readings during laparoscopic colorectal surgery would allow management of raised IOP by medication or changing position of the patient, this may be especially important in patients with existing glaucoma.

Our study showed significant variation between the correlation of measurements taken using the Tono-pen® XL tonometer and the SENSIMED Triggerfish® CLS. The heterogeneity chi-squared of correlation co-efficient between patients was 44.56. The overall correlation co-efficient calculated using a meta-analytical approach was 0.29 which indicates a weak positive correlation between the two methods of IOP measuring. One possibility is that there is a true poor correlation in IOP between fellow eyes when undergoing laparoscopic

surgery and that the SENSIMED device is accurately measuring this poor correlation between eyes – however the literature that exists for IOP measurements in normal and glaucoma patients suggests that there is a close correlation between fellow eye IOP (Sit *et al*., Liu *et al*., 2005) and so it is unlikely that poor correlation is the likely explanation. Another possibility is that the SENSIMED device in this situation is not accurately measuring the strain changes at the corneoscleral area possibly due to the supine position of the patient or because of the non-physiologic environment of the operating theatre. In either case the poor correlation means that the device cannot be relied upon to reflect accurately changes in the IOP that may be occurring during surgery.

In addition to our observation of poor correlation there are other drawbacks to the use of the CLS. Of our 25 patients, we had to exclude 3 patients from our study as after insertion of the lens it was not tolerated by the patients and they requested the lens be removed. This included the discomfort of the lens itself, of which the concern of 2 patients was related to the lens causing blurring of vision and the third patients suffered a corneal abrasion and did not tolerate the lens. The blurred vision has also been described in previous tolerability studies carried out by Mansouri *et al* who though found a good tolerability of the lens with a comfort score of 8/10 in a study of 10 patients. The tolerability of the lens in this study was also closely related to the visual analogue score (Mansouri *et al*., 2012). The blurred vision that can occur from the lens has been suggested to be due to the refractive power of the CLS itself

and due the orthokeratologic effect of the CLS as good close fit of the lens is required (Mansouri *et al*., 2012). Another drawback currently is that the SENSIMED does not provide “live data” as the data is recorded on the device and then has to be downloaded before a tracing of the IOP profile can be seen and evaluated – clearly for ongoing monitoring of IOP in a theatre environment this is unhelpful as the point of using SENSIMED in theatre is to provide an ongoing live reflection of the patients IOP and to allow clinicians to respond to dangerous fluctuations accordingly when they occur.

3.6.1 Limitations

There were several limitations to this study. The number of readings taken using the Tono-pen® XL applanation tonometer varied between patients. The number of readings taken depended on the length of surgery and how often the operating table was moved during surgery.

I was unable to measure IOP with the Tono-pen® XL applanation tonometer in the eye the CLS was in. The contralateral eye had to be used as a control in this study although any IOP variability is likely to be similar between eyes (Liu *et al*., 2005, Sit *et al*., 2006).

The data the CLS provides is relative to the first measurement it takes and uses a different unit of measure. National Institute of Clinical Excellence (UK) have suggested the SENSIMED Triggerfish® CLS produces a qualitative profile of relative intraocular pressure peaks and

patterns over 24 hours, whereas Goldmann applanation tonometer gives definitive IOP values at a fixed time point (NICE, 2014). As the data from the sensor are measured in electrical units referenced against a starting value of 0 at each recording session, data from the SENSIMED Triggerfish cannot be directly compared with results from currently used IOP measurement devices such as Goldmann Applanation Tonometry or Tono-pen® XL tonometer, which measure pressure in mmHg (Mansouri *et al*., 2015a).

3.7 Conclusions

This study suggests that the correlation between IOP measurements taken by Tonopen and IOP profile measured by SENSIMED in the contralateral eye of patients undergoing laparoscopic colorectal surgery is poor. In addition, there were a small but significant number of patient who were unable to tolerate the contact lens. The lack of a live data facility means that although measurement is continuous the current recording process does not allow clinicians to actively monitor IOP fluctuations and react appropriately when concerned. Refining of the current SENSIMED device to address these issues and importantly ideally develop an algorithm to present data outputs in terms of an IOP measurement may provide a useful tool in monitoring intraoperative IOP in patient undergoing laparoscopic colorectal surgery.

Chapter 4 : A randomised cross over study in healthy volunteers to assess the effect of acetazolamide on intraocular pressure after Trendelenburg positioning.

Abstract

Background

Laparoscopic surgery often requires positioning patients at very steep angles for many hours. Recent evidence suggests Trendelenburg positioning can produce a significant rise in IOP (Awad *et al*., 2009). Perioperative vision loss in patients undergoing laparoscopic colorectal surgery has been reported (Pinkney *et al*., 2012), the rise in intraocular pressure (IOP) has been suggested as a possible factor. Acetazolamide decreases IOP by reducing the formation of aqueous humor.

Aims

To investigate if acetazolamide reduces the IOP rise that can occur whilst in the Trendelenburg position.

Methods

Nine healthy volunteers were recruited and randomised to placebo or acetazolamide with a minimum of 4 days' washout period before the second study day. Volunteers and Investigators were masked to acetazolamide/placebo allocation. Baseline IOP was measured on both study days. After 1.5 hours of taking the medication, volunteers lay head-down at 17 degrees for 4 hours. IOP measurements were repeated in both eyes every 30 minutes over a 4-hour period.

Results

There were 2 males and 7 female volunteers, with an average age of 54 years (range: 21-76). The mean (± SD) increase in IOP following 4 hours

in the Trendelenburg position after the placebo was 3.17mmHg (± 4.63), and after acetazolamide the mean (± SD) increase in IOP was 0.02mmHg (± 4.01), ($P < 0.03$).

Conclusion

This study shows that acetazolamide can effectively reduce the rise that occurs in IOP whilst in the Trendelenburg position. This may have an important role in minimising the risk of IOP related visual disturbances in patients undergoing prolonged laparoscopic procedures.

4.1 Acetazolamide

Acetazolamide is a reversible inhibitor of the carbonic anhydrase enzyme. Carbonic anhydrase catalyses the conversion of:

$$CO_2 + H_2O \Leftrightarrow H_2CO_2 \Leftrightarrow HCO_3^- + H^+$$

Acetazolamide is used as a treatment for glaucoma. It reduces IOP by reducing aqueous humor formation. It is also used for altitude sickness, benign intracranial hypertension and a diuretic (Yano *et al*., 1998).

Isoenzyme carbonic anhydrase II has the highest distribution, it covers almost every tissue and organ, including osteoclasts in bone, choroid plexus epithelia, retinal muller cells, hepatocytes, kidney, oligodendrocytes in brain, salivary glands, erythrocytes and platelets. Within the eye, it is localised in the non-pigmented ciliary epithelium and it is here it helps with the production of aqueous humor. In the ciliary processes the formation of bicarbonate is related to the Na^+ ion in the production of aqueous humor. By inhibiting carbonic anhydrase, outflow of bicarbonate in the posterior chamber is reduced. Carbonic anhydrase inhibitors can reduce aqueous humor formation by 20 - 40% without significantly reducing flow (Centofanti *et al*., 1997). Carbonic anhydrase inhibitors work by reducing IOP when it is raised, in patients with normal or low IOP, carbonic anhydrase inhibitors have limited effect on IOP (Centofanti *et al*., 1997). The major role of the isoenzyme carbonic anhydrase II is the contribution of H^+ production and acid–base homeostasis, pH balance, metabolic acidosis. It triggers the CO_2

exchange in the erythrocytes, lungs and renal proximal tubules as well (Hassan *et al*., 2013).

Acetazolamide inactivates carbonic anhydrase enzyme which decreases aqueous humor formation therefore lowering IOP. Aqueous humor is richer in sodium and bicarbonate ions and has a higher osmolality compared to plasma. This creates an osmotic gradient that moves water into the posterior chamber. The higher concentration of ions within the aqueous humor is maintained by sodium pumps. Acetazolamide works by interfering with the sodium pump which reduces the osmolality of the aqueous humor which in turn reduces the osmolality gradient reducing the movement of water from plasma into the posterior chamber and therefore the volume of aqueous humor. This reduces IOP and improves optic perfusion pressure reducing the risk of optic nerve ischaemia. Carbonic anhydrase inhibitors also cause dilation of the blood vessels in the retina and optic nerve head (Saxena *et al*., 2002), (Leaf and Goldfarb, 2007).

The diuretic effect is achieved by reducing H^+ secretion and increasing excretion of Na^+, K^+, HCO_3^- and H_2O in the proximal tubule. Acetazolamide is also used to treat symptoms of mountain sickness which results from low O_2 pressure in arteries at higher altitudes. It does this by increasing pulmonary ventilation (Hassan *et al*., 2013).

Kiss *et al* studied the effect of acetazolamide induced cerebral and ocular vasodilation in humans is independent of nitric oxide. They found acetazolamide led to vasodilation in ocular and cerebral vessels (Kiss *et al*., 1999).

4.1.1 Side effects

Side effects include: malaise, fatigue, depression, weight loss, anorexia, and paraesthesia. These side effects are thought to be related to CO_2 retention leading to acidosis (Yano *et al*., 1998).

4.1.2 Metabolism

Although acetazolamide is available as topical drop, oral and IV preparations it is normally administered either orally or IV to counter significant elevations in IOP. Acetazolamide administered orally is absorbed rapidly from the gastrointestinal tract with a peak plasma concentrations occurring about 2 hours after administration. It has a plasma half-life of 4 hours and is excreted unchanged in urine (Diamox, 2015).

4.2 Aims

This study aims to explore the effect of orally administered acetazolamide on the prevention of the IOP rise associated with the Trendelenburg position.

4.3 Method

This study was reviewed and approval given by the University of Nottingham Research Ethics Committee (Ethics Reference No: C12022015 SoM NDDC TaPPs). The study was designed as a randomised double masked cross-over study.

4.3.1 Inclusion criteria

- Healthy volunteers aged 18 and above

4.3.2 Exclusion criteria

- Pre-existing eye conditions
- Pregnancy
- Intra-cranial lesions/pathology
- Inability to lie head-down

4.3.3 Randomisation procedure

The acetazolamide 500mgs tablets were placed in capsule covers and placebo capsules were prepared by Nottingham NHS Pharmacy Department. Computer randomisation was carried out and the appropriate medications were sealed into envelopes marked with the volunteer number and Day 1 or Day 2. This was done independent of the investigator carrying out the IOP readings on the study days. The generated computer list of randomisations was also placed in a sealed envelope.

4.3.4 Baseline Tests

Once written consent was obtained, a baseline eye examination was performed. This included intraocular pressure measurements using Goldmann's tonometer; central corneal thickness; Gonioscopy graded according to Scheie Classification System (Scheie, 1957); cup to disc ratio; and best corrected visual acuity. Tono-pen® XL applanation tonometer was also used to measure IOP whilst sitting and after lying

supine for 5 minutes. When the Tono-pen® XL applanation tonometer was used to measure IOP, three repeat measurements were taken at 5% accuracy and averaged. On both the control and intervention day all IOP measurements were taken using Tono-pen® XL applanation tonometer and taken in both eyes.

4.3.5 Intervention

On Day 1, a baseline IOP (1) was taken, Day 1's envelope was opened and the medication was administered. Both the volunteer and investigator were blinded to what was given. After 1 hour and 30 minutes, a repeat IOP was taken whilst sitting (2) and 5 minutes after lying supine (3). The bed was then tilted to a 17º head-down position for 4 hours. Repeat IOP measurements were taken 5 minutes after being in the Trendelenburg position (4) and then every 30 minutes (5-13). After 4 hours in the Trendelenburg position, the bed was returned to supine and after 5 minutes a repeat IOP measurement was taken (14). The patient was then sat up and after 5 minutes another IOP measurement was taken (15). The same protocol was followed on Day 1 and Day 2. Day 2 was carried out a minimum of 4 days after Day 1 to allow a washout period. Day 2 was commenced at the same time as Day 1 to avoid diurnal variation in IOP.

4.3.6 Statistical Analysis

A Statistical power analysis was performed for sample size estimation, based on data from Bucci *et al* who compared the effect of oral acetazolamide on IOP on 22 patients compared to no treatment. They detected a mean IOP 13.4 ± 2.5 (SD) mmHg after 4 hours compared to

IOP of 16.4 ± 2.5 (SD) mmHg in non-treatment group. With an alpha=0.05 and power=0.80, the projected sample size needed with this effect size (STATA 14.0) was n=8 (Centofanti *et al*.). We therefore chose to recruit 9 volunteers to our study.

This was a cross over trial so each volunteer was their own control. All measurements were taken in both eyes. For analysis, each eye was treated individually. On each study day, a baseline IOP was taken. The IOP measurements taken at each time point was subtracted from the baseline measurement taken at the start of the study day to give a 'change in IOP' at each time point. A comparison between the control and intervention was made using STATA 14.0 to perform student paired t-test and multilevel modelling (MLM) with mixed-effects repeated measures analysis. Multilevel modelling was conducted with 'change in IOP' as the primary outcome; and the baseline IOP, treatment, time point, and interaction of group time as covariate, was conducted to compare the treatment effect between groups across each time point was analysed using the MLM analysis with 95% confidence interval.

4.4 Results

Nine patients were included in this cross-over study (2 Male; 7 Female) with and average age of 54 years (range 21 to 76 years). Baseline IOP measured using Goldmann's applanation tonometer gave an average (±SD) IOP of 15.5mmHg (± 3.79). Baseline measurements taken after 5 minutes lying supine using a Tono-pen® XL gave a mean (± SD) IOP of

15.31 (± 4.13) mmHg. All the volunteers had open angles on gonioscopy, mean (± SD) corneal thickness was 558.94 (± 47.56) μm, and mean (±SD) cup to disc ratio was 0.37 (± 0.14).

Baseline IOP using a Tono-pen® XL applanation tonometer on the placebo day gave a mean (± SD) IOP of 14.06 (± 2.61) mmHg and on the acetazolamide day the mean (± SD) IOP was 14.9 (± 3.0) mmHg; MLM analysis (P > 0.05).

Time Point	**Event**	**Placebo Mean change from baseline (95% CI)**	**Acetazolamide Mean change from baseline (95% CI)**	**P Value**
3	**90 minutes after medication**	-0.24 mm Hg (-1.68, 1.199)	-1.13 mm Hg (-2.57, 0.311)	0.393
4	**5 minutes after supine**	0.81 mm Hg (-0.625, 2.255)	0.22 mm Hg (-1.217, 1.662)	0.569
5	**5 minutes after Trendelenburg position**	1.96 mm Hg (0.524, 3.403)	0.67 mm Hg (-0.773, 2.106)	0.212

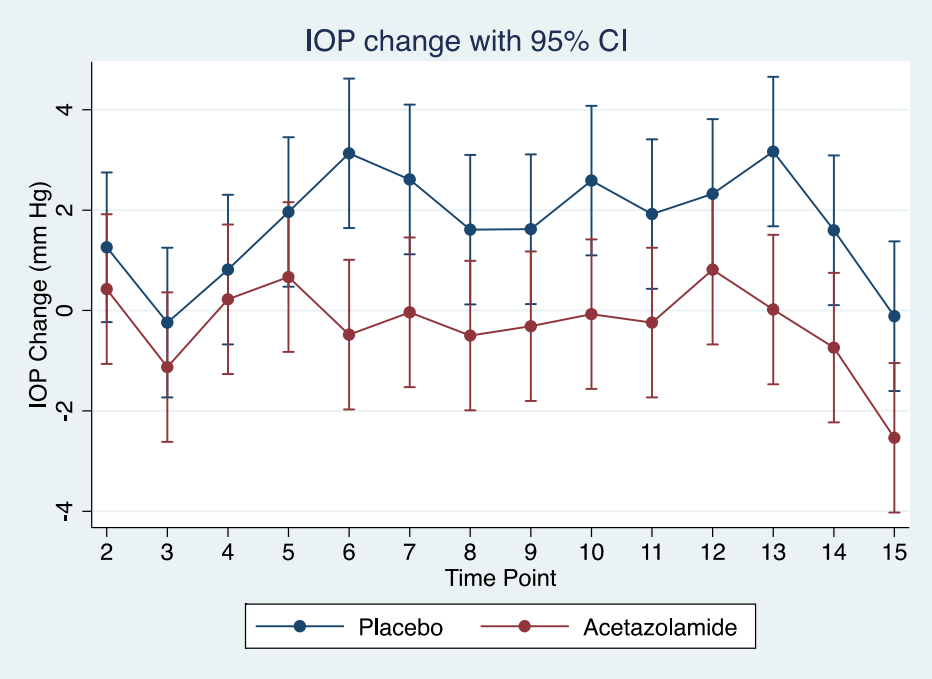
6	**30 minutes after Trendelenburg position**	3.13 mm Hg (1.691, 4.570)	-0.48 mmHg (-1.921, -0.959)	0.001
7	**60 minutes after Trendelenburg position**	2.61 mm Hg (1.171, 4.050)	-0.04 mm Hg (-1.476, 1.403)	0.011
8	**90 minutes after Trendelenburg position**	1.61 mm Hg (0.171, 3.050)	-0.50 mm Hg (-1.939,0.940)	0.042
9	**120 minutes after Trendelenburg position**	1.62 mm Hg (0.180, 3.060)	-0.31 mm Hg (-1.753, 1.126)	0.063
10	**150 minutes after Trendelenburg position**	2.59 mm Hg (1.149, 4.028)	-0.07 mmHg (-1.513, 1.366)	0.010
11	**180 minutes after Trendelenburg position**	1.92 mm Hg (0.482, 3.361)	-0.24 mm Hg (-1.680, 1.199)	0.037
12	**210 minutes after Trendelenburg position**	2.32 mm Hg (0.884, 3.763)	0.82 mm Hg (-0.626, 2.254)	0.146

13	**240 minutes after Trendelenburg position**	3.17 mm Hg (1.727, 4.606)	0.02 mmHg (-1.420, 1.459)	0.002
14	**Supine**	1.60 mm Hg (0.158, 3.037)	-0.74 mm Hg (-2.180, 0.700))	0.024
15	**Sitting**	-0.12 mm Hg (-1.554, 1.325)	-2.54 mm Hg (-3.976, -1.097)	0.020

TABLE 9: MEAN CHANGE FROM BASELINE IOP AT EACH TIME POINT WITH 95% CONFIDENCE INTERVALS. TIME POINT 1 IS THE BASELINE LEVEL, AND TIME POINT 2 WAS THE BASELINE WHILST SUPINE PRIOR TO TREATMENT SO ARE OMITTED FROM MLM ANALYSIS.

The effect of acetazolamide versus placebo at each time point was analysed with MLM analysis and presented in Table 9. Graph 1 shows the mean change in IOP at each time point with 95% CI. A statistically significant difference was noted between placebo and acetazolamide at 8 time points: 30 minutes after Trendelenburg position (6); 60 minutes after Trendelenburg position (7); 90 minutes after Trendelenburg position (8); 150 minutes after Trendelenburg position (10); 180 minutes after Trendelenburg position (11); 240 minutes after Trendelenburg position (13); 5 minutes after being supine (after 4 hours Trendelenburg)

(14); and 5 minutes after sitting after the Trendelenburg position (15). (Table 1)



GRAPH 31: IOP CHANGE AT EACH TIME POINT WITH 95% CONFIDENCE INTERVALS. 2- SUPINE, 3-1.5HRS AFTER MEDICATION, 4-SUPINE, 5-TRENDELENBURG (5MINS), 6-TRENDELENBURG (30MINS), 7-TRENDELENBURG (60MINS), 8-TRENDELENBURG (90MINS), 9-TRENDELENBURG (120MINS), 10-TRENDELENBURG (150MINS), 11-TRENDELENBURG (180MINS), 12-TRENDELENBURG (210MINS), 13-TRENDELENBURG (240MINS), 14- SUPINE, 15- SITTING. (TIME POINT 1 IS OMITTED ON THE X-AXIS AS THIS WAS THE BASELINE IOP)

4.5 Discussion

The results of our study do show that IOP does increase whilst in the Trendelenburg position. The mean maximum IOP rise of 3.17 mmHg

occurred after 4 hours on the placebo day. After acetazolamide, there was only a small increase after 4 hours of 0.02mmHg (P=0.002).

The IOP change from baseline following the acetazolamide ranged from 0.82 mmHg to -2.54 mmHg. On the Placebo day, the IOP change ranged from 3.17 mmHg to -0.24 mmHg. The increases that occurred whilst in the Trendelenburg was in healthy volunteers without pre-existing eye conditions. This increase would potentially be of significance in patients with pre-existing conditions such as glaucoma. Patients undergoing laparoscopic surgery have the added effect of the pneumoperitoneum. This also increases central venous pressure which could further increase IOP (Grosso *et al*., 2013).

Due to the absence of venous valves, episcleral venous pressure is directly correlated to changes in CVP. Any changes in CVP translate into changes of ocular venous pressures and therefore affect IOP (Grant *et al*., 2010). Consequently, any change in episcleral venous pressure can also affect IOP by changing the volume of aqueous humor. Abnormally high IOP can lead to death or degeneration of light sensitive and signal transmitting tissues within the eye leading to partial or complete vision loss (Goel *et al*., 2010).

Studies have shown Trendelenburg or prone positioning increase orbital venous pressure leading to congestion in the choroid, ultimately increasing IOP. Conversely, positions which reduce CVP such as reverse Trendelenburg position, can decrease IOP (Ozcan *et al*., 2004, Kiel, 1994, Grant *et al*., 2010).

On the placebo day, after the volunteer was sat up (10 minutes after spending 4 hours in the Trendelenburg position), IOP returned to below baseline level. This can be of clinical importance for patients undergoing laparoscopic surgery in the Trendelenburg position. Though the IOP rises whilst in this position, by placing the patient in a head-up or supine position may help reduce IOP.

Acetazolamide works by interfering with the sodium pump reducing the osmolality of aqueous humor, therefore reducing the volume of aqueous humor. This reduces IOP and improves optic perfusion pressure reducing the risk of optic nerve ischaemia. Carbonic anhydrase inhibitors also cause dilation of the blood vessels in the retina and optic nerve head, further improving optic nerve perfusion (Saxena *et al*., 2002). Carbonic anhydrase inhibitors can reduce aqueous humor formation by 20-40% without significantly reducing flow. In patients with normal/low IOP, carbonic anhydrase inhibitors have limited effect on IOP (Centofanti *et al*., 1997). This is important as IOP has been shown to be reduced when in the supine position after general anaesthetic. The balance

between the increase in IOP that may occur when in the Trendelenburg position and the reduction in IOP that occurs following general anaesthetic is likely to play an important role in the net ocular perfusion pressure.

Joo *et al* looked at the effect of a dexmedetomidine (α-2 agonist) infusion compared to a saline infusion in patients undergoing laparoscopic robotic surgery requiring the Trendelenburg position (Joo *et al*., 2016). They found after 4 hours in the Trendelenburg position, the placebo group had a rise of 11.3 mmHg compared to 4.2 mmHg in the dexmedetomidine infusion group ($P<0.003$). Dexmedetomide reduces IOP by aqueous humor production and causing vasoconstriction of afferent vessels in the ciliary body. It also promotes aqueous humor drainage by decreasing vasomotor tone in the ocular drainage system. This study used an infusion due to the relatively short half-life of 2 hours. For our study, acetazolamide was the drug of choice for reasons including: readily available; limited IOP lowering effects on patients with normal/low IOP (Centofanti *et al*., 1997); longer plasma half-life; and is cost effective (pack of 112 250mgs tablets costing £15.22) (Britain, 2014).

4.5.1 Limitations

There are limitations to this study which we attempted to overcome in the study design. The cross over design made each volunteer their own control. The study was randomised to commence with either the placebo or acetazolamide to prevent study bias and the volunteer and investigator were both masked to prevent investigator bias in the results.

A change in IOP was used for analysis to account for variation in baseline IOP on both days.

The main limitation of this study is that although there was an elevation in IOP associated with the adoption of the Trendelenburg position this was small compared to elevations noted in live surgical situations. It is likely therefore that the tilting of patients during surgery is only part of the mechanism accounting for IOP elevations and that there is a significant contribution to IOP elevation by the surgically induced pneumoperitoneum (Grosso *et al*., 2013). While the results of our study are positive it remains to be seen whether the effect of acetazolamide would be sufficient to dampen IOP elevations when they are significantly higher than those recorded in this study. The evidence in the literature suggests that acetazolamide is an effective medication for reducing elevated IOP and indeed it is the primary medication used to control the highly elevated IOP associated with sight threatening angle closure glaucoma (King *et al*., 2013).

Further studies are required to explore the value of acetazolamide in those undergoing surgical intervention and the value of IV acetazolamide which may be more appropriate in a surgical setting needs to be evaluated.

This study was designed to investigate if acetazolamide is an effective method of reducing the IOP rise that occurs during laparoscopic colorectal surgery. The results indicate that acetazolamide is effective at counteracting the rise that occurs due to the Trendelenburg position which is routinely used during laparoscopic colorectal resections to provide the surgeon good visualisation of the operative field.

4.6 Conclusion

This study showed IOP increases whilst in the Trendelenburg position. This increase can be effectively reduced with the use of acetazolamide. This may be an indication of important therapeutic value in prevention of Trendelenburg related IOP elevation during laparoscopic colorectal surgery.

Chapter 5 : Incidence of short and long term POCD following laparoscopic colorectal surgery

Abstract

Background

Postoperative cognitive dysfunction (POCD) is defined as a new cognitive impairment arising after surgical intervention. Cognitive function can be assessed using validated cognitive function tests including: N Back, Stroop; and Lexical Decision Making Task.

There is some concern that prolonged head-down positioning during laparoscopic colorectal surgery may cause POCD. Patients with POCD may experience prolonged hospitalisation and longer recovery returning to their normal level of functioning.

Aim

To assess percentage of short or long-term POCD following laparoscopic colorectal surgery.

Methods

Patients undergoing laparoscopic colorectal surgery were recruited. Cognitive tests including: 1,2 and 3 back, lexical decision making task and stroop task were carried out pre-operatively and repeated Day 1, and minimum 3 months post-operatively. For Day 1 the baseline was subtracted from Day 1 results for each test. This result was the divided by the standard deviation of the control group to give a Z score. A large positive Z score (>1.96) showed a deterioration in cognitive function from baseline for accuracy, and a large negative Z score (> -1.96) for

response time. (Abildstrom *et al*., 2000) An individual Z score of 1.96 or more was defined as cognitive dysfunction.

Results

Forty-six patients were recruited (26 males, 24 female), mean age 66years (SD± 5.18). Of which 55.4% had POCD on Day 1; and 37 patients completed long-term follow up of which 31.6% had POCD.

Conclusion

This study does show a significant number of patients develop both long and short term POCD following laparoscopic colorectal surgery.

5.1 Introduction

Long-term cognitive dysfunction is defined as POCD lasting more than 3 months. Patients affected by POCD may experience delayed transfer from the intensive care unit, prolonged hospitalisation and a longer recovery before returning to their normal level of functioning (Hudetz *et al*., 2010). Cardiac and major orthopaedic surgery are associated with persistent POCD in 50% of patients. Along with this, other non-modifiable risk factors include age, pre-existing dementia, and genetic risk factors that overlap with neurodegenerative disorders (e.g. Alzheimer's disease) include the apolipoprotein E gene. A higher education status has been shown to have a protective effect against cognitive decline at 1 week (Nadelson *et al*., 2014, Pratico *et al*., 2005).

5.2 Aim

The aim of this study was to assess the percentage of patients suffering with long and short-term POCD following laparoscopic colorectal surgery.

5.3 Methods

This was a prospective clinically based observational study. The study was reviewed and approved by the Northampton Research Ethics Committee (protocol number: 11GA019) and undertaken in accordance with the tenets of the Council of Helsinki.

5.3.1 Patient Population

All patients undergoing planned laparoscopic colorectal resection under the colorectal surgery service at Nottingham University Hospital were

invited to participate in the study. Those expressing an interest to participate were given a patient information leaflet and patients who were willing to participate signed a consent form prior to any study interventions.

5.3.1.1 Inclusion Criteria

- Patients undergoing laparoscopic colorectal surgery
- Aged 18 years and over

5.3.1.2 Exclusion Criteria

- Patients with a history of severe dementia
- Unable to read or understand English

5.3.2 Baseline Data and Tests

For each patient included in the study, demographic data including gender, age, smoking history, co-morbidities and medication history was collected. Practice tests carried out until the test rules were understood. Baseline cognitive function tests including mini mental state examination (MMSE), n-back (including 1, 2, and 3-back), Stroop, and lexical decision making tasks were carried out on all patients that agreed to take part.

5.3.3 Day of Surgery

On the day of surgery, the angle of tilt of the operating table was measured at the following time points: after induction of general anaesthetic; at the start of surgery after pneumoperitoneum created; every hour after the start of surgery; any time the table was tilted; and at

the end of surgery. The timings of these readings were documented along with the angle of the table tilt; positive end expiration pressure; CO_2 level; mean arterial pressure and pulse rate.

The following anaesthetic protocol was followed: general anaesthesia with either spinal or thoracic anaesthesia was given. Spinal anaesthesia consisted of intrathecal diamorphine (up to 500 mcgs) and bupivacaine (up to 20mgs). Epidural anaesthesia was maintained with 0.125% levobupivocaine & fentanyl 4mcgs/ml. Induction of general anaesthesia included midazolam (25-50mcgs/kg), remifentanyl (0.5-1 mcg/kg) or fentanyl (1-2 mcgs/kg), propofol (1-2.5mgs/kg) and neuromuscular blockade with either rocuronium or atracurium was given. Anaesthesia was maintained with Intra-operatively target controlled remifentanyl infusion at (0.05-2.0 mcg/kg/min) and oxygen/air/desflurane.

Following surgery, the same cognitive function tests were carried out on Day 1 post-operatively and Day 2 post-operatively. For patients who were willing to take part, the cognitive function tests were repeated a minimum of 3 months after surgery.

For further analysis, patients undergoing a right-sided colorectal procedure were placed in Group 1, and those undergoing left-sided procedures were placed in Group 2.

5.3.4 Statistical analysis

For analysis, a control group was used to calculate a 'normal' standard deviation. The control group carried out the tests 3 times on day 1. The 3rd test on day 1 was taken to be the baseline results. The tests were repeated on Day 2. The accuracy and response time on Day 2 was subtracted from the baseline tests on Day 1 and a standard deviation for each test was calculated.

For Day 1 the baseline was subtracted from Day 1 results for each test. This result was the divided by the standard deviation of the control group to give a Z score. A large positive Z score showed a deterioration in cognitive function from baseline for accuracy, and a large negative Z score for response time. (Abildstrom *et al*., 2000) An individual Z score of 1.96 or more was defined as cognitive dysfunction. This analysis was repeated for all the tests and for Day 2 post-operative day and long-term data collection.

For secondary data analysis, multiple logistics regression analysis was used to investigate association between risk factors and POCD. We looked at side of colorectal procedure; age; gender; ASA grade; length of surgery; tilt AUC; maximum head down tilt; blood loss; and maximum pneumoperitoneum pressure.

To compare group 1 (right-sided colectomies) with Group 2 (left-sided and sub-total colectomies) a Fisher exact test was used. This test was also used to compare patients with an AUC < 500 versus AUC ≥ 500.

Area under the curve (AUC) was calculated by multiplying degree of head-down tilt by the time spent in that position in minutes, if the table was in the head-up position, this value would be negative, (negative y-axis portion of graph Figure 21; section Chapter 0). All these were added up to give a cumulative tilt AUC in degrees X minutes. With this calculation method, anytime spent in the head-up position gave a negative value which was effectively 'subtracted' from the total AUC when added to the portion of the curve where the patient was in the Trendelenburg position.

5.4 Results

Of the 50 patients initially recruited to the study, 2 patients withdrew their consent on the day of surgery, and 1 withdrew their consent day 1 post-op prior to the tests being carried out. This left a total of 47 patients who completed the baseline tests and the tests on Day 1 post-op. Before the tests on Day 2, a further 4 patients withdrew their consent which left a total of 43 patients on Day 2 post-op. The long-term tests were carried out a minimum of 3 months post-operatively. By this time point a further 6 patients were either lost to follow-up or withdrew their consent. Table 1 is a summary of the demographic data of the patients included in our study.

Gender		
Male	n = 26	
Female	n = 24	
Age (years)	66.0 (±16.64) years	
BMI	27.2 (±5.18)	
ASA Grade		
ASA I	n = 3	
ASA II	n = 42	
ASA III	n = 2	
Operation		
Laparoscopic Right Hemicolectomy	22	
Laparoscopic Anterior Resection	15	
Laparoscopic Hartmann's	1	
Laparoscopic Subtotal colectomy	4	1 converted to open
Laparoscopic panproctocolectomy	1	
Laparoscopic completion proctectomy and ileoanal pouch	1	Converted to open
Extralevator abdominoperineal resection	1	
Operative Time (minutes)		
<100	n = 5	

100-199	n =22	
200-299	n = 14	
300-399	n = 3	
400-499	n = 4	
>500	n = 2	
Length of Stay (days)		
< 3	n = 2	
3-5	n = 24	
6-10	n = 15	
>10	n = 8	
Trendelenburg Tilt		
< 14^0	n = 18	
14-20^o	n = 19	
>20^0	n = 8	
Blood loss		
<100mls	n = 32	
100-500mls	n = 10	
>500mls	n = 8	

TABLE 10: SUMMARY OF DEMOGRAPHIC DATA OF PATIENTS

TABLE 11 and Figure 32 show the percentage of patients who suffered with POCD.

	Normal	POCD	% POCD
Day 1	21	25	55.4%
Day 2	32	12	27.3%
Long-Term	26	12	31.6%

TABLE 11 POCD AT EACH TIME POINT POST-OP USING THE ISPOCD METHOD OF ANALYSIS (ABILDSTROM ET AL., 2000).

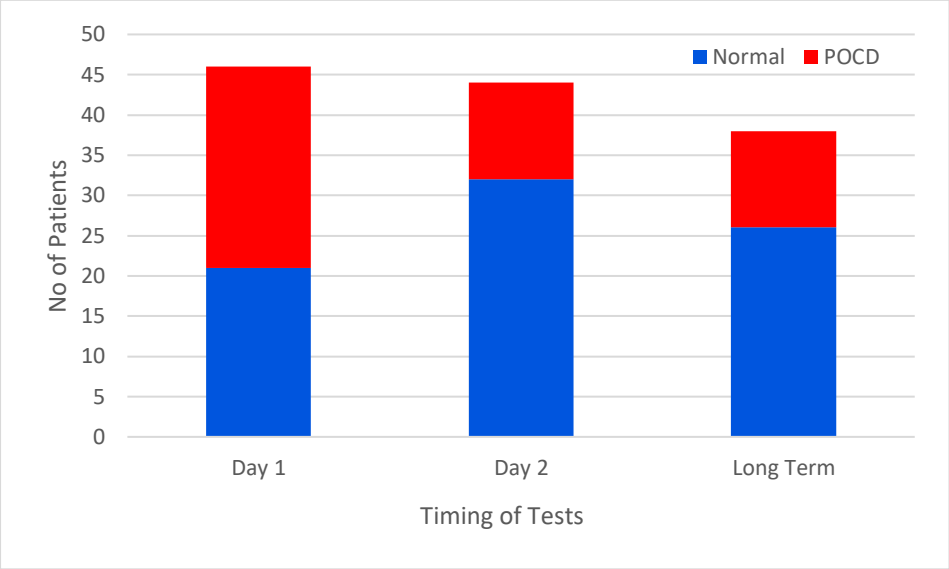


FIGURE 32 PATIENTS WHO TOOK PART IN COGNITIVE TESTING WITH A DECLINE IN COGNITIVE FUNCTION BY 2 STANDARD DEVIATIONS.

A logistics regression test was carried out on the average 'change in accuracy' for each patient on Day 1, Day 2 and long term follow up to assess the effect of type of surgery; age; gender; ASA; length of surgery; tilt AUC; maximum head down tilt; blood loss and maximum pneumoperitoneum pressure on long and short term POCD.

Table 12, Table 13 and Table 14 are a summary of comparison between various groups for Day 1 post-op, Day 2 post-op and long-term follow-up. On Day 1 and Day 2, Age was a significant risk factor. Along with age on Day 2, ASA grade, tilt AUC, and pneumoperitoneum pressure were all significant risk factors for POCD.

Change in CF	Co-Efficient (95% CI)	P-Value
Group	5.53 (-2.17, 13.23)	0.15
Age	**-0.21 (-0.40, -0.02)**	**0.03**
Gender	-5.05 (-10.28, 0.18)	0.06
ASA	5.59 (-3.74, 14.93)	0.23
Length of surgery	-0.0005 (-0.01, 0.01)	0.94
AUC (Tilt x time)	0.0005 (-0.00, 0.00)	0.22
Max head down tilt	-0.37 (0.40, 3.87)	0.17
Blood loss	-0.00 (-0.13, 0.01)	0.49
Max Pneumoperitoneum pressure	2.14 (-3.74, 14.93)	0.23

TABLE 12 LOGISTIC REGRESSION ANALYSIS FOR DAY 1

Change in CF	Co-Efficient (95% CI)	P-Value
Group	1.84 (-6.83,10.51)	0.67
Age	**-0.23 (-0.45, -0.01)**	**0.045**
Gender	-5.29 (-10.72, 0.15)	0.06
ASA	**10.51 (0.45, 20.56)**	**0.04**
Length of surgery	-0.001 (-0.01, 0.01)	0.93
AUC (Tilt x time)	**0.003 (-0.001, 0.006)**	**0.02**
Max head down tilt	-0.33 (0.88, 0.22)	0.23
Blood loss	-0.001 (-0.01, 0.01)	0.82
Max Pneumoperitoneum pressure	**1.53 (-0.29, 0.30)**	**0.04**

TABLE 13 LOGISTIC REGRESSION ANALYSIS FOR DAY 2

Change in CF	Co-Efficient (95% CI)	P-Value
Group	-3.90 (-15.78, 7.87)	0.50
Age	-0.10 (-0.42, 0.22)	0.52
Gender	-3.90 (-9.12, 8.44)	0.94
ASA	8.74 (-11.27, 28.75))	0.06
Length of surgery	-0.001 (-0.06, 0.06)	0.98
AUC (Tilt x time)	0.004 (-0.06, 0.06)	0.06
Max head down tilt	-0.84 (-1.72, 0.05)	0.06
Blood loss	-0.0002 (-0.01, 0.01)	0.97
Max Pneumoperitoneum pressure	1.84 (-1.72, 0.05)	0.06

TABLE 14 LOGISTIC REGRESSION ANALYSIS FOR LONG-TERM DATA

Figure 33 and Figure 34 show the average accuracy for each test and average response time for each test at each test point respectively.

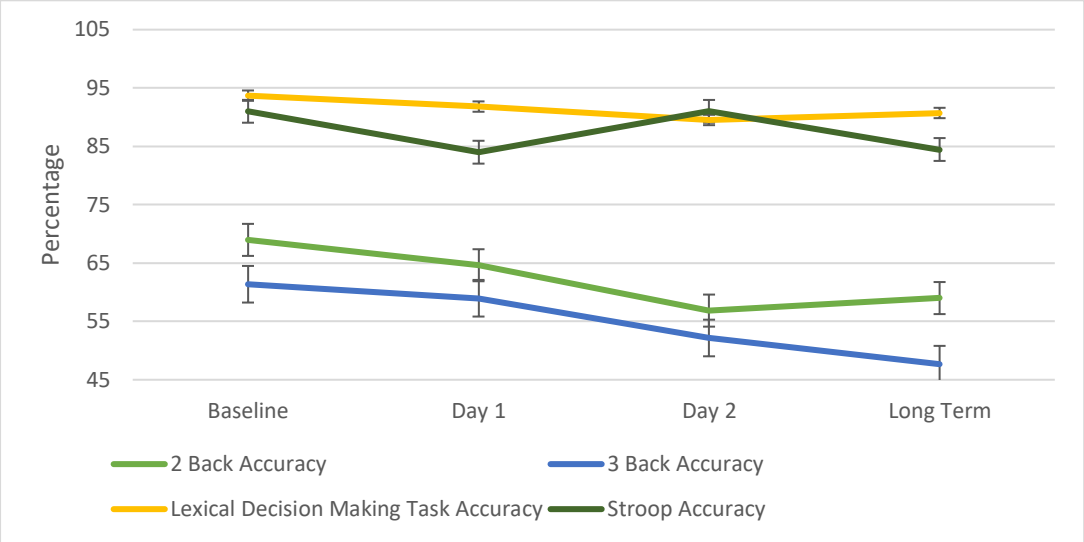


FIGURE 33 COMPARISON OF AVERAGE ACCURACY LEVELS AT EACH TIME POINT BETWEEN EACH TEST.

FIGURE 34 COMPARISON OF AVERAGE RESPONSE TIMES AT EACH TIME POINT FOR EACH TEST

	Group 1 (%)	Group 2 (%)	Fisher (P value)
Day 1			
Normal	12 (26.1%)	15 (32.6%)	0.765
POCD	10 (21.7%)	9 (19.6%)	P > 0.05
Day 2			
Normal	15 (34.9%)	16 (37.2%)	0.745
POCD	5 (11.6%)	7 (16.3%)	P > 0.05
Long-term			
Normal	12 (31.6%)	14 (36.8%)	1
POCD	6 (15.8%)	6 (15.8%)	P > 0.05

TABLE 15 GROUP 1 VERSUS GROUP 2 AT EACH TIME POINT

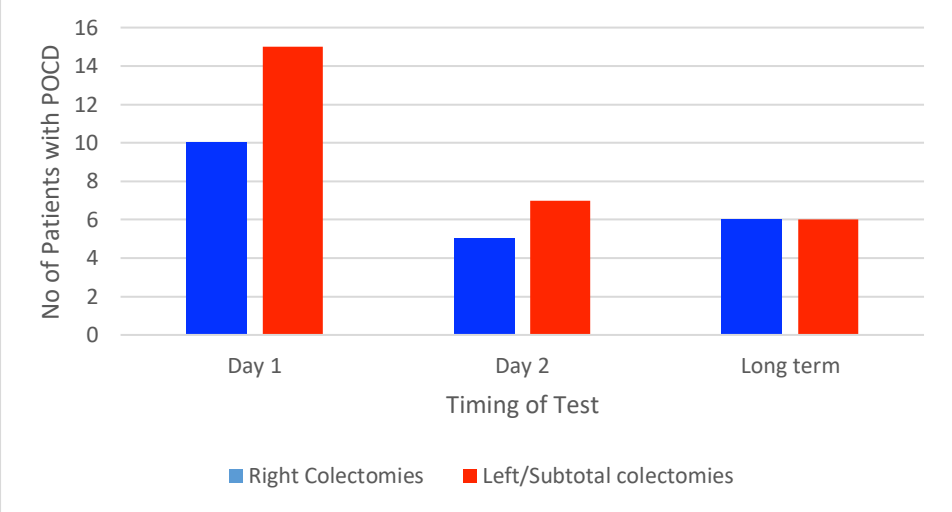


FIGURE 35 SHOWING GROUP 1 VERSUS GROUP 2 AT EACH TIME POINT

Table 15 and Figure 34 show a comparison of right-sided colectomies versus left-sided and subtotal colectomies. The percentage of patients with POCD at each time point were compared with a fisher exact test at each time point.

	AUC <500 (%)	**AUC ≥ 500 (%)**	**Fisher (P value)**
Day 1			
Normal	11 (23.9%)	10 (21.7%)	0.553
POCD	10 (21.7%)	15 (32.6%)	P > 0.05
Day 2			
Normal	13 (30.2%)	18 (41.9%)	1
POCD	5 (11.6%)	7 (16.3%)	P > 0.05
Long-term			
Normal	13 (34.2%)	13 (34.2%)	1
POCD	6 (15.8%)	6 (15.8%)	P > 0.05

TABLE 16 COMPARISON OF COGNITIVE DECLINE IN AUC < 500 VERSUS AUC ≥ 500 AT EACH TIME POINT

Table 16 shows a comparison AUC < 500 versus AUC ≥ 500. The percentage of patients with POCD at each time point were compared with a fisher exact test at each time point.

5.5 Discussion

This study showed that anaesthesia and laparoscopic colorectal surgery does cause cognitive decline. Cognitive assessment on post-operative

Day 1 post-operative showed 55.4% of patients had POCD, 27.3% had POCD on Day 2 and in our long-term assessment, 31.6% of patients had POCD.

Wang *et al* found that patients who received intravenous opioids (patient controlled analgesia) were more likely to develop POCD than those who only received oral analgesia (Wang *et al*., 2002). All patients included in our study received a PCA post-operatively. Zhi *et al* found a combination of remifentanil and propofol induce cognitive decline after anaesthesia (Zhi *et al*., 2016). Both of which were given as part of the GA protocol.

The percentage of patients with POCD was compared between laparoscopic right hemicolectomies and laparoscopic left-sided/subtotal colectomies. Patients undergoing right-sided resections were positioned supine, whereas the left-sided and subtotal resections were positioned in Lloyd-Davis. Right hemicolectomies also had a shorter operative time and spent less time in Trendelenburg position. On Day 1, 45.5% of the right hemicolectomy patients had POCD compared to 62.5% in the left/subtotal colectomy group and Day 2, 25% versus 30.4% respectively. Though not statistically significant, this difference in percentage of patients with POCD did not translate in the long-term assessment of POCD.

Previous studies including the ISPOCD1 trial (Moller *et al*., 1998) have suggested age to be a significant risk factor for POCD (Rundshagen, 2014), our results also showed age was a significant risk factor for short-term POCD. This did not translate in the long-term follow-up, where both younger and older than 65 year olds suffered a 31% POCD incidence. This could be due to the higher drop-out rates in those over 65 year olds; the 5 patients who dropped out/lost to follow-up between Day 2 and long-term were all over 65 years old.

Along with age as a risk factor for short-term POCD, tilt AUC and pneumoperitoneum pressure were also significant risk factors. Both increase CVP which along with decreasing CPP, it also increases hydrostatic and osmotic pressure which can lead to cerebral oedema and may contribute to POCD.

ASA grade was also a significant risk factor for short-term POCD. The ASA grade is based in co-morbidities (Daabiss, 2011):

- ASA I: Patient is a completely healthy fit patient.
    - Healthy, non-smoking, no or minimal alcohol use
- ASA II: Patient has mild systemic disease
    - E.g. current smoker, social alcohol drinker, pregnancy, obesity (30 < BMI < 40), well-controlled diabetes, hypertension, mild lung disease

- ASA III: Patient has severe systemic disease that is not incapacitating
    - E.g. poorly controlled diabetes or hypertension, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, end stage renal disease undergoing regularly scheduled dialysis, history (>3 months) of myocardial infarction, cerebrovascular accident, transient ischaemic attacks, or coronary artery disease/stents.
- ASA IV: Patient has incapacitating disease that is a constant threat to life
    - E.g. recent (< 3 months) myocardial infarction, cerebrovascular accident, transient ischaemic attacks, or coronary artery disease/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, disseminated intravascular coagulopathy, acute respiratory distress or end stage renal dysfunction not undergoing regularly scheduled dialysis.
- ASA V: A moribund patient who is not expected to live 24 hour with or without surgery
    - E.g. ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel

in the face of significant cardiac pathology or multiple organ/system dysfunction

The higher the ASA grade, the more significant the co-morbidities. This may have a confounding effect with the Trendelenburg tilt and pneumoperitoneum which may explain the increase in POCD incidence with higher ASA grades.

When the percentage of patients with POCD in Group 1 and Group 2 were compared at each time point, there was a higher incidence of patients with POCD in Group 2 Day 2 follow-up (16.3% versus 11.6%), but this was not the case in long-term follow-up (15.8% had POCD in both Group 1 and Group 2). However, this difference was not statistically significant. A similar comparison was made looking at POCD incidence in patients with a tilt AUC of < 500 versus ≥ 500. This comparison on Day 2 showed 16.3% had POCD versus 11.6% in the short-term. This did not occur in the long-term follow-up with POCD noted in 15.8% in both groups. Again, this difference was not statistically significant. Trendelenburg positioning leads to increased CVP followed by reduced outflow of venous blood from the brain. This increases hydrostatic pressure within the vasculature which pushes fluid into surrounding tissues resulting in cerebral oedema. This results in increased cerebrovascular resistance and reduced cerebral perfusion. This is a potential reason for the higher percentage of POCD in Group 2 and AUC ≥ 500 group on Day 2. The lack of distinction between the two groups at

long-term follow-up may be due to resolution of the cerebral effects that occurred due to Trendelenburg positioning.

5.5.1 Limitations

This was an observational study assessing short and long term cognitive function. Limitations of this study include a lack of agreed definition for POCD. I did try to overcome the learning effect by practice tests prior to baseline measurements. Patients also dropped out of our long-term POCD follow-up which may have affected the analysis of long-term data. All the patients who dropped out between Day 2 and long-term follow-up were over 65 years old.

5.6 Conclusion

This study does show a significant number of patients develop both long and short term POCD following laparoscopic colorectal surgery. Further studies to compare open versus laparoscopic data would add value to the studies already carried out.

Chapter 6 : A study assessing the effect of Trendelenburg positioning on Brain function and volume using MEG and MRI.

Abstract

Background

Trendelenburg positioning leads to an increase in CVP which leads to an increase in hydrostatic pressure potentially resulting in cerebral oedema. An increase in cerebral oedema may decrease cerebral perfusion pressure and therefore result in cognitive decline. Brookes *et al* looked at changes in electrical brain activity during working memory tasks using MEG and found an increase in theta oscillations and a decrease in beta oscillations in the medial frontal cortex with increased task difficulty. The n back tasks are used for assessing cognitive functions including: executive function and working memory.

Aim

The aim of this study was to assess for cognitive decline and cerebral oedema following Trendelenburg positioning by comparing performance in accuracy and response time on the n back task; change in brain wave activity on MEG whilst performing the n back tasks; and comparison of brain volume.

Method

A pilot study with fifteen healthy volunteers were recruited and practice n back tests were performed to reduce the effect of the learning curve in the n back tasks. They then performed the n back tasks in the MEG scanner lying supine (Run 1). A structural MRI was performed and the volunteers then lay head-down at 17^0 for 2 hours. This was then

immediately followed by a repeat MEG scan whilst performing the n back tasks (Run 2), and then an MRI immediately after this. A learning effect calculated using a control group was subtracted from Run 2 for the n back tasks for analysis.

Results

Fifteen volunteers completed the study, 5 male and 10 female average age of 34 years (range 21-81). Except for 0 back, there was a decrease in accuracy in Run 2. This was only statistically significant for 2-back ($p=0.0016$). There was also an increase in response time except for 2 back, but this was only statistically significant for 0-back ($p=0.0059$).

Comparing theta activity graphs in the frontal lobe for Run 1 and Run 2 did show an overall increase in theta activity, however overall activity graphs did not reveal an obvious difference in activity. Brain volume increased by 515.92mm^3 in Run 2, however this was not statistically significant ($P>0.05$)

Conclusion

The results of my pilot study although not statistically significant, suggest Trendelenburg positionmay lead to cerebral oedema and decreased cognitive function. Further clinical studies or volunteer studies with larger sample sizes would be beneficial to evaluate this further.

6.1 Cognition

Cognitive control refers to the set of processes that guide thought and action in accordance with current goals (Gazzaniga, 2009). It allows context and goal relevant information processing in the face of distraction and other stimuli.

6.1.1 Prefrontal cortex

The prefrontal cortex is the fundamental neural circuit that supports cognitive control. It can integrate the effect of past experiences to influence and optimise present behaviour.

There are four main sub-regions within the prefrontal cortex: ventrolateral; dorsolateral; frontopolar; and medial prefrontal cortex.

6.1.1.1.Ventrolateral prefrontal cortex (VLPFC)

Ventrolateral prefrontal cortex (VLPFC) includes the inferior frontal gyrus encompassing the pars orbitalis (anterior VLPFC), pars triangularis (mid VLPFC), and pars opercularis (posterior VLPFC). Dorsolateral prefrontal cortex (DLPFC) refers to the regions within the middle frontal gyrus. The ventral bound border is defined by the inferior frontal sulcas, and the dorsal by the superior frontal sulcus. Though anatomically distinct, lateral and medial PFC subregions have been shown to be interconnected with each other and with the medial and lateral temporal cortex and the posterior parietal cortex.

6.2 Attention

This refers to a set of mechanisms that allow people to selectively perceive and respond to events that are relevant to them. This forms a complex goal directed interaction of various complex brain networks that may be involved to respond to a variety of tasks that may include language, visual or motor stimuli. The dorsal frontoparietal attention network is what performs the final integration step and is therefore used for assessment. Dorsal frontoparietal activations have been observed during both visual and auditory stimuli in functional MRI studies (fMRI).

6.3 Memory

The medial temporal lobe functions include: visual perception; working memory, habit learning, recollection and familiarity, path integration, remote memory, and conscious awareness. The medial temporal lobe memory system includes the hippocampal region (hippocampus proper, dentate gyrus and subicular complex) and the perirhinal, entorhinal and parahippocampal cortices.

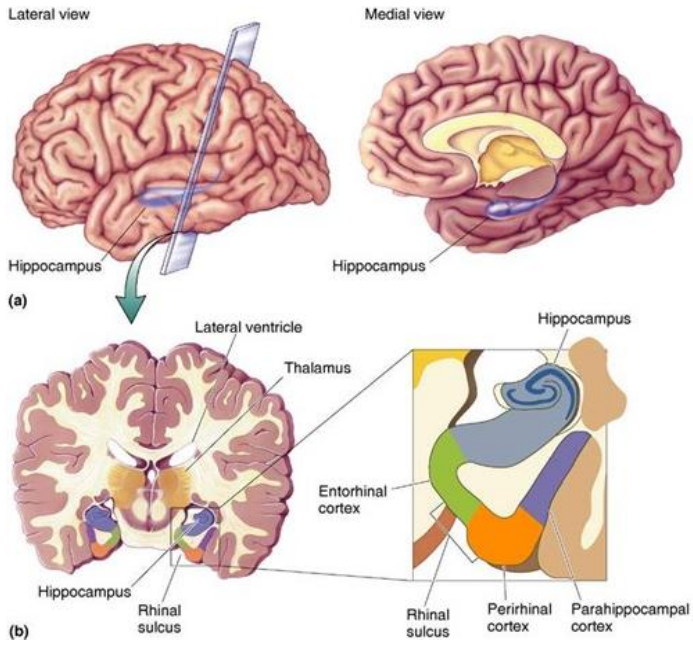


FIGURE 36 (REPRODUCED) MEDIAL TEMPORAL LOBE MEMORY SYSTEM (REPRODUCED (DALE PURVES, 2004)

Damage to the medial temporal lobe impairs only declarative memory which is the capacity to recollect facts and events. Non-declarative memory is a collection of memory abilities such as skills and habits, simple forms of conditioning and experiences that change the way we interact with the world. It is expressed through modifications in our actions as opposed to recall. Patients with hippocampal or hippocampal perirhinal cortex damage were found to have impaired performance on tests involving perceptual ability that involved discrimination between objects/shapes/faces (Lee *et al*., 2005).

6.3.1 Working Memory

The frontal cortex comprises one third of the brain and mediates working memory which is what we use for temporary storage (over seconds) and executive processes that utilise the contents of storage. Short-term

storage involves active maintenance of a limited amount of information and is mediated in part by the prefrontal cortex (Bunge *et al*., 2001, Gazzaniga, 2009, Miller and Cohen, 2001). Recent neuroimaging studies have identified that different frontal regions are activated for different kinds of information: Broca's area and left hemisphere supplementary and premotor areas store verbal content; the right hemisphere premotor cortex stores spatial information; and other areas of the prefrontal cortex stores object information. Patients with amnesia who have damaged medial temporal lobes have shown the ability to exhibit intact working memory. This suggests that working memory in independent to the temporal lobe (Smith and Jonides, 1999).

6.4 Executive Function

Executive function is mediated by the prefrontal cortex which has widespread connection with other brain areas and plays a crucial role in generating, maintaining and applying a task set (Gazzaniga, 2009, Smith and Jonides, 1999).

Executive function include (Smith and Jonides, 1999):

1. Attention and inhibition - focussing attention on relevant information and inhibiting irrelevant information;
2. Task management - scheduling processes in complex tasks that involves switching focused attention between tasks;

3. Planning – planning the sequence of actions required to accomplish the task;
4. Monitoring - updating and checking the contents of working memory to determine the next step;
5. Coding – allocating representations within working memory for time and place of appearance.

The medial prefrontal cortex which includes the anterior cingulate cortex acts to regulate cognitive control (Bunge *et al*., 2001). The anterior cingulate cortex is active in tasks involving conflict or uncertainty and also signals to the lateral prefrontal cortex to increase top-down bias of task appropriate information (Gazzaniga, 2009, De Pisapia *et al*., 2007, Bunge *et al*., 2001, Miller and Cohen, 2001). For example, the anterior cingulate cortex detects the presence of simultaneously active but competing stimuli such as the Stroop paradigm providing feedback signals to the lateral prefrontal cortex that up-regulates control (Gazzaniga, 2009, Cohen *et al*., 1990, Bunge *et al*., 2001). This suggests the anterior cingulate cortex is likely involved in resolution of cognitive conflict (Smith and Jonides, 1999).

Patients with prefrontal cortex lesions struggle to perform complex behaviours, especially those with multiple steps involved. They are prone to distraction by irrelevant environmental stimuli (Gazzaniga, 2009).

Neurons within the prefrontal cortex respond to cues that instruct a task and maintain this instruction throughout temporal delay in the absence of sensory stimuli (Bunge *et al*., 2001, Gazzaniga, 2009). The prefrontal cortex is important in tasks where cue guided behaviour must be flexibly changed over time. In the absence of cognitive control, automatic behaviours are activated by input cues. These behaviours can be innate and are inflexible reactions elicited by a particular stimulus and can be thought of as 'bottom-up' processing i.e. determined largely by sensory stimuli (Miller and Cohen, 2001). The prefrontal cortex controls signals to bias the flow of signals to favour task relevant signals and overcome task irrelevant signals (Cohen *et al*., 1990). This is known as 'top-down' processing and is also supportive of cognitive functions including selective attention, controlled retrieval of long-term memory, task switching, response inhibition and response selection (Miller and Cohen, 2001, Gazzaniga, 2009).

The dorsal-ventral hypothesis suggests the dorsal and ventral regions of the lateral prefrontal cortex mediate interactive forms of cognitive control. The dorsolateral prefrontal cortex support monitoring and manipulation of representations retrieved and maintained by the ventrolateral prefrontal cortex (Gazzaniga, 2009, Rugg *et al*., 2003). The dorsolateral frontal cortex has been shown to be activated in many functions that are required by the n-back task including holding spatial

information, monitoring and manipulating information within the working memory, response selection and employing strategies to facilitate memory (Owen *et al*., 2005). The mid-ventrolateral frontal cortex has also been shown to be activated during the n-back task. It carries out the cognitive task of 'selection, comparison, and judgement of stimuli held within short- and long-term memory (Owen *et al*., 2005). Patients with lesions within the mid-dorsolateral prefrontal cortex produce impairments in the ability to order information in working memory (Gazzaniga, 2009). Functional MRI studies have also shown an increase in activity in this area when the difficulty of a task is increased (Gazzaniga, 2009, Bunge *et al*., 2001), and when stimuli must be held within working memory and be reordered or updated (Gazzaniga, 2009, Demb *et al*., 1995). The ventrolateral prefrontal cortex is involved in controlled retrieval and selection of information from long-term memory (Gazzaniga, 2009).

The frontal pole cortex is consistently active during complex working memory tasks and during higher level cognitive tasks. For example, when task relevant information must be maintained in a pending state whilst ongoing subtasks are executed such as during the n-back task (Gazzaniga, 2009). The frontal pole cortex is engaged with tasks involving more than one discrete cognitive process such as remembering the rule along with simultaneously monitoring a series of stimuli. Such as in the n-back task, the participant must remember the value of 'n' along with remembering and processing the stimuli

presented. Multiple related cognitive functions can be carried out simultaneously successfully if they are coordinated. The frontal pole cortex is thought to be responsible for accurate coordination also known as hierarchical cognitive control (Owen *et al*., 2005).

The bilateral and medial premotor cortex are active during maintenance of visuospatial attention during working memory. This is of importance where delays are imposed between a stimulus and the response. For example, during the n-back task where the response is not determined by presence of a certain stimulus alone, but by the presence of an identical stimulus 'n' trials later (Gazzaniga, 2009, Owen *et al*., 2005).

Activation within the left dorsal aspect of the inferior parietal cortex are observed in contrast with working load where attention demands are high (such as higher n-back tasks) (De Pisapia *et al*., 2007). It is suggested that the dorsal inferior parietal cortex may be important in retaining temporal information, for attentively reactivating information in neural regions or for preparing for a given task (Owen *et al*., 2005).

The basal ganglia are thought to regulate prefrontal cortex mediated control processes. Current theories suggest that prefrontal cortex and basal ganglia interactions support working memory performance, and activation of basal ganglia prior to the onset of the working task is

predictive to some extent to which task-irrelevant information is successfully gated or denied processing.

There have been two different putative control networks identified: an anterior cingulofrontal operculum network and a frontoparietal network. These are suggested due to functional separation of task control and stimulus selection systems. The anterior cingulofrontal operculum network was defined based on three putative signals:

1. Sustained signal maintained throughout a block of trials
2. Transient signal at the start and end of a block of trials, possibly representing the loading and unloading of the tasks instructions
3. A transient signal representing an error.

The co-localisation of these three signals across a large number of different tasks to the same cingularopercular regions supports the theory that these regions form a functional network involved in high level functional control.

Whilst performing a task, the instructions are maintained by ‘working memory’. Working memory is short-term memory storage where information can be easily accessed and manipulated. Parietal regions

have shown load dependant activity which correlate with memory performance.

6.5 MEG

Magnetoencephalography (MEG) is a non-invasive brain imaging technique that records and maps magnetic fields first pioneered by Cohen in 1968 (Peter C. Hansen, 2010). It allows investigation of the brains basis of sensory processing, motor planning, cognition and social interaction (2012, Hari *et al*., 2010). At a cellular level, individual neurons within the brain have electrochemical properties that result in a flow of electricity through the cell.

6.5.1 How it works

MEG signals recorded at the scalp are generated by thousands of neurons generating activity at the same time. A sensory stimulus activates a small portion of the cortex (Peter C. Hansen, 2010). Chemical and electrical synapses are the main form of synaptic junctions. The main aim of the chemical synapse is to transmit a signal within the central nervous system. Within a chemical synapse, a neurotransmitter (such as: acetylcholine, norepinephrine, epinephrine, histamine, gamma aminobutyric acid (GABA), glycine, serotonin, and glutamate) is released from the pre-synaptic junction and binds to receptors on the post-synaptic junction. This either excites or inhibits the neuron. Electrical synapses conduct electricity from cell to cell by opening of fluid channels. Most of these consist of gap junctions that

allow free movement of ions across from one neuron to the next (Arthur C. Guyton, 2006).

The second is due to synaptic activation and is mediated by several neurotransmitter systems and results in a more prolonged change in membrane potentials. The action potential results in a change in intracellular potential from a negative to positive in milliseconds. It is this speed that allows travel of signal across multiple neurons with minimal loss in amplitude. Post-synaptic potentials can either be excitatory or inhibitory potentials dependent upon which neurotransmitters are released, which receptor is activated and their interaction with specific ionic channels and second messengers (Peter C. Hansen, 2010).

The pre- and post-synaptic terminals are separated by a synaptic cleft. The transmitter vesicles contain transmitter substances that either excite or inhibit the post-synaptic neuron. The mitochondria provide the adenosine triphosphate for synthesis of new transmitter substance. When an action potential spreads over the pre-synaptic terminal, depolarisation of its membrane causes a small number of vesicles to empty into the cleft. Dependent on which neuron receptors are activated determines if it is an inhibition or excitation of the post-synaptic neuron (Arthur C. Guyton, 2006).

The pre-synaptic membrane contains a large number of voltage-gated calcium channels. When an action potential depolarises the pre-synaptic membrane, the calcium channels open and calcium ions move into the

terminal and bind with special protein molecules on the inside surface of the pre-synaptic membrane, called release sites (Arthur C. Guyton, 2006).

The post-synaptic neuron membrane has cation and anion channels. The cation channels are lined with negative charge and attracts positively charged sodium ions to pass through but repels negatively charged ions. The anion channels allow chloride ions to pass through. When the transmitter activates the ion channel, it usually opens within a fraction of a millisecond. When the transmitter is no longer present, the channel closes rapidly. Due to this rapid response that occurs over milliseconds, the ion channels are not suited for providing prolonged post-synaptic neuronal excitation or inhibition. Prolonged post-synaptic neuronal excitation or inhibition is achieved by ‘second messenger’ chemical systems within the post-synaptic neuron (Arthur C. Guyton, 2006).

The resting potential of neurons is -65 millivolts. This is determined largely by the concentration difference of sodium, potassium and chloride ions within the extracellular fluid compared to within the neuron (Figure 37) (Arthur C. Guyton, 2006).

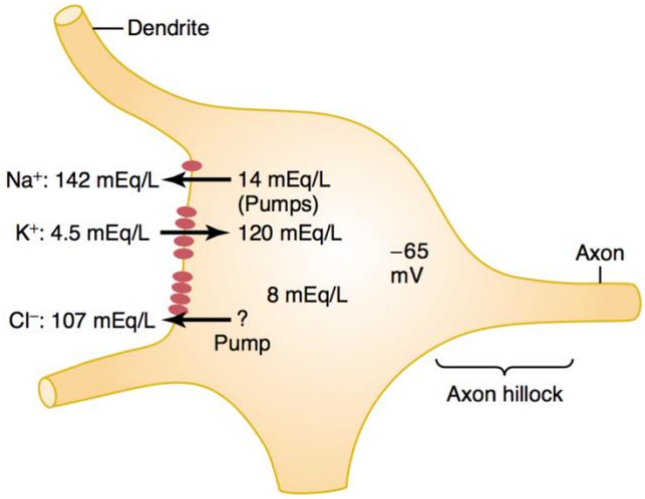


FIGURE 37: (REPRODUCED) DISTRIBUTION OF SODIUM, POTASSIUM AND CHLORIDE IONS ACROSS NEURON AND EXTRACELLULAR SPACE (ARTHUR C. GUYTON, 2006).

When an excitatory transmitter is released into the synaptic cleft, positive charge is increased by:

1. Sodium channels opening and positive electrical charges flowing to the interior of the post-synaptic cell raising the intracellular membrane potential towards the threshold level.
2. Reduced movement of chloride ions to the inside of the post-synaptic neuron or decreased diffusion of potassium ions to the outside.

Inhibitory transmitters occur due to increase in cell negativity by:

1. Chloride ion channels open on the post-synaptic membrane allowing rapid diffusion of negatively charged chloride ions from outside the post-synaptic neuron to the inside.

2. Increase in movement of potassium ions out of the neuron.

If both excitatory and inhibitory transmitters are released at the same time, the action potential threshold is not reached and therefore excitation does not occur.

The effect of this slow electrical current is an electromagnetic field. The magnitude of the magnetic field of each individual neuron is negligible, however, when tens of thousands are activated together in a specific area, a magnetic field that is measurable outside the head is generated (Hari *et al*., 2010). Even this does not exceed a few hundred-feme tesla ($^{10-}$15 T). For comparison, the earth has a magnetic field of $5x10^{-4}$ T (Singh, 2014). The flow of current leads to the generation of a magnetic field as per Fleming's right-hand rule (Figure 38).

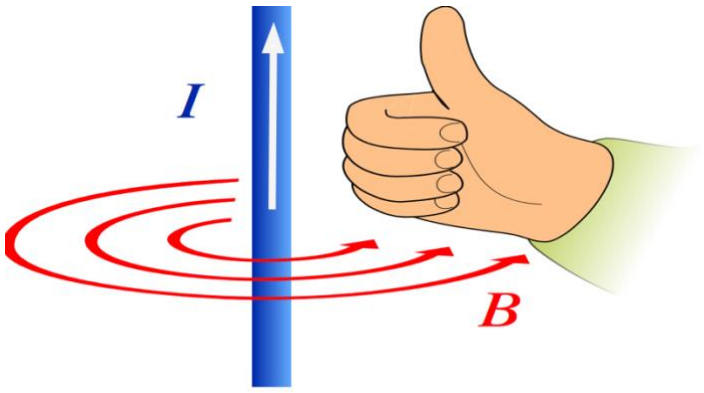


FIGURE 38: (REPRODUCED) RIGHT-HAND GRIP RULE (WIKIPEDIA, 2016B)

Right-hand grip rule shows the direction of current flow and the direction of the magnetic field. The strength of the electric current is measured in amperes. All currents generate a magnetic field around them. The magnetic field can be measured as the magnetising field measured in amperes or by the magnetic flux density which is measured in Teslas and is commonly called the magnetic field (Peter C. Hansen, 2010).

These signals are still quite small, a billionth of the earth's magnetic field, therefore MEG scanners require superconducting sensors - superconducting Quantum Interference Devices (SQUID) magnetometers. The SQUID sensors can pick up signals a few centimetres away and are placed within the helmet of the scanner (Figure 39) (2012).

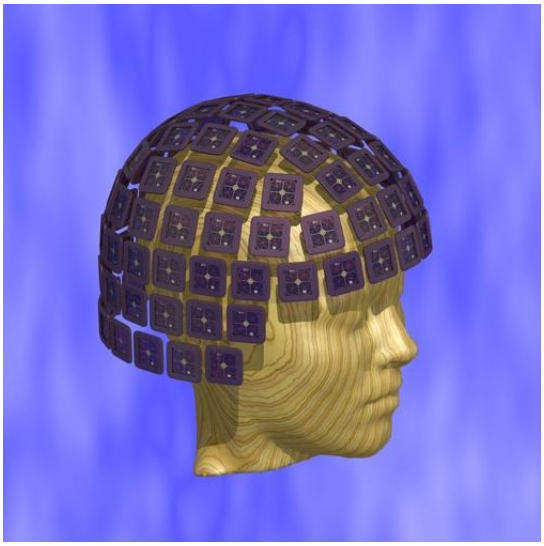


FIGURE 39 (REPRODUCED) SQUID SENSORS WITHIN MEG HELMET (2012)

We are surrounded by magnetic fields that are stronger than those produced by activated neurons, therefore the MEG recording is done within a magnetically shielded room made of mu-metal to reduce interference (2008). Magnetic fields are unaffected by the scalp, however, the signal does decrease the further away it gets (Singh, 2014).

$1/r^3$ (where r=distance) (Singh, 2014)

When neurotransmitters excite pyramidal cells, the electrical current that passes through produces a magnetic field (Figure 38). This magnetic field is influenced by other magnetic fields that occur within extracellular currents (Hashizume).

The SQUIDS are able to pick up signals from the activation of multiple neurons. The magnetic field is not picked up if the current is in the same direction away or towards the coil (Hashizume). The strongest signal is detected when the direction of current is perpendicular to the coil (Figure 40).

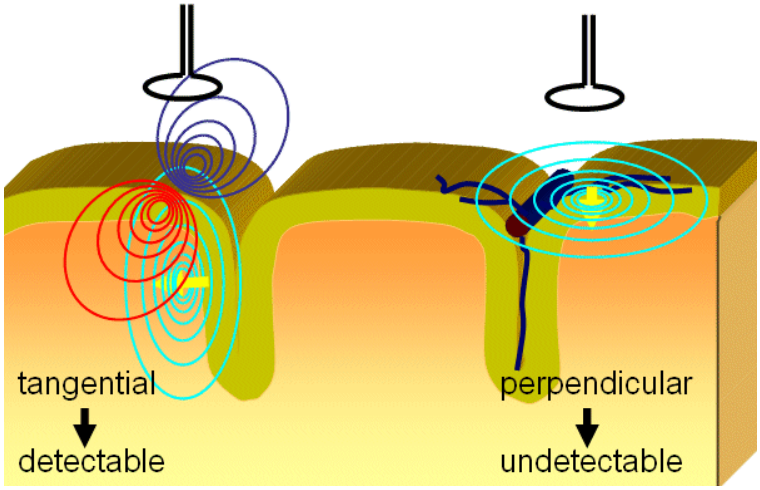


FIGURE 40: (REPRODUCED) SQUIDS AND DETECTION OF ELECTRICAL ACTIVITY DIRECTION (HASHIZUME)

The MEG provides temporal characteristics about brain activation within sub-millisecond precision. Unlike functional MRI which measures brain activity indirectly by recording the oxygenation of blood flowing near active neurons (BOLD). MEG and EEG are unrivalled in recording brain activity as it happens. With the addition of spatial accuracy with MRI brain images, it allows a true 3 dimensional reconstruction (Peter C. Hansen, 2010).

Prior to analysis, the MEG data needs to be processed to remove artefacts, filter the data and average the readings taken. The mathematics for which is complex and are therefore not explained here. Software programs have been designed to carry out the data processing prior to analysis.

Before MEG scanning can take place, the scanner should be checked as should the magnetic shielded room to allow optimal recording and minimal interference. This is also assured by taking a noise measurement of an empty room. This allows any changes within the magnetic environment and sensors to be picked up. If any of the sensors are faulty or there is magnetic interference within the empty room this can be dealt with before participants are scanned. This also allows the stimulus delivery system to be checked. This is done before the first MEG scan is carried out.

Along with preparing the scanner, prior to scanning, the participants also need to be guided and prepared. The participants need to be demagnetised. This includes removing all metal objects including hairpins, underwire bra, mascara, make up, clothing that may contain metal and any clothing that was worn in the structural MRI as this can magnetise clothes. Metal work in the body or mouth mean the participant cannot take part. Participants with certain hair dyes or tattoos may mean they cannot take part. Just prior to starting the scanning, checks are made to ensure minimal interference which includes blinking, chewing and breathing. If significant interference is noted during the initial checks this can be resolved prior to scanning.

To allow accurate co-registration of the structural MRI to allow

localisation of the MEG readings, a minimum of 3 coils are placed are placed and secured to avoid any movement whilst in the scanner (Figure 41).

FIGURE 41: LOCALISATION COIL POSITIONS. (GREEN COIL PLACED IN SAME POSITION AS RED ONE BUT ON LEFT SIDE)

These indicator coils are localised by using a digitising device that records the position of these coils in a 3D space. A minimum number of drawing points are made on the scalp in relation to the 3 localisation coils. These are then expressed on a head co-ordinate frame. This frame is then co-registered with the structural MRI (Figure 42). All readings taken by each SQUID within the MEG scanner is mapped in relation to the 3 localisation coils.

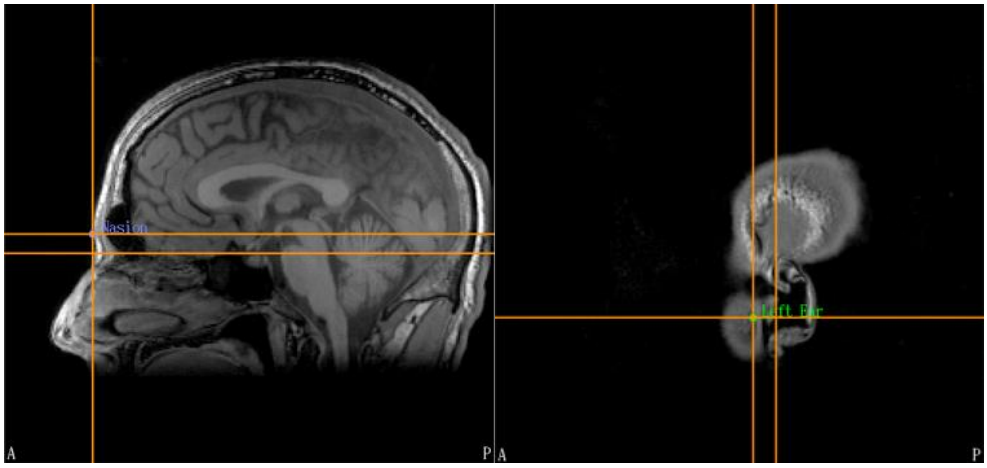


FIGURE 42 CO-REGISTRATION OF LOCALISATION COILS ON STRUCTURAL MRI

This also requires accurate positioning of the participant within the MEG scanner. As we were comparing two MEG scans, the 3 localisation coils positions were kept the same for both scans. As the participants were going to be lying head-down for the second scan, padding with hats and sponges were used to ensure limited head movement and more accurate positioning of the head within the MEG scanner during both scans.

Any movement of the participant would result in brain activity, it is therefore important to ensure the participants are comfortable before recording is started and the same finger is used to respond to the stimulus throughout all recording. The participant is also asked to keep eye movements to a minimum during the scan. A resting mark is therefore used during rest periods to focus the eye and all stimuli are presented at the same position on the screen. As they are in a magnetised closed room, a security camera and speaker are kept within the room with the participant. It allows the participant to communicate with the investigator if needed.

After the artefact checks are done (to ensure the participant is demagnetised prior to starting the scan), the head position with respect to the MEG. This is done by briefly energising each of the location coils.

These signals are captured by the MEG sensors and based on these signals, the coil locations are estimated in the MEG device coordinate systems. With help from the digitisation readings (3D digital image of the head), the transformation between the head and the MEG devise co-ordinate system is calculated.

Once the head position measurements are successful, MEG data collection can be started. Along with stimulus data collection, rest data collection is also carried out. This allows direct comparison between activity that occurred during the tasks compared to no activity. During the rest periods, the participant is asked to remain still and to reduce eye movements a focus screen with a dot in the centre is kept up for the participant.

6.6 Brain waves

Brain waves are brain activity of varying electrical activity. These change dependent on what the person is doing. In normal healthy people, most waves can be classified as: Gamma; Beta; Alpha; Theta; Delta.

6.6.1 Gamma waves

Gamma waves occur at 27Hz and above. They are associated with the formation of ideas, language and memory processing. Essentially, they are associated with learning. They are not present when asleep, but return when transitioning into a wakeful state (Neuro-programmer, 2006).

6.6.2 Alpha Waves

Alpha waves are rhythmical waves that have frequency between 8 Hz to 13 Hz (Arthur C. Guyton, 2006). They are present when awake but relaxed. In other words, when not processing much information. This state is naturally present when just waking up and just prior to sleeping. Alpha activity can be increased by closing your eyes (Neuro-programmer, 2006), but disappear when in deep sleep (Arthur C. Guyton, 2006).

Alpha activity has been connected with meditation. It is also thought to be present when recalling memories, when discomfort or pain is lessened and when stress and anxiety is reduced (Neuro-programmer, 2006). When the person's attention is directed to specific mental activity, the alpha waves are replaced with beta waves (Arthur C. Guyton, 2006).

6.6.3 Beta Waves

Beta waves have a frequency between 12 Hz to 27 Hz. They are asynchronous, higher frequency but lower voltage compared to alpha waves (Arthur C. Guyton, 2006). They are present when wide awake and alert. Beta activity is poorly understood, but helps improve emotional stability, energy levels, alertness and concentration (Neuro-programmer, 2006).

6.6.4 Theta Waves

Theta waves have a frequency between 3 Hz to 8 Hz. It is present during light sleep or extreme relaxation. It is a receptive state and has been

shown to be useful for hypnotherapy, as well as self-hypnosis (Neuro-programmer, 2006). They are also present during emotional stress, particularly during frustration or disappointment (Arthur C. Guyton, 2006).

6.6.5 Delta Waves

Delta waves have a frequency between 0.2 Hz to 3 Hz They are present during a deep, dreamless sleep. It is the slowest band of brainwaves. It is thought to be present when the body is healing itself and the person is in a complete state of unconsciousness (Neuro-programmer, 2006).

6.7 MRI

MRI is a non-invasive imaging modality that produces three dimensional anatomical images without the use of radiation. Instead it uses the protons found in living tissue to generate images (Bioengineering).

6.7.1 How it works

Hydrogen protons are found in abundance in water and fat. Even in living tissues, protons spin on their axis like small magnets. Within the body, these axes are randomly aligned.

The MRI has a strong magnetic field forcing all these axes to align. The higher the strength of the MRI (e.g. 1.5 T, 3T), the stronger the magnet and the better aligned the protons which therefore generate more detailed images. When a radiofrequency current is turned on, it stimulates the protons which then spin out of equilibrium. Once the radiofrequency is then turned off, the energy released as the protons

realign themselves within this magnetic field are picked up and images can then be generated (Bioengineering, Binder, 2011).

6.8 Aim

The aim of this study was to investigate if Trendelenburg positioning decreased cognitive function and lead to cerebral oedema.

- Outcome 1: Decrease in accuracy or increase in response time in n-back task.
- Outcome 2: Increase in Frontal lobe theta activity and decrease in beta activity
- Outcome 3: Increase in brain volume on MRI.

6.9 Methods

A Statistical power analysis was performed for sample size estimation, based on data from Brookes *et al* who compared the effect of increased task difficulty on MEG activity. They detected a mean accuracy for 1-back task as 98% ± 2 (SD) and 2-back test as 91% ± 8 (SD). With an alpha=0.05 and power=0.80, the projected sample size needed with this effect size (STATA 14.0) was n=10 (Brookes *et al*., 2011). We chose to recruit 15 volunteers to our study to allow for MRI changes as well as this could not be powered.

Fifteen healthy volunteers will be recruited who are aged 18 years and over.

6.9.1 Inclusion criteria:

- 18 years and over

6.9.2 Exclusions criteria:

- Cognitive impairment
- Inability to read or understand English
- Visual impairment
- Smokers
- Permanent metal piercings
- Permanent metal braces
- Metallic ink in tattoos/hair dye
- Pacemaker
- Any metal implants
- Under the age of 18
- Refusal to give written informed consent

6.9.3 Baseline Tests

If the volunteers meet the above criteria, written consent is then obtained.

FIGURE 43 N BACK IMAGES USED FOR THE TESTS

To avoid activation of emotional association with colours, or language or numbers as they may affect performance on the n back tests, the above symbols were used in the test. (Figure 43)

Each test is practiced 3 times to reduce the effect of the learning curve and ensure participants were clear on what was involved in the n back tasks.

6.9.3.1 N Back Task

For each test, an initial instruction screen was shown for 5 seconds explaining what the next task was.

Once the task commenced, a slide with a different shape in the centre was shown for 1 seconds followed by a rest screen for 0.5 seconds. A total of 40 image slides were shown for each task i.e. 40 trials per task.

Each task was followed by a 30 second rest period where a simple slide to keep the eyes focused was displayed.

6.9.3.1.1 Zero back

If the instruction screen had the following target:

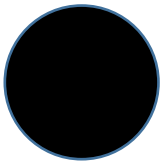


FIGURE 44 EXAMPLE OF SHAPE ON INSTRUCTION SCREEN FOR ZERO BACK TASK

Every time this image appeared in the following slides, it was the correct target for the zero back and the button on the keyboard should be pressed.

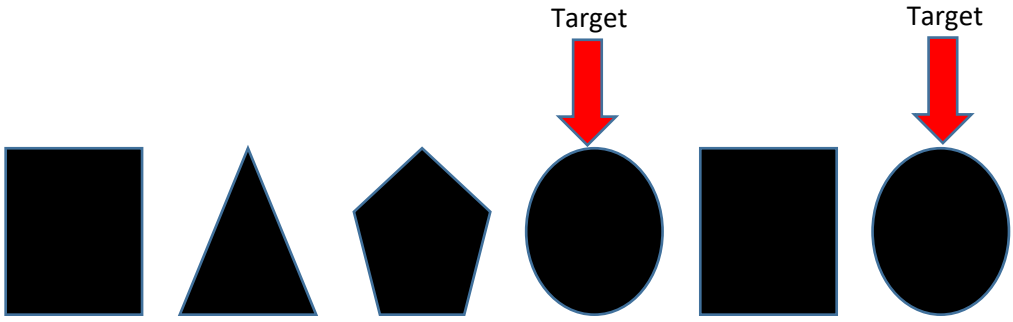
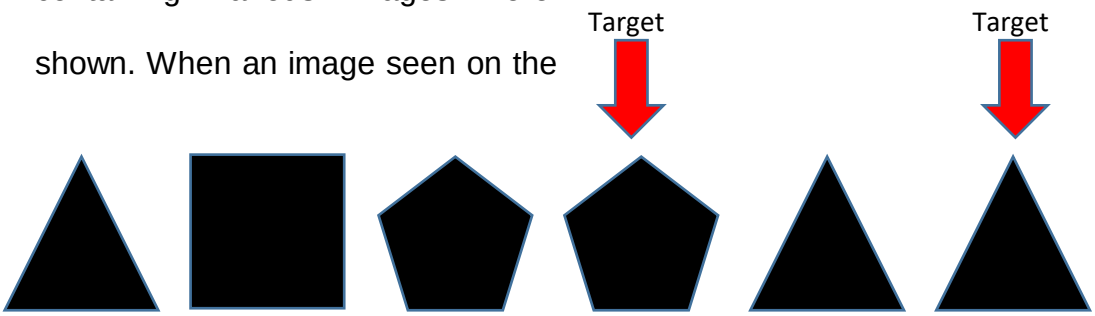


FIGURE 45 EXAMPLE OF ZERO BACK TASK WITH TARGETS IDENTIFIED.

6.9.3.1.2 One Back

If the instruction screen stated a one back task was to follow, slides containing various images were shown. When an image seen on the



screen was the same as that seen one image back, the keyboard had to be pressed.

6.9.3.1.3 Two Back

If the instruction screen stated a two back task was to follow, slides containing various images were shown. When an image seen on the screen was the same as that seen two images back, the keyboard had to be pressed.

FIGURE 46 EXAMPLE OF ONE BACK TASK WITH TARGETS IDENTIFIED

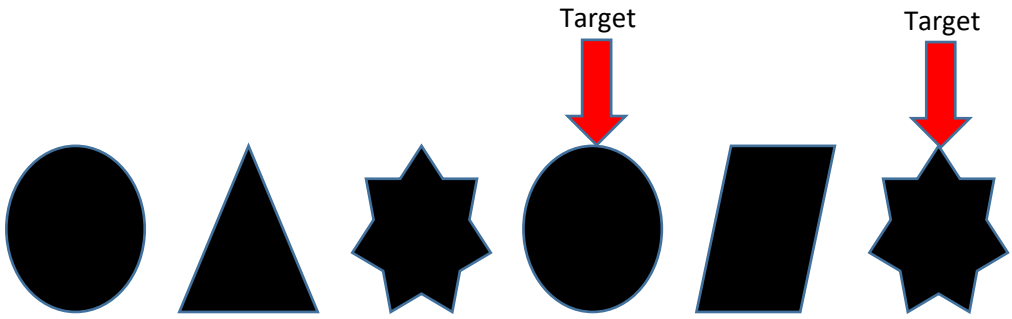
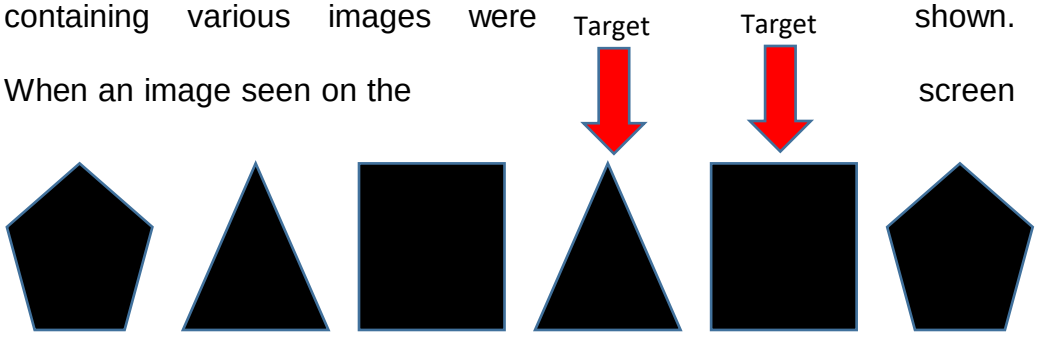


FIGURE 47 EXAMPLE OF TWO BACK TASK WITH TARGETS IDENTIFIED

6.9.3.1.4 Three Back

If the instruction screen stated a three back task was to follow, slides containing various images were shown. When an image seen on the screen was the same as that seen three images back, the keyboard had to be pressed.



The MEG scan is carried out supine, during which the volunteers perform 0 back, 1 back, 2 back and 3 back three times each with rest

FIGURE 48 EXAMPLE OF THREE BACK TASK WITH TARGETS IDENTIFIED

periods in between. A structural MRI is then carried out for a baseline and for location mapping for the MEG scan. The MRI was carried out after the MEG due to the magnetising effect the MRI has on participants. After the MRI, participants changed their clothes and lay head-down at 17^0 on the bed designed for this study (Figure 49). They stayed in this position for 2 hours.

FIGURE 49 BED DESIGNED FOR THE 17 DEGREE HEAD DOWN POSITIONING FOR 2 HOURS

After 2 hours, a repeat MEG scan is carried out immediately with the volunteer at 17^0 head-down. A wooden bed had to be designed for use within the MEG scanner (Figure 50). This was to maintain the head-down tilt until the MRI scan to maintain any structural changes that may have occurred whilst head-down. N back tasks- 0, 1, 2, 3 were repeated whilst in the MEG scanner (Figure 43).

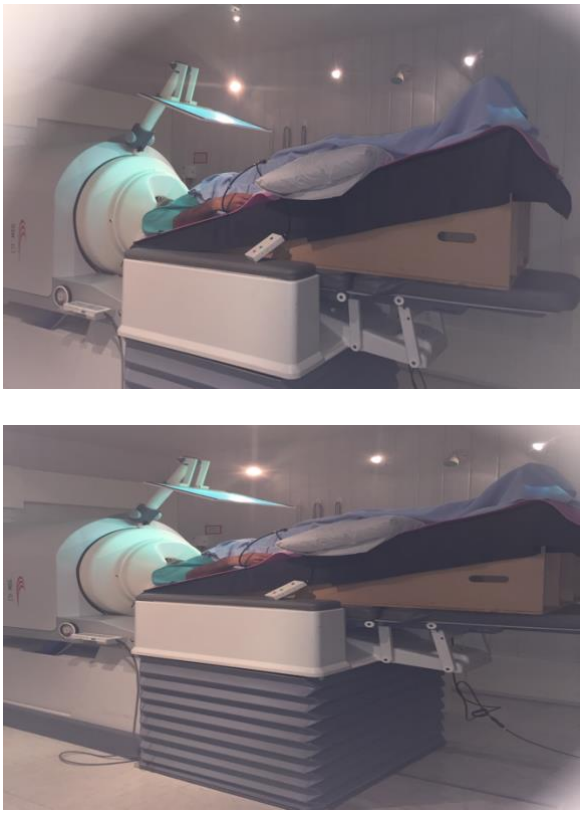


FIGURE 50 WOODEN TILT BED FOR MEG SCANNER

A repeat structural MRI is carried out immediately after the MEG scan.

6.9.4 Data Analysis

6.9.4.1 Behavioural Analysis

6.9.4.1.1 Control Data

Five healthy volunteers were recruited to provide control data for our analysis. Each volunteer repeated each test 4 times. Each test was analysed individually and the mean and standard deviation was calculated for both a change in accuracy and a change in response time between the 3rd and 4th attempt of the tests. The mean change was taken

to represent the learning effect for the tests which is known to occur when the same tasks are repeated multiple times.

The learning effect was subtracted from Run 2 results and a student t test was performed to compare the two groups accuracy and response time.

6.9.4.2 MEG data Analysis

The MEG data collected was first 'cleaned' prior to analysis. This was done by removing trials containing excessive 'noise'. Excessive noise refers to magnetic fields that interfere with those generated from the brain. The remaining trials were then further analysed by removing the channel level data of the rest periods from the trial period for each trial. The data was then analysed using an adaptive beam former. Beamforming is a spatial filtering approach to MEG inverse modelling in which signals origination at a predetermined brain location are retained whilst signals originating elsewhere are supressed (Brookes *et al*., 2011, Brookes *et al*., 2007). The output generated is based on a weighted sum of the measurements of each sensor, and the weights are determined by minimising signal variance in a time frequency window of interest. Sequential application to all voxels generates a set of time courses that can be further analysed to create volumetric image changes of electrical activity. This can be combined with the multisphere head model to indicate various regions in the brain that are activated. This data can then be further filtered into bands of interest to analyse activity of different brain waves.

For our data, each of the trials for each n back task was averaged and the above analysis performed to generate images where the highest level of activity occurred for each brain wave.

6.9.4.3 MRI Data Analysis

MRI analysis was carried out to assess for structural changes within the brain pre- and post-Trendelenburg tilt for 2 hours. Volume analysis was carried out on each MRI scan. The pre and post MRI volumes were then compared for each volunteer to look for changes. A paired t test was performed to compare the two volumes.

6.10 Results

Fifteen volunteers completed the study, 5 male and 10 female average age of 34 years (range 21-81).

6.10.1 Behavioural Results

The learning effect from the control group data was subtracted from Run 2. The mean accuracy percentage was then compared between Run 1 and Run 2. A Paired T-test was carried out to compare the 2 groups (Table 17 and Figure 51).

	Run 1	Run 2	P Value
Accuracy 0 Back	83.40 (± 18.72)	98.50 (± 1.17)	0.0616
Accuracy 1 Back	91.53 (± 16.33)	90.03 (± 16.54)	0.868
Accuracy 2 Back	90.18 (± 8.13)	76.62 (± 8.82)	0.0016
Accuracy 3 Back	68.09 (± 10.62)	65.17 (± 17.44)	0.7198

TABLE 17 COMPARISON OF MEAN ACCURACY BETWEEN RUN 1 AND RUN 2

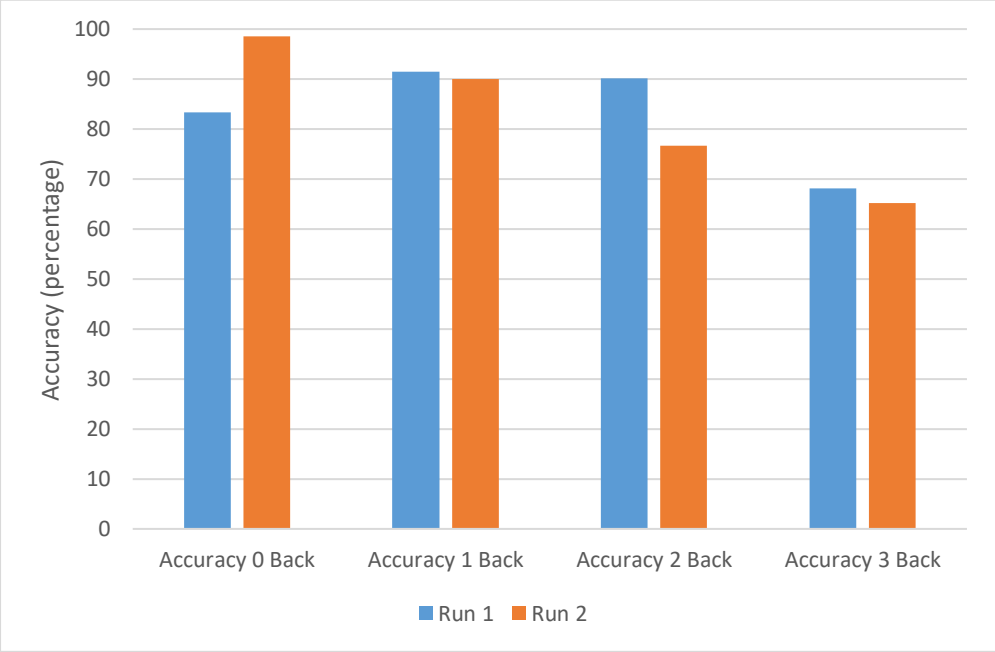


FIGURE 51 GRAPH COMPARING MEAN ACCURACY OF TESTS BETWEEN RUN 1 AND RUN 2

The average response time was also compared between Run 1 and Run 2 after subtracting the control groups learning effect from Run 2. (Figure 52 and Table 18)

	Run 1	**Run 2**	**P Value**
0 Back response time	0.19 (± 0.02)	0.24 (± 0.03)	0.0059
1 Back response time	1.16 (± 0.073)	1.18 (± 0.07)	0.5884
2 Back response time	1.08 (± 0.45)	1.06 (± 0.12)	0.8743
3 Back response time	2.17 (± 0.61)	2.31 (± 0.65)	0.332

TABLE 18 COMPARISON OF MEAN RESPONSE TIME BETWEEN RUN 1 AND RUN 2

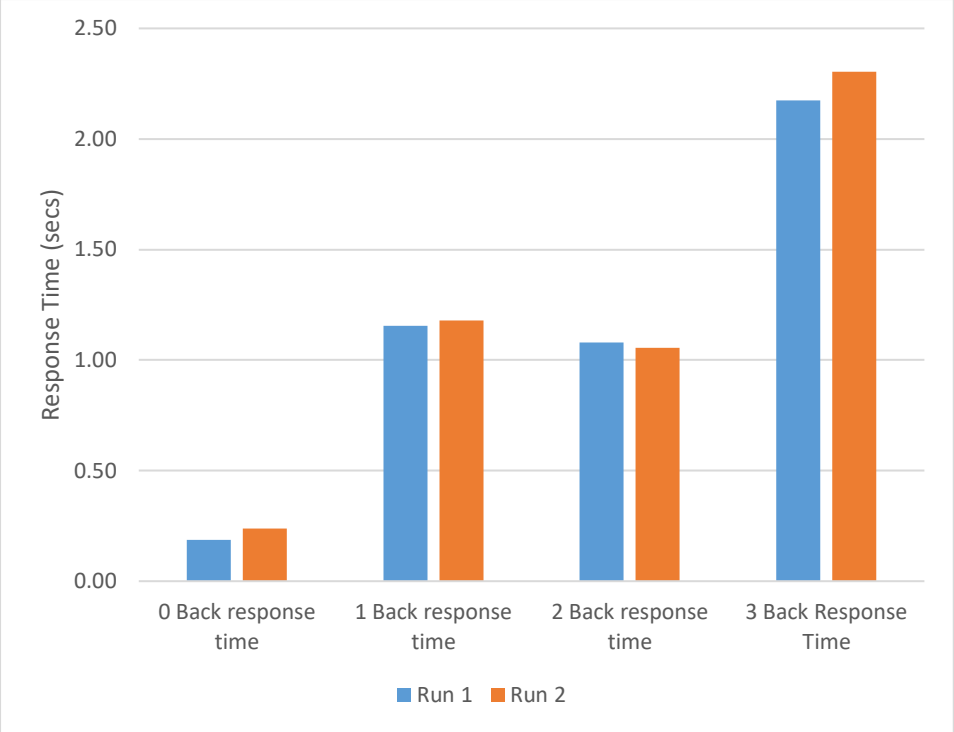


FIGURE 52 COMPARISON OF MEAN RESPONSE TIME BETWEEN RUN 1 AND RUN 2

6.10.2 MEG Results

As our study also looked at working memory of varying difficulty. Zero back is an easier task compared to the three back task. The images generated from beamformer analysis looking at theta activity in the frontal cortex is shown below.

Figure 53 compares the theta activity for 0 back task to the 3 back task which is increased difficulty and therefore increased workload. Though only a minor difference, there in an increase in theta activity in the pre-frontal cortex.

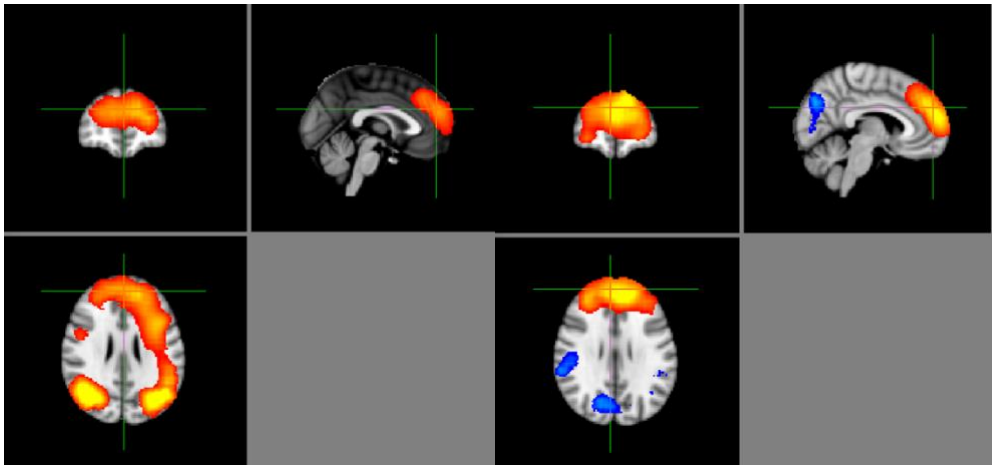


FIGURE 53: ZERO BACK THETA ACTIVITY RUN 1 (LEFT IMAGE) AND THREE BACK THETA ACTIVITY RUN 1 (RIGHT IMAGE)

Figures 55-58 compare theta activity images for Run 1 and Run 2 for each of the n back tasks. The scale in Figure 54 was used to determine if there was increased or decreased theta activity during the task in Run 1 compared to Run 2. In 1 and 2 back there was potentially slight increase in theta activity during Run 2 compared to Run 1. (Figures 55-58)

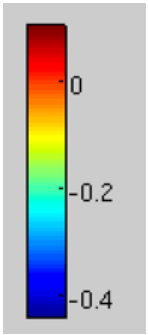


FIGURE 54 BRAIN WAVE ACTIVITY SCALE

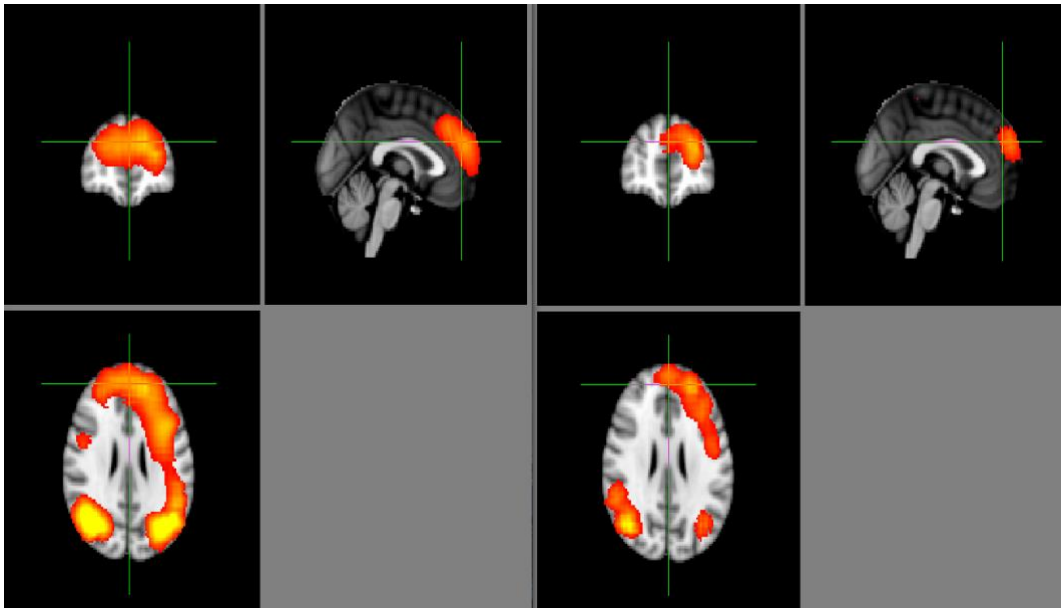


FIGURE 55 ZERO BACK THETA ACTIVITY RUN 1 (LEFT) AND ZERO BACK THETA ACTIVITY RUN 2 (RIGHT)

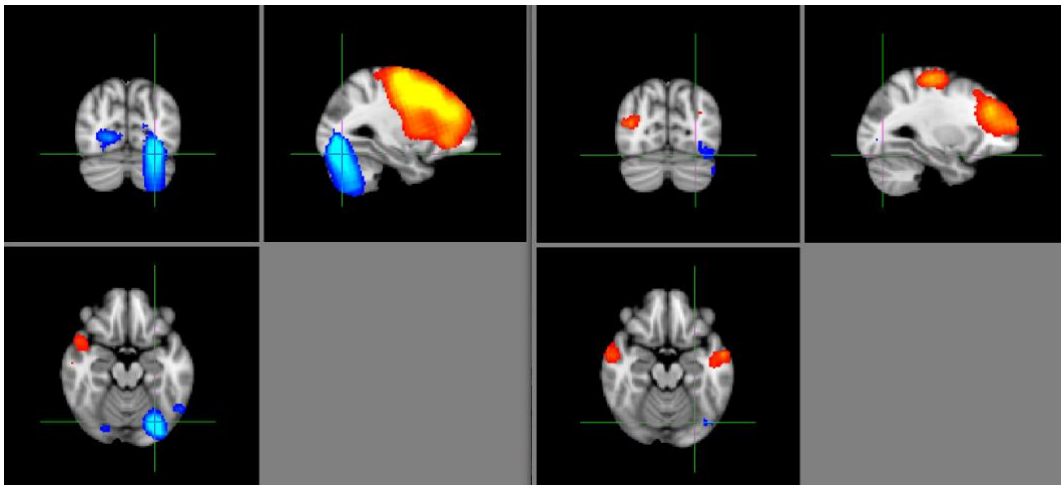


FIGURE 56: ONE BACK THETA ACTIVITY RUN 1(LEFT) AND ONE BACK THETA ACTIVITY RUN 2 (RIGHT)

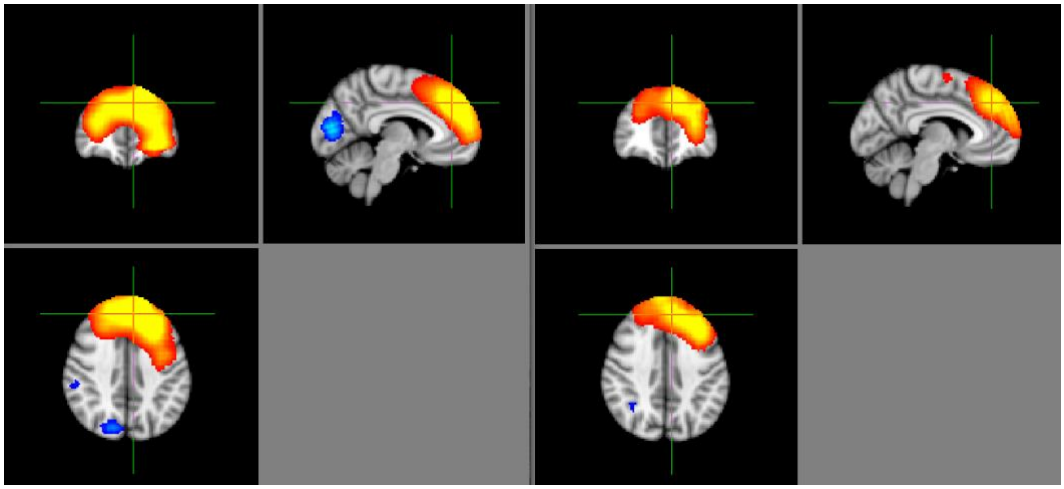


FIGURE 57: TWO BACK THETA ACTIVITY RUN 1 (LEFT) AND TWO BACK THETA ACTIVITY RUN 2 (RIGHT)

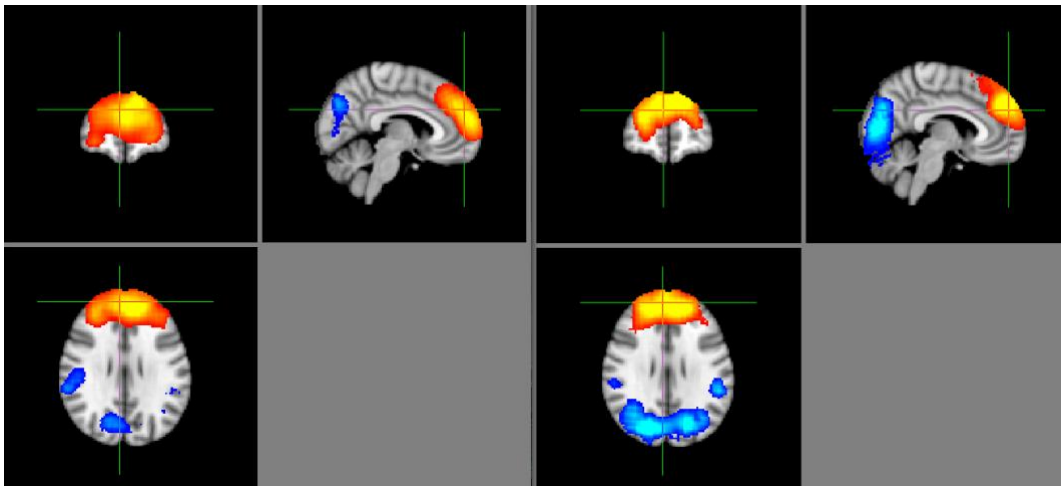


FIGURE 58: THREE BACK THETA ACTIVITY RUN 1 (LEFT) AND THREE BACK THETA ACTIVITY RUN 2 (RIGHT)

We compared beta activity between Run 1 and Run 2 for each n back task. Figures 59-62 shows beta activity for 0, 1, 2 and 3 back tasks comparing Run 1 and Run 2. There is a slight decrease in beta activity in all tasks, but appears to be more pronounced in 1 and 3 back tasks.

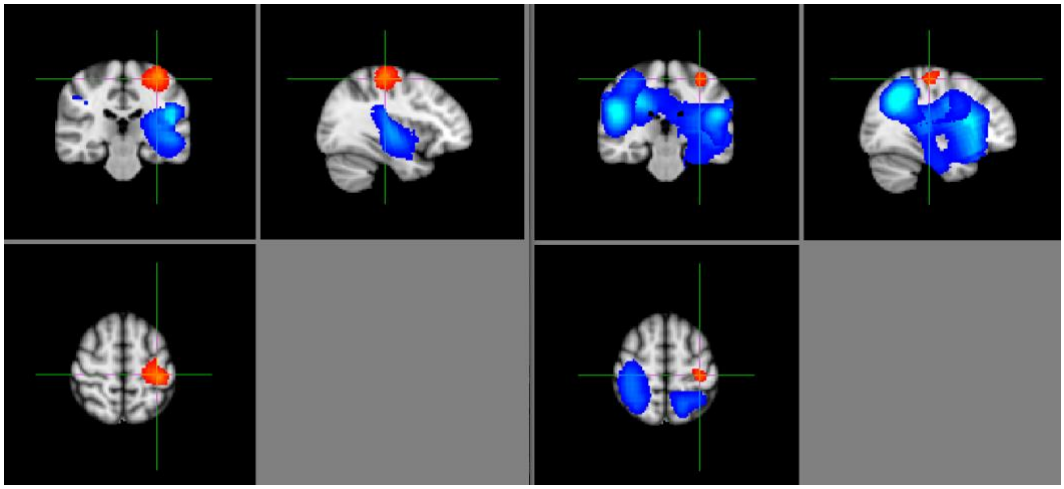


FIGURE 59: ZERO BACK BETA ACTIVITY RUN 1 (LEFT) AND ZERO BACK BETA ACTIVITY RUN 2 (RIGHT)

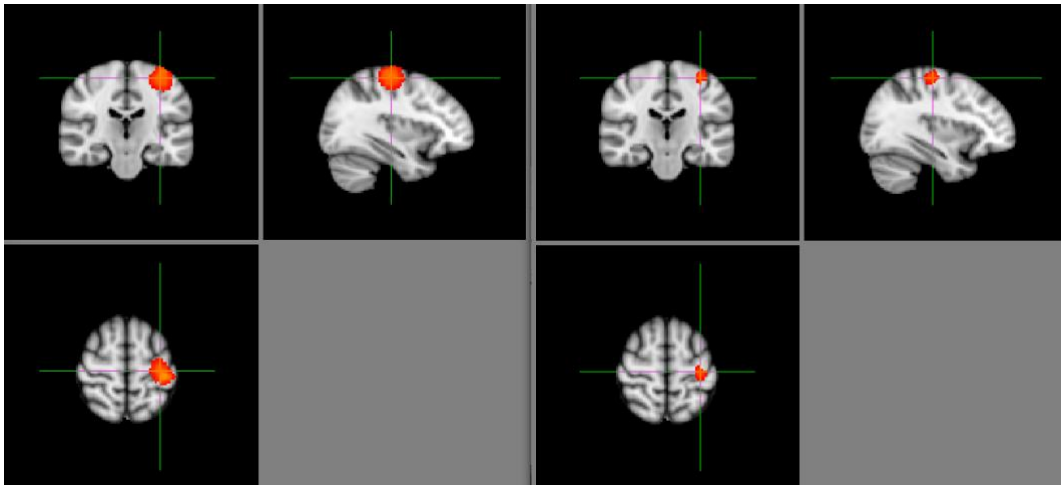


FIGURE 60: ONE BACK BETA ACTIVITY RUN 1(LEFT) AND ONE BACK BETA ACTIVITY RUN 2 (RIGHT)

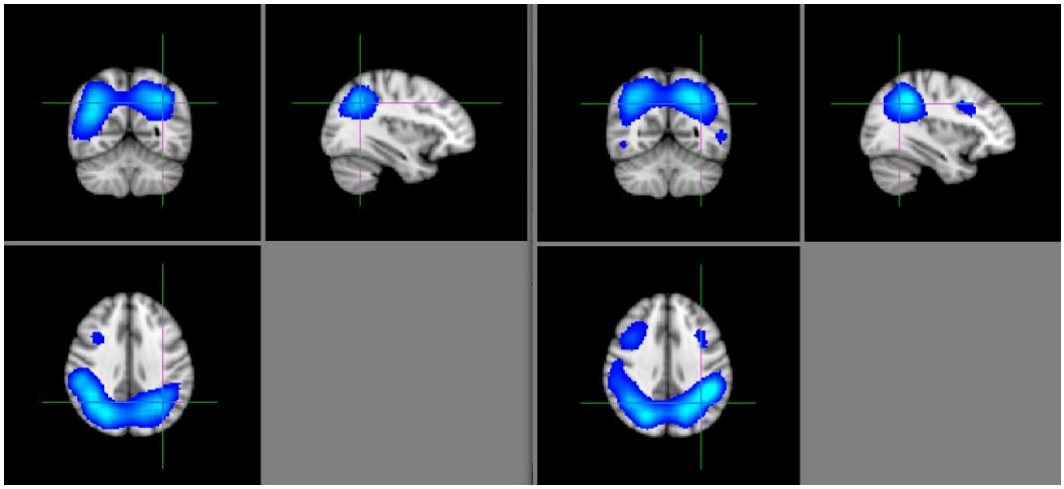


FIGURE 61: TWO BACK BETA ACTIVITY RUN 1 (LEFT) AND TWO BACK BETA ACTIVITY RUN 2 (RIGHT)

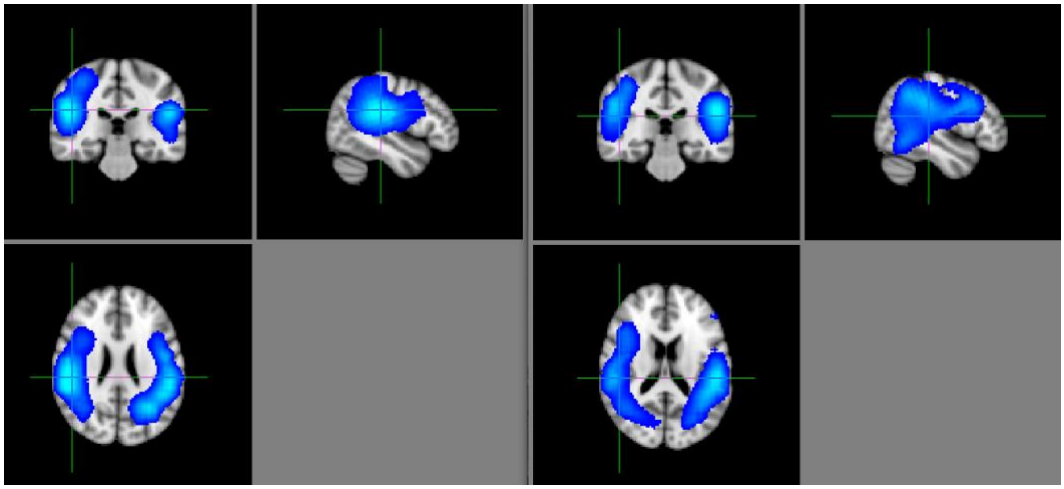


FIGURE 62: THREE BACK BETA ACTIVITY RUN 1 (LEFT) AND THREE BACK BETA ACTIVITY RUN 2 (RIGHT)

The graphs generated below (Figures 64-71) are a summary of the activity within various regions of the brain. Figure 63 shows what each graph in the Figures is an analysis of, and the caption for each Figure describes which region was analysed. In the pre-frontal region (frontal cortex), there is increased activity during Run 2 compared to Run 1 with

the exception of the 2 back task. There is minimal difference in the other regions analysed.

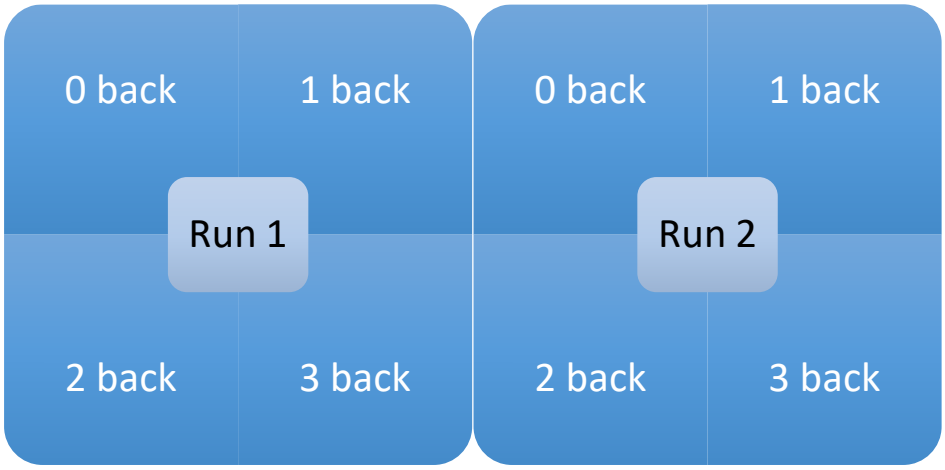


FIGURE 63 DIAGRAM TO SHOW THE TESTS SHOWN IN THE FOLLOWING GRAPHS (FIGURES 64 TO 71)

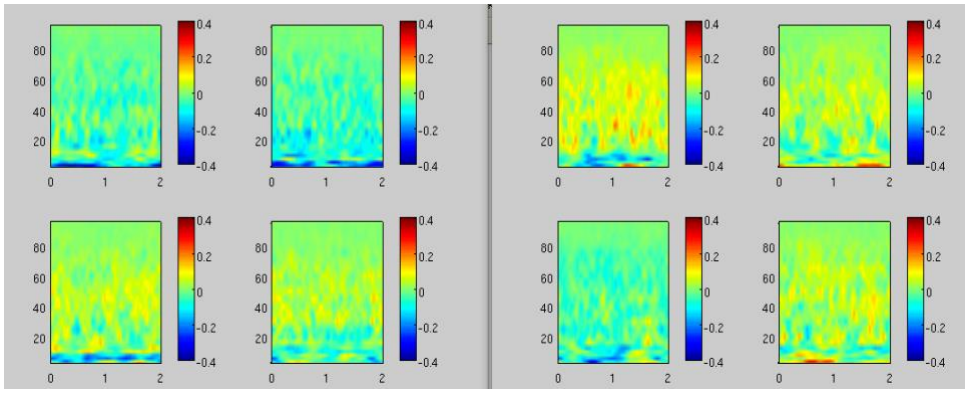


FIGURE 64 FRONTAL RIGHT REGION

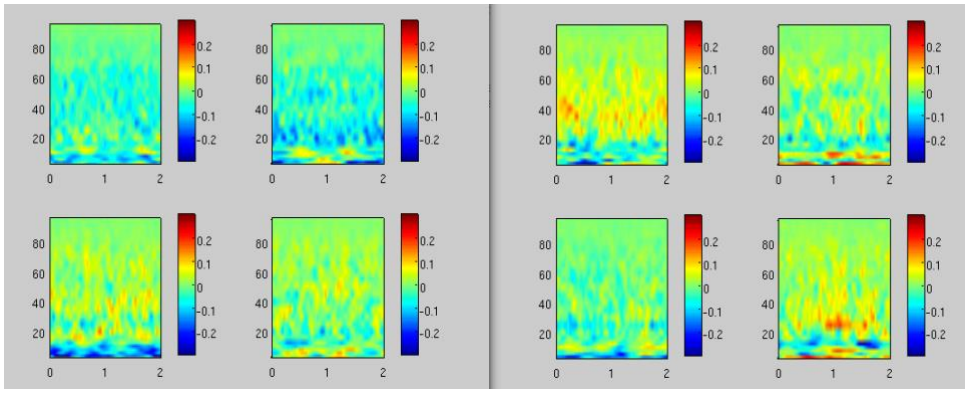


FIGURE 65 FRONTAL LEFT REGION

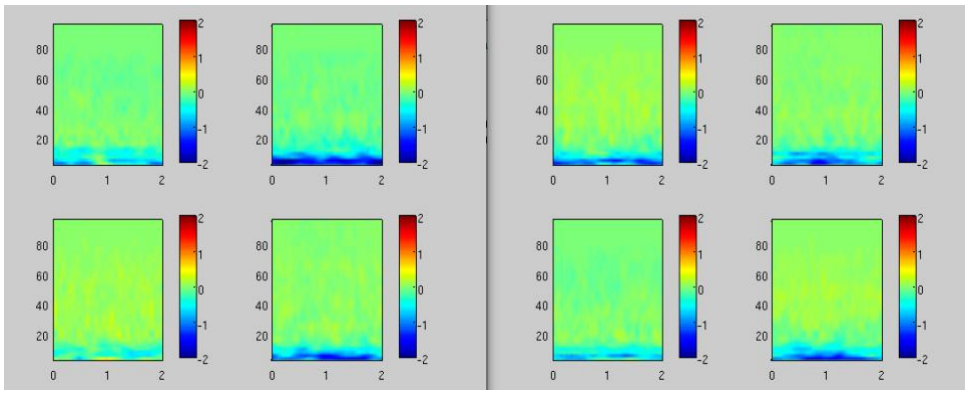


FIGURE 66 LEFT MOTOR CORTEX

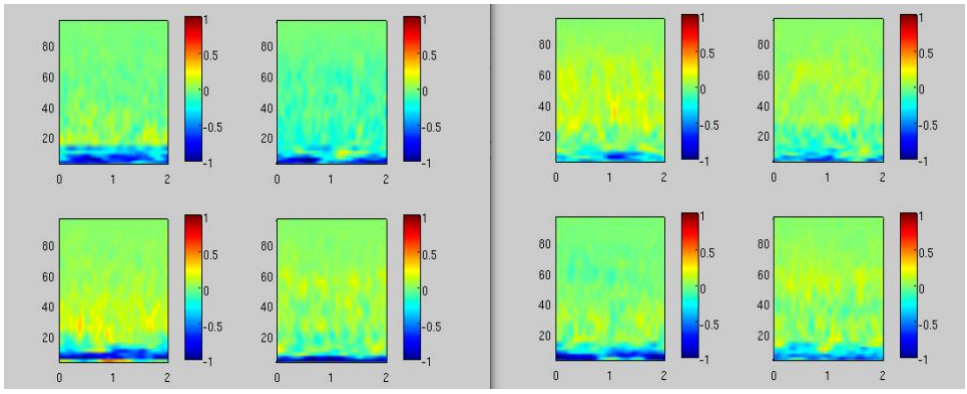


FIGURE 67 RIGHT MOTOR CORTEX

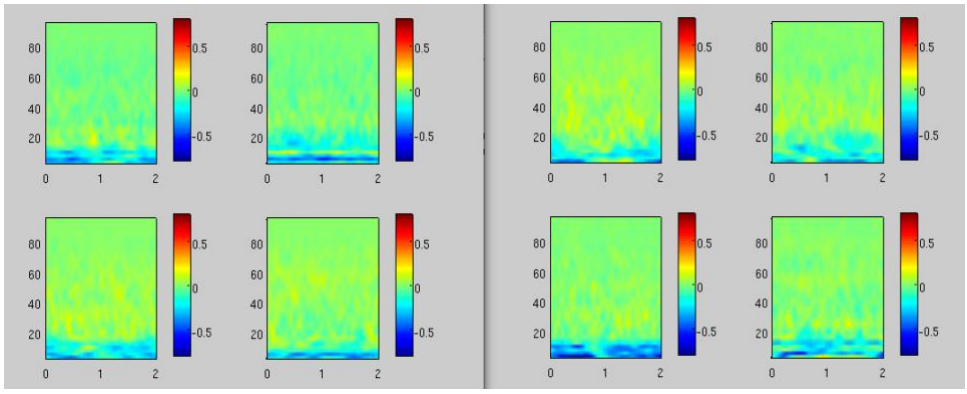


FIGURE 68 RIGHT PARIETAL LOBE

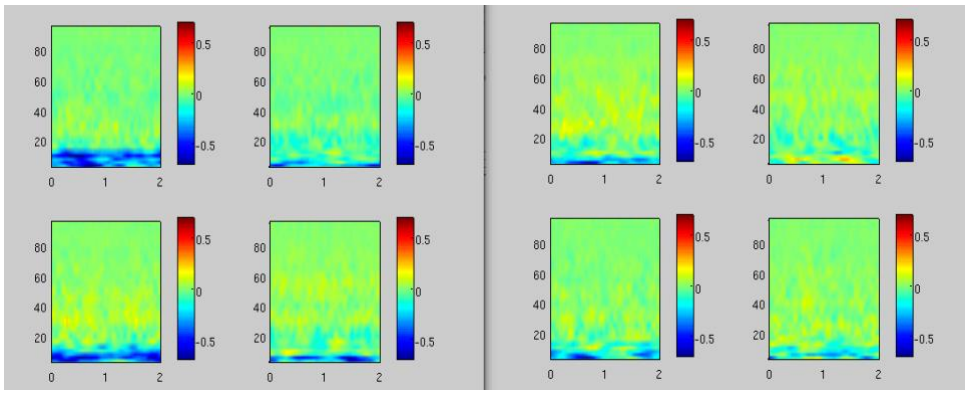


FIGURE 69 LEFT PARIETAL LOBE

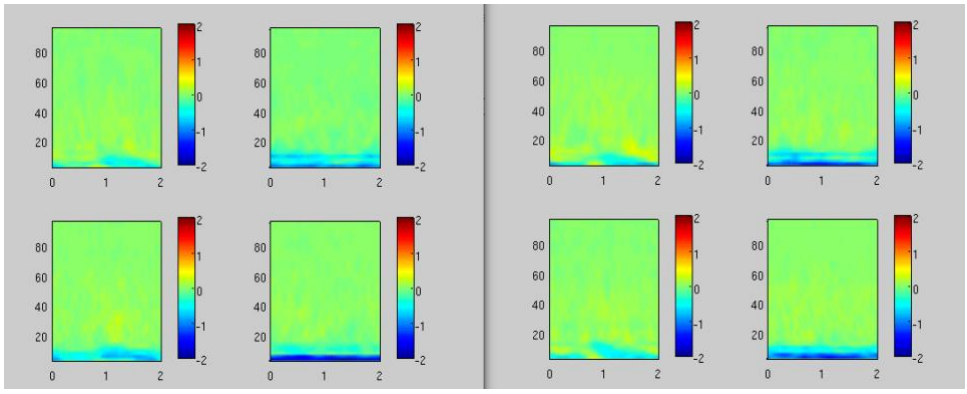


FIGURE 70 RIGHT VISUAL CORTEX

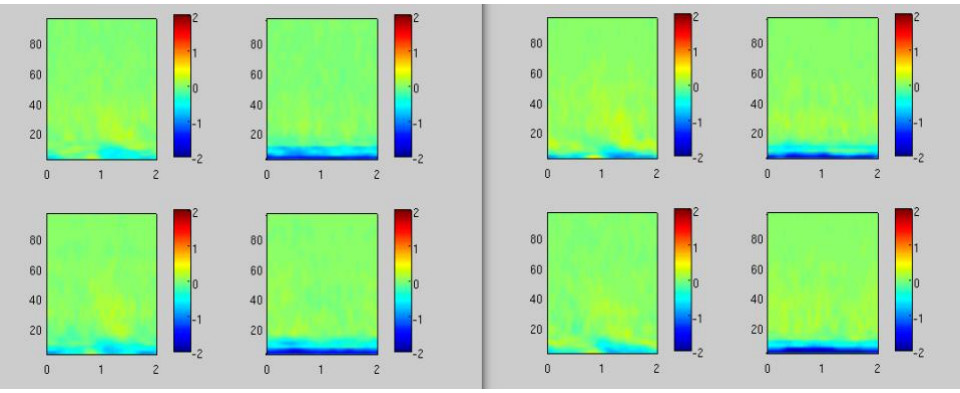


FIGURE 71 LEFT VISUAL CORTEX

6.10.3 MRI Results

The basic concept of MRI analysis was to assess for any changes in volume within various areas of the brain detailed in the table. As the volunteers were their own control, any volume changes could be attributed to the Trendelenburg position.

Volumes for each brain region was calculated on the initial MRI and then on the second MRI. The two volumes were then compared using a paired t test to look for statistically significant changes in volume within each of the brain regions. This was carried out using specially designed software programmes that is routinely used for volume testing of MRI's. The paired t test performed did not reveal any statistically significant difference between MRI 1 or MRI 2. (Appendix 1)

Run 1 (average vol)	Run 2 (average vol)	Difference	P value
7816.38	8332.30	515.92	P>0.05

TABLE 19 COMPARISON OF PRE AND POST TRENDELENBURG VOLUME ON MRI

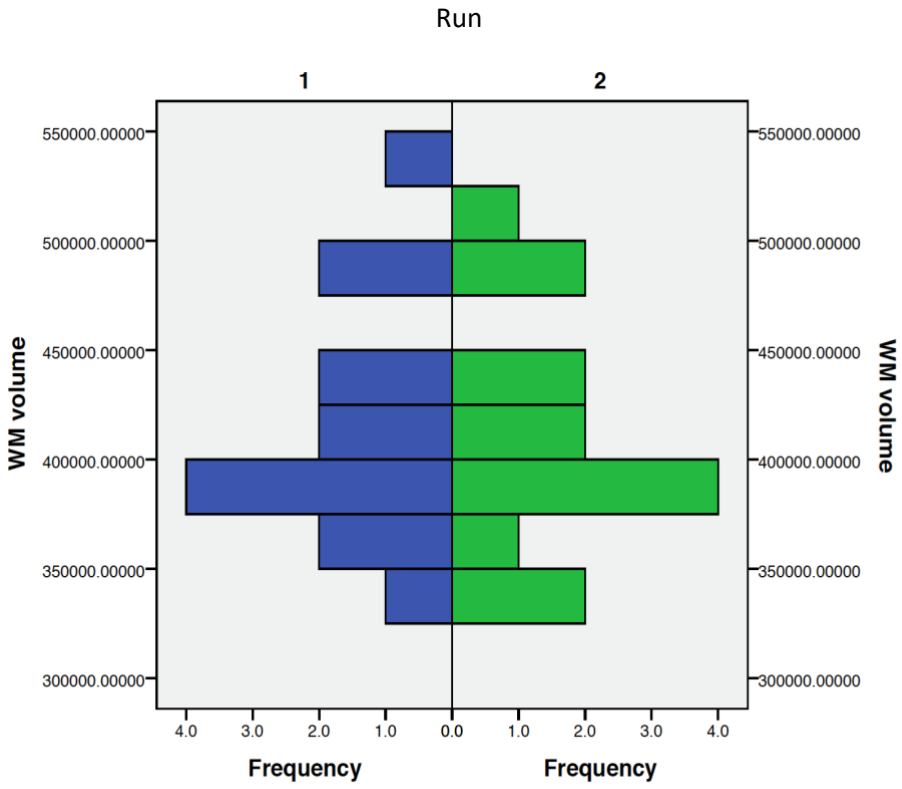


FIGURE 72 MRI WHITE MATTER (WM) VOLUME COMPARISON RUN 1 AND RUN 2

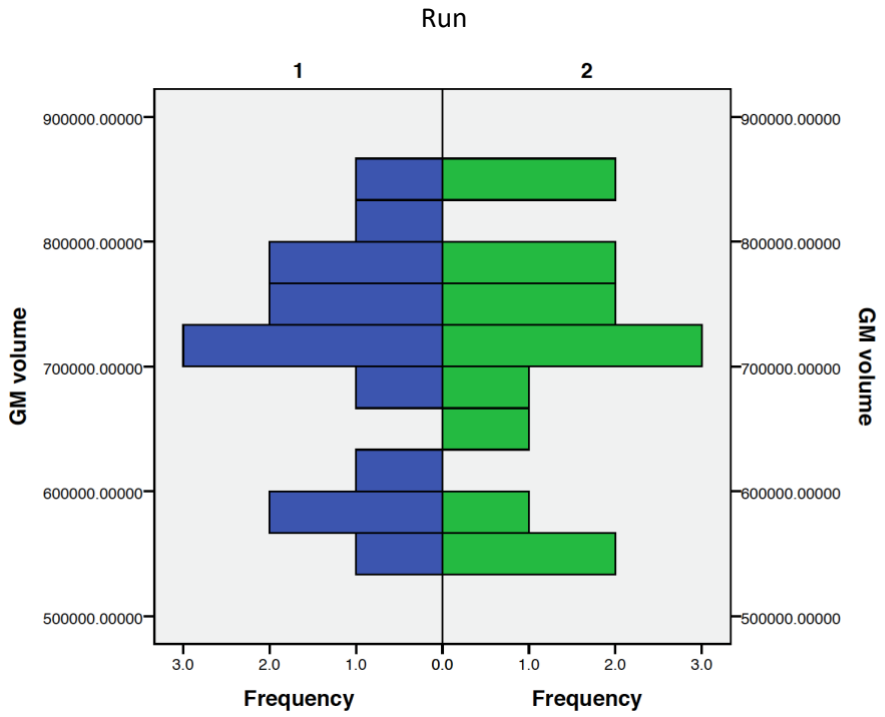


FIGURE 73 MRI GREY MATTER(GM) VOLUME COMPARISON RUN 1 AND RUN 2

6.11 Discussion

Though accuracy was reduced in Run 2 for 1, 2 and 3 back, this was only statistically significant for the 2 back test where the mean accuracy was 90% compared to 76.6% in Run 2. During Run 2, response time was slower for 0, 1 and 3 back tasks, it was only slightly quicker for the 2 back task (0.08 versus 0.06 seconds). The difference was only statistically significant for 0 back task. Though not statistically significant, there was an overall decrease in accuracy, except in the zero back task; and an increase in response time, except in the two back task in Run 2 compared to Run 1.

Brookes *et al* looked at changes in electrical brain activity during working memory tasks using MEG. They concluded that with working memory, there was an increase in theta oscillations and a decrease in beta oscillations in the medial frontal cortex. With increased memory load (or task difficulty), there was an increase in theta oscillations and further decrease in beta activity. Increased activity is indicated with red and decreased activity blue (Figure 54) (Brookes *et al*., 2011). For our data, the data was divided into each n back task. Though minimal, there is a slight increase in theta activity in Run 2 compared to Run 1 which was more pronounced in 1 and 2 back tasks. Beta activity did show a slight decrease in Run 2, but this didn't occur in all the tasks and was more pronounced in the 1 and 3 back task.

Brookes *et al* studied the changes in brain activity during working memory tasks including the N back and Sternberg tasks. An increase in theta oscillations in the medial frontal cortex which increased further with higher task difficulty and increased memory load. A decrease in Beta and gamma waveforms was also noted in response to an increase in theta (Brookes *et al*., 2011). Our results did show a similar response between Run 1 and Run 2 suggesting Trendelenburg positioning increased the cognitive work load to carry out the same tasks.

Our second hypothesis was cerebral oedema resulting from being in the Trendelenburg position. This is thought to be due to an increase in CVP

which leads to an increase in hydrostatic pressure which results in cerebral oedema. A paired T test carried out to compare the volume of various regions of the brain pre- and post-Trendelenburg position did not reveal a statistically significant difference. This could be due to a small data sample, as although not statistically significant, there was a slight increase in the average overall brain volume of 515.92mm^3 ($p>0.05$). This could explain the slight decline in cognitive function during Run 2 that was noted and the increase in theta activity that is usually seen with increased workload/task difficulty.

Overall though the only significant difference was accuracy of the 2 back task; when Run 1 was compared to Run 2 with accuracy, response time, theta and beta activity, there was a decrease in accuracy, increase in response time and theta and beta activity did suggest an increase in work load when Run 1 was compared to Run 2 for the 1, 2 and 3 back tasks. The MRI performed in Run 2 did also show a slight increase in cerebral volume potentially indicating mild cerebral oedema did result from the Trendelenburg position.

6.11.1 Limitations

There were limitations to this study. As this was a pilot study, the sample size was kept to a minimum. I also had to adapt the MEG scanner to allow the volunteer to remain in the Trendelenburg until the second MRI was carried out to pick up subtle changes. The placements of the scanners in the MRI Centre meant the volunteers had to walk up the

stairs to have the MRI scan which in a healthy volunteer may reverse the effects of the Trendelenburg position as suggested in previous studies, where if the volunteer is placed supine or stood up, the effects of the raised CVP were reversed (Deegan *et al*., 2010).

To allow comparisons between the MEG data during Run 1 and Run 2, I attempted to keep the location coil positions the same. However, as the MRI leads to magnetisation of the volunteers, the initial MEG was carried out first followed by the MRI which meant we had to mark where the coils were and remove them prior to the MRI. Before the second MEG these coils were placed back on the marked area, however there was potential for slight error at this point.

Also, to carry out the MEG in a head-down tilt position, I had to make a wooden tilt bed to be used within the MEG scanner. As the head needed to be in the same position within the MEG scanner and due to limited movement of the MEG to between 90 degrees, the head of the volunteer had to remain at 0 degrees, though I could tilt the rest of the body to 17 degrees which was the same as the tilt bed used between scans. The time the volunteer was at this angle could also have led to slight resolution of any cerebral oedema. There is also the potential of an added emotional response to being placed in such a position at quite a height within the scanner that may affect performance in Run 2.

6.12 Conclusion

The results of this pilot study although not statistically significant, suggest a Trendelenburg may lead to cerebral oedema and decreased cognitive function. Further clinical studies or volunteer studies with larger sample sizes would be beneficial to evaluate this further.

Chapter 7 : A study looking at the effect of the time spent in Trendelenburg position on cognitive function

Abstract

Background

Postoperative cognitive dysfunction (POCD) is defined as a new cognitive impairment arising after surgical intervention. Cognitive function can be assessed using validated cognitive function tests including: 1 back; 2 back; 3 back; 4 Stroop; and 5 Lexical Decision Making Task. There is some concern that prolonged head down positioning during laparoscopic colorectal surgery may cause POCD.

Aim

To assess the effect of the time spent in Trendelenburg position on cognitive function.

Method

Volunteers were placed in Trendelenburg for 3hours, then supine for 1 hour. Validated cognitive function tests including: 1,2 3 back; Stroop; and Lexical Decision Making Task were performed at baseline and every 30 minutes. Cognitive decline was defined as accuracy decline or increase in response time (RT) by > 2 control group standard deviations (SD) from baseline.

Results

Fifteen healthy volunteers were recruited (8 male, 7 female), average age of 69 years (range:57-81) and average BMI of 27.7 kg/m^2 (range:20.9-33). Accuracy remained within 2SDs at all time-points. An

increase in RT did occur with 20% showing cognitive decline after 30 minutes in Trendelenburg position, 26.7% after 1 hour, 33.3% after 90 minutes, 26.7% after 120 and 150 minutes; and 40% after 180 minutes. When moved supine, 33.3% had cognitive decline.

Discussion

The results of this study indicate that Trendelenburg positioning appears to lead to cognitive decline. This may have implications for patients undergoing prolonged head down positioning in laparoscopic colorectal surgery.

7.1 Introduction

This study has been designed to look at what effect if any the duration of time spent in the Trendelenburg position had on cognitive function in healthy volunteers.

7.2 Aim

1. To assess the effect of the amount of time spent in Trendelenburg position on cognitive function
2. If cognitive function is affected, assess how long it takes to recover back to baseline

7.3 Method

Fifteen healthy volunteers were recruited. As we were assessing cognitive function in a study with relatively few participants, including patients with pre-existing cognitive impairment would distort our results, they were therefore excluded from our study.

Confounding factors that may affect our measurements of cognitive function were excluded from our study. Nicotine is the primary psychoactive agent in cigarettes. Research looking into the effect of nicotine and cognitive function showed abstinence or change in smoking (nicotine) levels disturbed cognitive function (Levin *et al*., 2006). Therefore, smokers were excluded from our study to avoid skewing our results. As this study required completion of cognitive tasks with response time and accuracy were primary outcomes. Visual impairment

and inability to read English would affect the response times and accuracy of our tests. The lexical decision making task and stroop task required recognition of English words and all three tasks required the ability to read/recognise images on the screen.

7.3.1 Inclusion Criteria:

- Healthy volunteers over the age of 18

7.3.2 Exclusion Criteria:

- Cognitive impairment
- Inability to read or understand English – this is required for patients to complete the cognitive function assessments.
- Visual impairment (inability to carry out the computer based tasks)
- Smokers
- Refusal to give written informed consent – only consenting volunteers will be included

After practicing each test 3 times, a baseline performance for each cognitive function tasks were recorded whilst sitting:

- 1 back
- 2 back
- 3 back

- Stroop
- Lexical Decision Making Task

The volunteers were then placed in the Trendelenburg position at 17^0 head down for 3 hours, then moved to supine position for 1 hour and then sat up. The above tests were then repeated after:

1. 30 minutes
2. 1 hour
3. 1.5 hours
4. 2 hours
5. 2.5 hours
6. 3 hours (volunteer moved to supine position after 3 hours, so these tests would be taken whilst supine). The tests will be repeated at the given time points whilst still supine:
7. 3.5 hours
8. 4 hours – After 4 hours, the volunteer was sat up in a chair and the tests would be taken whilst sitting up.

7.3.3 Control Data

Five healthy volunteers were recruited to provide control data for our analysis. Each volunteer repeated each test 4 times. Each test was analysed individually and the mean and standard deviation was calculated for both a change in accuracy and a change in response time between the 3rd and 4th attempt of the tests. The mean change was

taken to represent the learning effect for the tests which is known to occur when the same tasks are repeated multiple times.

7.3.4 Statistical Analysis

A Statistical power analysis was performed for sample size estimation, based on data from Brookes *et al* who compared the effect of increased task difficulty on MEG activity. They detected a mean accuracy for 1-back task as 98% ± 2 (SD) and 2-back test as 91% ± 8 (SD). With an alpha=0.05 and power=0.80, the projected sample size needed with this effect size (STATA 14.0) was n=10 (Brookes *et al*., 2011). We therefore chose to recruit 15 volunteers to our study.

A repeated measures analysis was performed to compare the change in accuracy and response time at each time point. For each volunteer, the accuracy at each time point was subtracted from their baseline. A repeated measures test was then performed using STATA.

For each volunteer, the baseline was subtracted from each time point, and then the learning effect was also subtracted. This result was then divided by the standard deviation of the control group to give a Z score. A large positive Z score ($z>1.96$) showed a deterioration in cognitive function from baseline for accuracy, and a large negative Z ($z< -1.96$) score for response time (Abildstrom *et al*., 2000).

The British Geriatric Society (BGS) carried out a study to look for POCD in patients post-operatively. They analysed the data in the same manner, but defined POCD as mild, moderate and severe: mild = greater than 1 SD decline in at least one of the cognitive tests; moderate = greater than 1.5 SD decline in at least one of the cognitive tests; severe (POCD) = greater than 1.96 SD decline in at least two of the cognitive tests. This was the criteria we used to categorise cognitive decline.

7.4 Results

Fifteen healthy volunteers completed the study. Of the 15 volunteers, 8 were male, 7 were female. They had an average age of 69 years (± 6.98) and average BMI of 27.7 kg/m^2 (± 3.4).

Time Point	Event	Accuracy Mean change from baseline (95% CI)	P Value
2	**30 minutes after Trendelenburg Position**	-0.04 (-0.072, 0.001)	0.06
3	**60 minutes after Trendelenburg position**	-0.01 (-0.05, 0.03)	0.66
4	**90 minutes after Trendelenburg position**	0.01 (-0.03, 0.05)	0.67
5	**120 minutes after Trendelenburg position**	0.02 (-0.02, 0.05)	0.44
6	**150 minutes after Trendelenburg position**	0.002 (-0.35, 0.04)	0.91
7	**Supine (after 180 minutes in Trendelenburg)**	0.02 (-0.01, 0.06)	0.20
8	**30 minutes after Supine position**	0.01 (-0.03, 0.04)	0.82
9	**Sitting up (60 minutes after Supine position)**	0.02 (-0.02, 0.06)	0.29

TABLE 20 REPEATED MEASURES ANALYSIS OF CHANGE IN ACCURACY

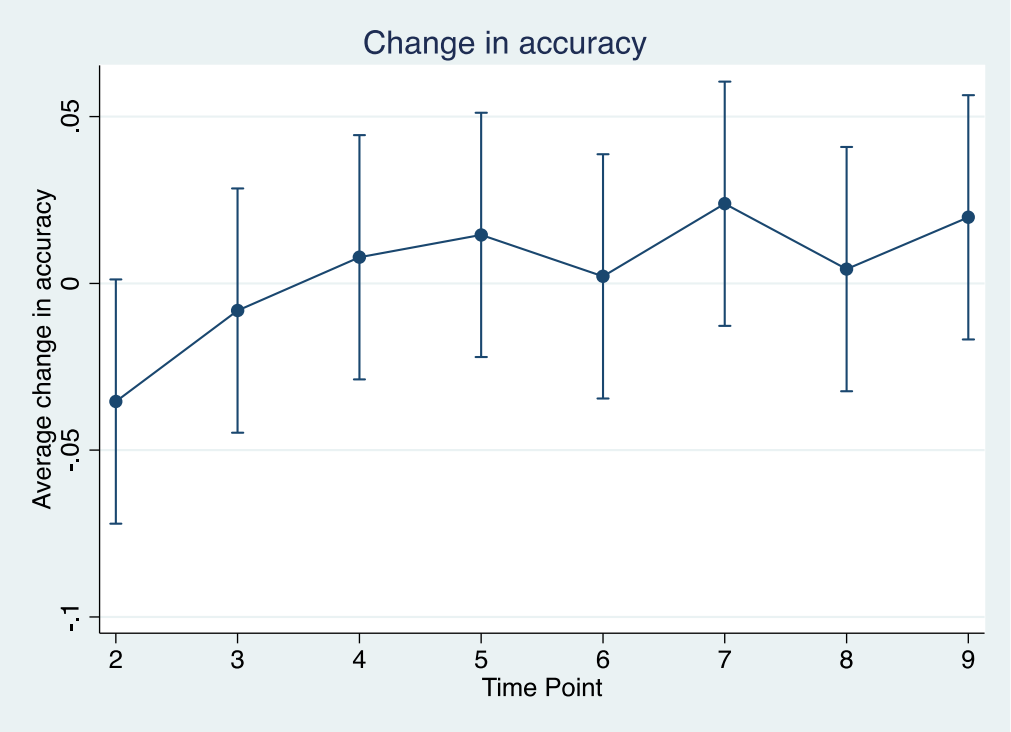


FIGURE 74 CHANGE IN ACCURACY OF TESTS AT EACH TIME POINT. AVERAGE ACCURACY OF TESTS AT EACH TIME POINT. 2-TRENDELENBURG 30 MINUTES, 3- TRENDELENBURG 60 MINUTES, 4- TRENDELENBURG 90 MINUTES, 5- TRENDELENBURG 120 MINUTES, 6- TRENDELENBURG 150 MINUTES, 7- TRENDELENBURG 180 MINUTES/SUPINE 0 MINUTES, 8- SUPINE 30 MINUTES, 9- SUPINE 60 MINUTES/VOLUNTEER SAT-UP

Table 21 and Figure 75 show the results of repeated measures analysis of change in response time.

Time Point	Event	Response time Mean change from baseline (95% CI)	P Value
2	**30 minutes after Trendelenburg Position**	-0.04 (-0.11, 0.04)	0.34
3	**60 minutes after Trendelenburg position**	-0.08 (-0.16, 0.01)	0.03
4	**90 minutes after Trendelenburg position**	-0.11 (-0.18, -0.03)	0.004
5	**120 minutes after Trendelenburg position**	-0.15 (-0.22, -0.07)	<0.001
6	**150 minutes after Trendelenburg position**	-0.14 (-0.22, -0.07)	<0.001
7	**Supine (after 180 minutes in Trendelenburg)**	-0.19 (-0.26, -0.11)	<0.001
8	**30 minutes after Supine position**	-0.15 (-0.22, -0.7)	<0.001
9	**Sitting up** **(60 minutes after Supine position)**	-0.16 (-0.23, -0.08)	<0.001

TABLE 21 REPEATED MEASURES ANALYSIS OF CHANGE IN RESPONSE TIME

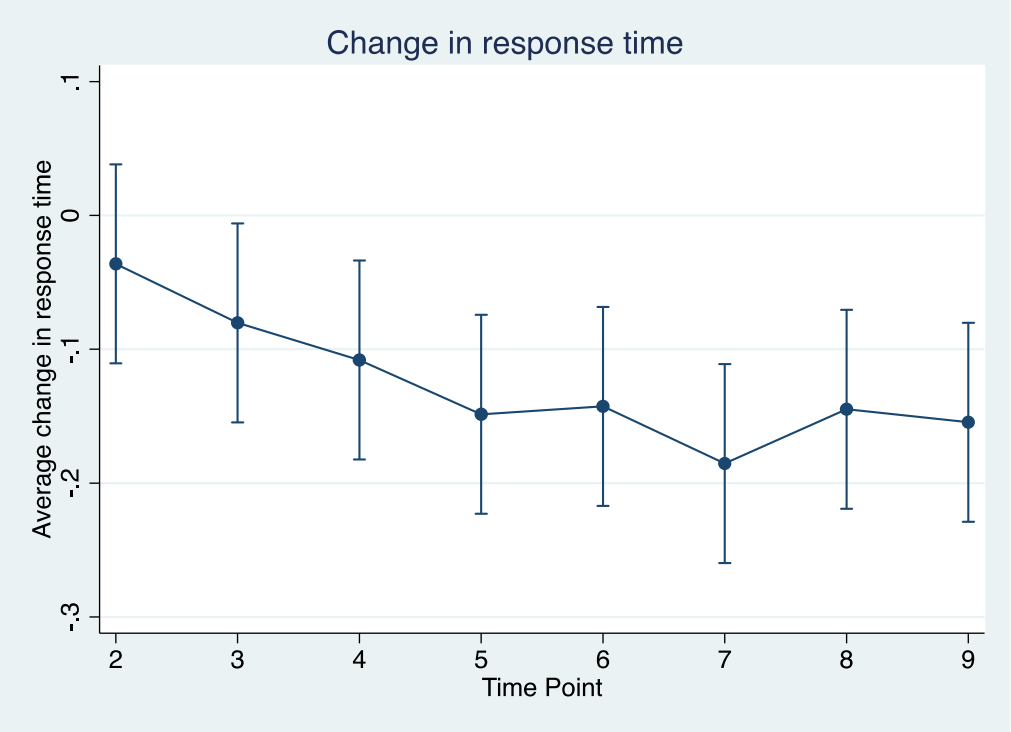


FIGURE 75 CHANGE IN RESPONSE TIME AT EACH TIME POINT. 2- TRENDELENBURG 30 MINUTES, 3- TRENDELENBURG 60 MINUTES, 4- TRENDELENBURG 90 MINUTES, 5- TRENDELENBURG 120 MINUTES, 6- TRENDELENBURG 150 MINUTES, 7- TRENDELENBURG 180 MINUTES/SUPINE 0 MINUTES, 8- SUPINE 30 MINUTES, 9- SUPINE 60 MINUTES/VOLUNTEER SAT-UP

The percentage of volunteers with cognitive decline was analysed (Table 22 and Table 23). When accuracy alone was evaluated, 1 volunteer showed a decline in accuracy at time point 7, which was 3.5 hours into the study and 30 minutes after lying supine following the 3 hours' head-down.

Time point	Number of volunteers with cognitive decline	Percentage cognitive function decline
1	0	0.00
2	0	0.00
3	0	0.00
4	0	0.00
5	0	0.00
6	0	0.00
7	1	6.67
8	0	0.00

TABLE 22 AVERAGE ACCURACY OF TESTS AT EACH TIME POINT. 1- TRENDELENBURG 30 MINUTES, 2- TRENDELENBURG 60 MINUTES, 3- TRENDELENBURG 90 MINUTES, 4- TRENDELENBURG 120 MINUTES, 5- TRENDELENBURG 150 MINUTES, 6- TRENDELENBURG 180 MINUTES/SUPINE 0 MINUTES, 7- SUPINE 30 MINUTES, 8- SUPINE 60 MINUTES/VOLUNTEER SAT-UP

When response time was evaluated, a larger percentage of volunteers suffered cognitive decline of at least 1 standard deviation above baseline. (Table 23)

Time point	Normal cognitive function	Number of volunteers with cognitive decline	Percentage of volunteers with cognitive decline
1	80.00	3	20.00
2	73.33	4	26.67
3	66.67	5	33.33
4	73.33	4	26.67
5	73.33	4	26.67
6	60.00	6	40.00
7	66.67	5	33.33
8	60.00	6	40.00

TABLE 23 AVERAGE RESPONSE TIME OF TESTS AT EACH TIME POINT. 1- TRENDELENBURG 30 MINUTES, 2- TRENDELENBURG 60 MINUTES, 3- TRENDELENBURG 90 MINUTES, 4- TRENDELENBURG 120 MINUTES, 5- TRENDELENBURG 150 MINUTES, 6- TRENDELENBURG 180 MINUTES/SUPINE 0 MINUTES, 7- SUPINE 30 MINUTES, 8- SUPINE 60 MINUTES/VOLUNTEER SAT-UP

Figure 76 is a graph to show the overall percentage of volunteers who demonstrated cognitive decline at each time point compared to those who did not show a significant change in cognitive function in the tests.

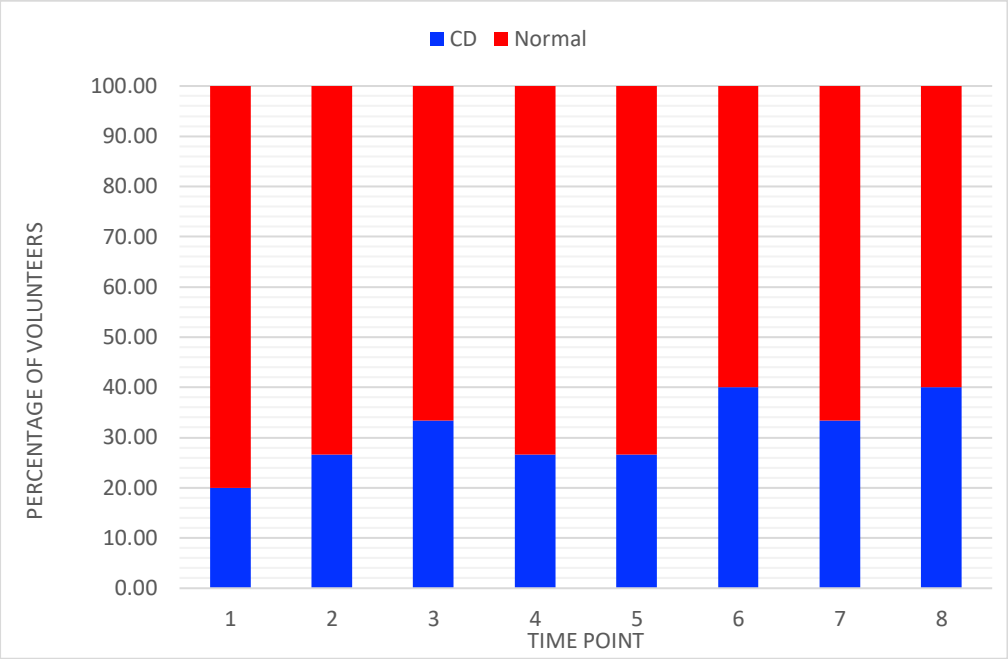


FIGURE 76 PERCENTAGE OF VOLUNTEERS WITH COGNITIVE DECLINE AT EACH TIME POINT. 1-TRENDELENBURG 30 MINUTES, 2- TRENDELENBURG 60 MINUTES, 3- TRENDELENBURG 90 MINUTES, 4- TRENDELENBURG 120 MINUTES, 5- TRENDELENBURG 150 MINUTES, 6- TRENDELENBURG 180 MINUTES/SUPINE 0 MINUTES, 7- SUPINE 30 MINUTES, 8- SUPINE 60 MINUTES/VOLUNTEER SAT-UP

7.4.1 British Geriatric Society analysis

The degree of cognitive decline was divided into mild, moderate and severe as defined by a study carried out by British Geriatric Society. (Table 24 and Figure 77)

Time point	Normal cognitive function	Mild cognitive dysfunction	Moderate cognitive dysfunction	Severe cognitive dysfunction
1	20	40.00	20.00	20.00
2	20	40.00	13.33	26.67
3	6.67	40.00	20.00	33.33
4	0	40.00	33.33	26.67
5	6.67	40.00	26.67	26.67
6	13.33	26.67	20.00	40.00
7	26.67	26.67	13.33	33.33
8	26.67	33.33	0.00	40.00

TABLE 24 PERCENTAGE OF VOLUNTEERS WITH COGNITIVE DECLINE AT EACH TIME POINT. 1-TRENDELENBURG 30 MINUTES, 2- TRENDELENBURG 60 MINUTES, 3- TRENDELENBURG 90 MINUTES, 4- TRENDELENBURG 120 MINUTES, 5- TRENDELENBURG 150 MINUTES, 6- TRENDELENBURG 180 MINUTES/SUPINE 0 MINUTES, 7- SUPINE 30 MINUTES, 8- SUPINE 60 MINUTES/ VOLUNTEER SAT-UP

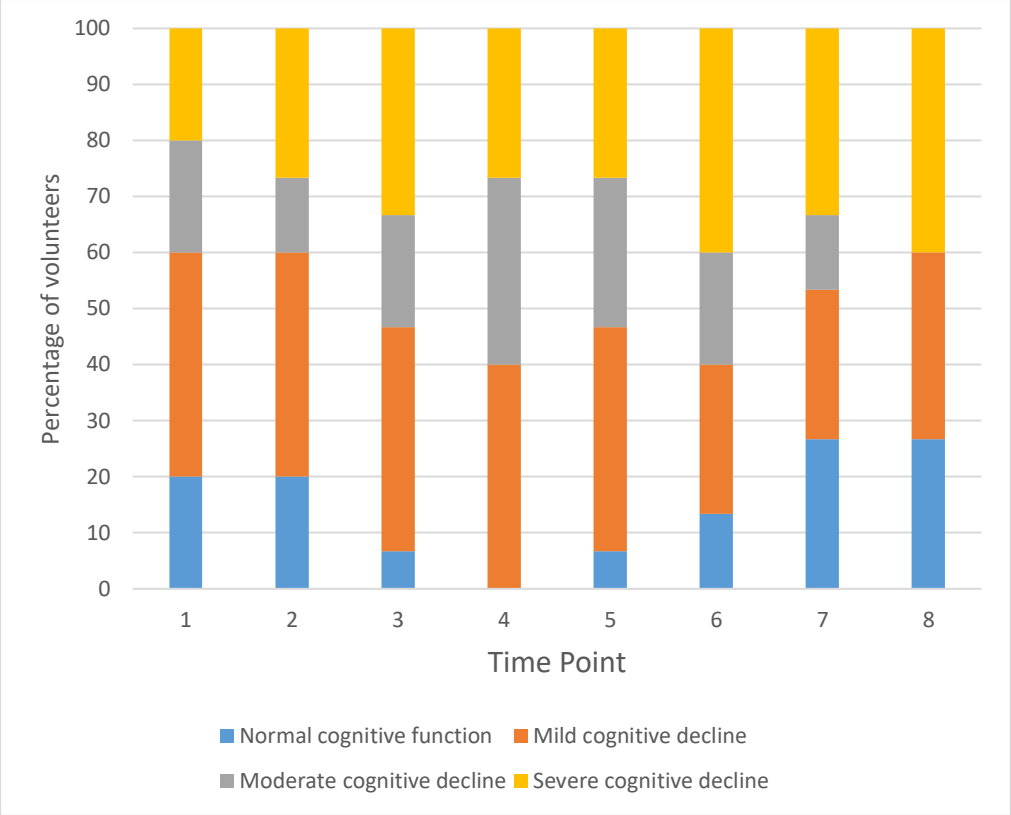


FIGURE 77 PERCENTAGE OF VOLUNTEERS WITH COGNITIVE DECLINE DIVIDED INTO SEVERITY. 1-TRENDELENBURG 30 MINUTES, 2-TRENDELENBURG 60 MINUTES, 3- TRENDELENBURG 90 MINUTES, 4-TRENDELENBURG 120 MINUTES, 5- TRENDELENBURG 150 MINUTES, 6-TRENDELENBURG 180 MINUTES/SUPINE 0 MINUTES, 7- SUPINE 30 MINUTES, 8- SUPINE 60 MINUTES/VOLUNTEER SAT-UP

7.5 Discussion

This study showed a decline in cognitive function following Trendelenburg positioning. Of our volunteers the percentage with cognitive decline increased gradually whilst in the Trendelenburg position along with the severity of cognitive decline (defined as per BGS). After 30 mins, 20% had severe cognitive decline and after 1.5 hours this had risen to 33.3%.

The overall percentage of volunteers with cognitive decline increased to 40% after 3 hours in the Trendelenburg position. After 1.5 hours when 33.3% had cognitive, but the severity of cognitive decline reduced to 26.7% after 2 hours. This could be due to adaptation to being placed in the Trendelenburg position as per the Monroe-Kellie doctrine, or possibly due to 5 of the 15 volunteers requiring a toilet break between 1.5 hours and 2 hours into the test. The Monroe-Kellie doctrine divides the brain into four compartments: cerebrospinal fluid (CSF); brain tissue; venous blood; and arterial blood. It states that the cranial compartment is fixed in volume. The 4 compartments aim to remain in equilibrium where possible to maintain this. The relationship between these four compartments and ICP is known as the Monroe-Kellie doctrine hypothesis. CSF and blood volume are the buffers for this equilibrium and are able to maintain a normal ICP for any change in volume less than 120mls (Arthur C. Guyton, 2006).

The severity of cognitive decline also increased the longer volunteers remained in the head down position. The severity reduced almost immediately once the volunteer was placed in the supine position as the overall percentage with cognitive decline reduced from 86.7% to 33.3%, and those with severe cognitive decline reduced from 40% to 33.3%. After 30 minutes in the supine position, the overall percentage with cognitive decline reduced to 73.3%, and those with severe cognitive decline reduced from 40% to 33.3%. This shows that even a short break from Trendelenburg positioning can improve cognitive function.

Once the patient was sat up (after 3 hours in the Trendelenburg position and 1 hour supine), the initial tests revealed a slight increase again in those with overall cognitive decline from 33.3% to 40%. When sitting from a supine position, there are many physiological changes that initially occur. Deegan *et al* recruited 19 healthy volunteers and induced transient hypotension whilst in both the seated and supine position and measured mean arterial pressure, cerebral blood flow in the middle and anterior cerebral artery along with cerebral autoregulation response. They found auto regulatory responses were worse in the seated position in both the anterior and middle cerebral artery which was thought to be due to the hydrostatic gradient that occurs whilst seated (Deegan *et al*., 2010). Previous studies have shown that cerebral autoregulation is dependent on vascular tone (Aaslid *et al*., 1989). Deegan *et al* found a drop in cerebral perfusion pressure lead to dilatation of cerebral vessels which resulted in reduced cerebral vascular resistance. They also looked at the theory of reduced cerebral perfusion pressure resulting from a shift in the auto regulatory curve to the right. However, the subjects included in their study did respond with an increased heart rate suggesting a sympathetic response which should result in vasoconstriction and therefore an increase in cerebral vascular resistance (Deegan *et al*., 2010). This could explain the increase in severity of cognitive decline that occurred at time point 8. Seven of the 15 volunteers required a 'toilet break', the time of which was recorded.

This break was taken between time points 3 and 4 and lasted a maximum of 5 minutes. The volunteers then returned to the Trendelenburg position. This break could explain the reduction in severity of cognitive decline at time point 4. The resulting reduction in cognitive decline that may have occurred following a short period in the upright position compared to the worsened cognitive decline that occurred when in the sitting position, further supports the reduced cerebral perfusion pressure that has been shown to occur when in the seated position versus the supine position. Patients undergoing laparoscopic left sided resections are often placed in either a modified lithotomy position (with the legs slightly flexed) or Lloyd-Davis. Further studies to re-asses the response of a standing/head-up tilt on recovery of cognitive function would be of clinical benefit.

7.5.1 Limitations

There were limitations to this study which included the ‘toilet break’ that was taken that may have affected the results achieved at time point 4. Test fatigue could also be a contributing factor with repetitive tests being carried out in such a short time period. The control group was also younger than study group. Using an age matched group may improve the quality of future studies. A repeat set of tests 24 hours after the end of the study would possibly have been beneficial for assessing the clinical impact.

A further limitation is due to the lack of a clear definition for defining POCD. ISPOCD is the largest study in this area so far, but treats POCD as a binary definition. The use of BGS guidelines on severity of POCD requires clinical validation. BGS defined the criteria for mild POCD as the same as age related decline. It is therefore of limited value in long-term evaluation of POCD.

My results suggest that when in a clinical setting, simply reducing the tilt of the table when the patient is in the modified lithotomy of Lloyd-Davis position may not be the beneficial as this most likely would mimic the physiology of sitting. Our results suggest this could further impair cognitive function due to reduced cerebral vascular resistance that occurs (Deegan *et al*., 2010).

7.6 Conclusion

The results of my study do indicate that Trendelenburg positioning does lead to cognitive decline. This severity did reduce when the volunteer was placed supine for 30 minutes. A study with larger numbers would be of value. Further studies to assess the effect of a ‘break from Trendelenburg’ whilst in the modified lithotomy of Lloyd-Davis position versus supine would also be clinically relevant.

Chapter 8 : Conclusions and Future work

8.1 Summary

The Laparoscopic approach is the gold-standard for colorectal resections as compared to the open approach, it has reported reduced morbidity and a shorter recovery. Studies have shown reduced pain, earlier feeding, earlier mobilisation and reduced hospital stay (Basse *et al*., 2005, Group, 2000). When laparoscopic surgery was initially introduced for colorectal resections, patients were carefully selected to have fewer co-morbidities and smaller tumours. Now laparoscopic surgeons are more comfortable and have more experience with laparoscopic surgery, most cases are at least attempted laparoscopically. This has led to patients with multiple co-morbidities, older patients and more technically demanding procedures being carried out laparoscopically (Frost, 2010, Molloy, 2011). When patients are undergoing pelvic resections in left-sided colectomies, the patient is placed in the Trendelenburg position to move the small bowel out of the pelvis and allow the pelvic dissection to be carried out. With more complex cases, this dissection may take longer and therefore patients may remain in the Trendelenburg position for longer. This is resulting in a potential increase in significant complications such as POVL and POCD. Both complications significantly affect quality of life and independence of patients. This thesis looked at potential causes for these conditions and ways laparoscopic colorectal surgery could be adapted to still offer the benefits over open surgery whilst preventing the increase in risk of POVL and POCD.

8.2.1 IOP: Findings, follow-on study and future work

Chapter 2 was an observational study looking at the effect of varying Trendelenburg position on IOP during laparoscopic colorectal surgery. A correlation co-efficient of 0.78 was calculated showing a strong correlation between degree of Trendelenburg Tilt and IOP. The most significant finding from this observational study showed by reducing the head-down tilt by even a few degrees led to a reduction in IOP and by placing the patient supine, the majority of patients IOP returned to baseline after 5 minutes. This suggests an intra-operative break by placing the patient supine after a given time would reduce the cumulative increase that occurs whilst in the Trendelenburg position. It also presented the need for a preventative solution especially for high risk patients such as those with Glaucoma which led onto the design of the TaPPs Study (chapter 4).

Chapter 4 looked at Acetazolamide as prophylaxis for high risk patients undergoing laparoscopic colorectal surgery. This study showed acetazolamide was effective at reducing the IOP rise that occurred with the Trendelenburg position. This study did not show the same increase in IOP as shown in laparoscopic studies in this area. This could be due to the lack of pneumoperitoneum and GA. As not all patients are placed head-down during laparoscopic colorectal surgery, acetazolamide has the added benefit of not reducing the IOP significantly below the baseline IOP.

A blinded randomised controlled study to assess the effectiveness of acetazolamide versus placebo in patients undergoing laparoscopic colorectal surgery would add significant clinical value.

8.2.2 Cognitive Function: Findings, follow-on studies and future work

Chapter 5 was an observational study looking at the incidence of POCD following laparoscopic colorectal surgery. POCD can significantly affect quality of life in patients who were previously independent but due to the decline in cognition may lose their independence. POCD has also been shown to increase the time to return to work and an increase length of hospital stay.

This observational study did show a significant incidence of POCD in the short-term, however long-term incidence was not statistically significant. This could be due to the patients who were lost to follow-up, were at higher risk of POCD. I therefore designed a study to directly look at the effect of Trendelenburg positioning on cognitive function using healthy volunteers. This led to the Intelligence Study and the BRAIN Study. The limitation in both these studies was the limit on length of time volunteers could tolerate the Trendelenburg position along with the lack of the pneumoperitoneum which has been shown to further increase CVP. The Brain study did show an increase in brain volume on the post-Trendelenburg MRI, though this was not statistically significant. A

potential further study with an MRI's pre- and post- surgery to compare brain matter volume to look for cerebral oedema. As in patient undergoing laparoscopic colorectal surgery, they have the addition of the pneumoperitoneum, potentially longer time spent in Trendelenburg position and the neuroinflammation that occurs due to surgery.

The Intelligence study also revealed an interesting finding in that unlike when the volunteers was supine, if the volunteer was sitting cognitive function decreased. This finding is echoed in Deegan *et al* research who found auto regulatory responses were worse in the seated position in both the anterior and middle cerebral artery which was thought to be due to the hydrostatic gradient that occurs whilst seated (Deegan *et al*., 2010). A randomised controlled study to compare change in cognitive function following laparoscopic colorectal surgery in patients 'intra-operative break' where the patient is kept in the Lloyd-Davis position but the table returned to 0^{o}, to patients who are placed completely supine. This would help to further establish the potential clinical implications of the Intelligence study's findings.

This thesis has provided the framework for future work in this area to further define measures to reduce even further the incidence of rare yet significant complications that can arise from laparoscopic colorectal surgery. The benefits of laparoscopic surgery over open surgery are well documented, and although POVL is a rare complication, it is a significant

complication as it alters the patients' quality of life significantly. POCD has been shown to increase hospital stay and increase the time needed off work. Further studies to assess potential ways to reduce the incidence in patients would have a financial benefit for all involved.

8.3 Conclusion

In conclusion, the work in this thesis has shown Trendelenburg positioning during laparoscopic colorectal surgery does increase IOP which is a known risk factor for POVL. This rise is proportional to the degree of head-down tilt and time spent in this position. Acetazolamide was shown to be effective in reducing the IOP rise that occurs due to Trendelenburg positioning in healthy volunteers. Patients undergoing laparoscopic colorectal surgery also showed evidence of short and long term POCD. In the short-term, the incidence of POCD was higher in the left-sided colorectal resection group. Healthy volunteer studies showed the longer volunteers spent in Trendelenburg position increased the percentage of volunteers who showed evidence of cognitive decline.

The results of this thesis are of clinical significance in patients undergoing complex procedures that would require long periods in the Trendelenburg position. An introduction of a 'break period' during these procedures where the patient is placed completely supine to reduce the risk of POVL and POCD. With further studies to assess the effectiveness of acetazolamide in patients undergoing laparoscopic colorectal surgery looking at both its effect on IOP and POCD.

List of abbreviations

ASA	American Society of Anaesthesiologist
ATP	Adenosine triphosphate
AUC	Area under the curve
BMI	Body mass index
CA	Carbonic anhydrase
CI	Confidence interval
CLS	Contact lens sensor
CO_2	Carbon dioxide
CPP	Cerebral perfusion pressure
CVP	Central venous pressure
DC	Direct current
Df	Degrees of freedom
Dk/t units	Oxygen permeability x thickness
H^+	Hydrogen ions
H_2O	Water
HCO_3^-	Bicarbonate
ICP	Intracerebral pressure

IOP	Intraocular pressure
IV	intravenous
K^+	Potassium
KG	Kilograms
MAP	Mean arterial pressure
Mcg	micrograms
Min	minutes
mm	millimetres
mmHg	Millimetres of mercury
MMSE	Mini mental state examination
mVeq	Millivolts equivalents
Na^+	Sodium ions
O_2	Oxygen
$PaCO_2$	Partial pressure of carbon dioxide
PaO_2	Partial pressure of oxygen
PCA	Patient controlled analgesia
PEEP	Positive end expiratory pressure
pH	Potential of hydrogen
POCD	Post-operative cognitive decline

POVL	Post-operative vision loss
SD	Standard deviation
UK	United Kingdom
µm	micrometre
µA	Micro Ampere

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Appendix

		Mean	Standard Error Mean	95% Confidence Interval of the Difference		t	Sig. (2-tailed)
				Lower	Upper		
Pair 1	Frontal Pole	167.85	340.44	-567.63	903.34	0.49	0.63
Pair 2	Insular Cortex	-9.84	85.47	-194.49	174.80	-0.12	0.91
Pair 3	Superior Frontal Gyrus.	-1.45	169.43	-367.48	364.58	-0.01	0.99
Pair 4	Middle Frontal Gyrus.	48.799	169.67	-317.75	415.35	0.29	0.78
Pair 5	Inferior Frontal Gyrus pars triangularis	26.82	32.46	-43.32	96.97	.826	0.42
Pair 6	Inferior Frontal Gyrus pars opercularis	-4.73	35.48	-81.39	71.92	-0.13	0.90
Pair 7	Precentral Gyrus	59.69	229.57	-436.27	555.65	0.26	0.80
Pair 8	Temporal Pole	-80.02	124.18	-348.29	188.24	-0.64	0.53
Pair 9	Superior Temporal Gyrus anterior division	-27.11	19.02	-68.19	13.98	-1.43	0.18
Pair 10	Superior Temporal Gyrus posterior division	-38.97	43.91	-133.84	55.90	-0.89	0.39

Pair 11	Middle Temporal Gyrus anterior division	11.28	21.91	-36.06	58.62	0.52	0.62
Pair 12	Middle Temporal Gyrus posterior division	-0.53	47.48	-103.11	102.05	-0.01	0.99
Pair 13	Middle Temporal Gyrus temporo-occipital part	-12.49	40.61	-100.23	75.24	-0.31	0.76
Pair 14	Temporal Gyrus anterior division	-16.56	24.92	-70.39	37.28	-0.66	0.52
Pair 15	Inferior Temporal Gyrus posterior division	-72.19	50.96	-182.28	37.90	-1.42	0.18
Pair 16	Inferior Temporal Gyrus temporo-occipital part	-36.98	38.30	-119.73	45.77	-0.97	0.35
Pair 17	Postcentral Gyrus	-11.45	253.08	-558.19	535.30	-0.05	0.97
Pair 18	Superior Parietal Lobule	-4.73	74.49	-165.66	156.19	-0.06	0.95
Pair 19	Supra marginal Gyrus	-27.16	46.71	-128.07	73.75	-0.58	0.57

	anterior division						
Pair 20	Supra marginal Gyrus posterior division	-31.53	58.33	-157.55	94.48	-0.54	0.60
Pair 21	Angular Gyrus	-33.67	40.62	-121.41	54.08	-0.83	0.42
Pair 22	Lateral Occipital Cortex superior division	-43.36	158.85	-386.54	299.82	-0.27	0.79
Pair 23	Lateral Occipital Cortex inferior division	-71.15	90.91	-267.55	125.25	-0.78	0.45
Pair 24	Intra-calcarine Cortex	-39.42	46.93	-140.81	61.96	-0.84	0.42
Pair 25	Frontal Medial Cortex	-3.60	30.79	-70.13	62.91	-0.12	0.91
Pair 26	Juxta positional Lobule Cortex	-8.41	55.60	-128.52	111.70	-0.15	0.88
Pair 27	Subcallosal Cortex	-31.23	38.24	-113.85	51.39	-0.82	0.43
Pair 28	Para cingulate Gyrus	-13.01	76.75	-178.82	152.81	-0.17	0.87
Pair 29	Cingulate Gyrus anterior division	-26.61	81.99	-203.75	150.52	-0.33	0.75

Pair 30	Cingulate Gyrus posterior division	-82.03	65.51	-223.56	59.51	-1.25	0.23
Pair 31	Precuneous Cortex	-178.87	132.89	-465.96	108.23	-1.35	0.20
Pair 32	Cuneal Cortex	-25.86	23.26	-76.11	24.40	-1.11	0.29
Pair 33	Frontal Orbital Cortex	19.33	64.85	-120.77	159.43	0.30	0.77
Pair 34	Parahippocampal Gyrus anterior division	23.95	70.66	-128.70	176.61	0.34	0.74
Pair 35	Parahippocampal Gyrus posterior division	-28.73	46.95	-130.1	72.69	-0.61	0.55
Pair 36	Lingual Gyrus	-202.96	119.03	-460.12	54.19	-1.72	0.11
Pair 37	Temporal Fusiform Cortex anterior division	-39.21	29.84	-103.68	25.27	-1.31	0.21
Pair 38	Temporal Fusiform Cortex posterior division	-47.05	43.78	-141.64	47.54	-1.08	0.30
Pair 39	Temporal Occipital	-68.55	53.55	-184.24	47.15	-1.28	0.22

	Fusiform Cortex						
Pair 40	Occipital Fusiform Gyrus	-85.60	63.79	-223.41	52.20	-1.34	0.20
Pair 41	Frontal Opercul um Cortex	-5.25	19.03	-46.35	35.86	-0.28	0.79
Pair 42	Central Opercul ar Cortex	-46.70	61.17	-178.85	85.45	-0.76	0.46
Pair 43	Parietal Opercul um Cortex	6.35	41.36	-83.01	95.70	0.15	0.88
Pair 44	Planum Polare	-15.17	30.78	-81.67	51.32	-0.49	0.63
Pair 45	Heschls Gyrus	12.64	19.17	-28.77	54.05	0.66	0.52
Pair 46	Planum Tempor ale	21.37	33.95	-51.98	94.71	0.63	0.54
Pair 47	Supra calcarin e Cortex	-15.42	8.72	-34.25	3.42	-1.77	0.10
Pair 48	Occipital Pole	-80.19	217.92	-550.98	390.60	-0.37	0.72

Table 25 Paired T test analysis of structural MRI Run 1 compared to Run 2