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The Effect Of Body Position On Cerebral Bllod Flow, Cognition, Cardiac Output, Map,and Motor Function In Patients Undergoing Shoulder Surgery : Lateral Versus Beach Chair Position Under General Anesthesia

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THE EFFECT OF BODY POSITION ON CEREBRAL BLOOD FLOW, COGNITION, CARDIAC OUTPUT, MAP, AND MOTOR FUNCTION IN PATIENTS UNDERGOING SHOULDER SURGERY: LATERAL VERSUS BEACH CHAIR POSITION UNDER GENERAL ANESTHESIA

by

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DISSERTATION

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Approved by:

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Advisor   Date

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DEDICATION

I would like to dedicate this dissertation to my family. To my father and mother who encouraged my educational interests. You babysat so I could pursue my career and instilled dedication, perseverance, and a work ethic when I was young. To my husband and daughter who have been my driving force to succeed and who have always been my backbone of support and biggest cheerleaders. You pushed me when I needed it and most importantly understood the time commitment. Lastly, to my dog Roxy for teaching me what loyalty is and for all my foster pets that are the epitome of strength and forgiveness and surround me with love at the end of the day. Thank you all!

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

AERIS- Adaptive extraction and recognition of importance signals

ANCOVA- Analysis of covariance

ATP- Adenosine tri phosphate

BBB- Blood brain barrier

BJR- Bezold Jarisch reflex

BP- Beach chair position

CBF- Cerebral blood flow

CDE- Cerebral desaturation events

$CmRO_2$- Cerebral metabolic rate of oxygen consumption

CO- Cardiac output

CO_2- Carbon dioxide

CPP- Cerebral perfusion pressure

CSF- Cerebral spinal fluid

CPP- Cerebral perfusion pressure

CVLT- California verbal learning test

CVP- Central venous pressure

DAG- Diacyglycerol

EEG- Electroencephalogram

20-HETE-20-hydroxy eicosatertraenoic

HMGB1-

ICG- Impedance cardiography

ICP- Intracranial pressure

GA- General anesthesia

K_a-Activated potassium channels

LD- Lateral decubitus position

MAC- Minimum alveolar concentration

MAP- Mean arterial pressure

NIPS- Near infrared spectroscopy

NO- Nitric Oxide

PACU- Post anesthesia care unit

PAO_2- Partial pressure of arterial oxygen content

PaO_2-Partial pressure of alveolar oxygen content

PO_2- Partial pressure of oxygen

PCO_2- Partial pressure of carbon dioxide

PLC- Phospholipase C

RA- Regional anesthesia

RAVLT- Rey Auditory Verbal Learning Test

RN- Registered nurse

rSO_2- Regional cerebral oxygen saturation

sCO_2- Cerebral oxygen concentration

tPA- Tissue plasminogen activator

WAISIII-Wechsler adult Intelligence scale

WTAR- Wechsler test of adult reading

Z MARC- Modulation aortic compliance

CHAPTER 1

Introduction

In recent years, multiple reports of catastrophic brain injuries have been reported on patients undergoing general anesthesia in surgical positioning that requires the head to be higher than the body; such as beach chair position or reverse trendelenberg position. At my institution of employment we too have had the unfortunate incident of a cerebral vascular accident on a relatively young and healthy patient during a laparoscopic cholecystectomy in reverse trendelenberg position. Over time, this patient's symptoms improved, however, according to Anesthesia Patient Safety Foundation (*APSF) Newsletter*, the other reported cases led to permanent disability and even death (10) (*See appendix 2 for case reports).* Because many surgical procedures require a position where the head is elevated above the level of the heart, and this is not an isolated incidence but one of many, it is critical we as medical providers immediately evaluate the cause of these events and implement appropriate practice changes to decrease patient morbidity. Procedures that require a head up position include shoulder surgery, craniotomies, laparoscopic cholecystectomies, plastic surgery, and bariatric surgery to name a few. Normal physiological changes which occur in the sitting position are mainly attributed to gravity. The rationale for decreased cerebral perfusion in this position comes with several hypotheses. The purpose of this study will be to evaluate cerebral perfusion on patients in various positions under general anesthesia with several non invasive monitors which recognize alterations to blood flow in addition to evaluating brain insult with the Beta S-100 lab values and their correlation with neuro-cognitive testing.

Recent analysis of the literature suggests that the sitting position creates specific

physiological conditions conducive to cerebral and spinal cord ischemia. Smelt et al (67) found that a half an hour after positioning anesthetized patients into a sitting position, mean arterial pressure (MAP) decreased to the extent that in one third of patient's cerebral perfusion was threatened. Parvizi et al (52) found 6 cases of stroke or transient ischemic attack in a series of 1636 reviewed orthopedic cases (0.37%). This is roughly 90 times greater than the previously estimated rate (55). From this review, they identified the beach chair position to be an independent risk factor for intra-operative cerebrovascular events (18). In addition, Cullen and Kirby (10) recently published four case reports on relatively healthy patient's having shoulder surgeries in the beach chair position with catastrophic outcomes. The patients' ages ranged from 47- 57 years and the end result for each was permanent neurological damage from cerebral infarcts (temporal lobe cortical infarct, posterior circulation infarct involving the midbrain, left hemispheric watershed infarct, and spinal cord/.medulla infarct). Three of the four patient's remained in a vegetative state and one was brain dead. In the last case report the blood pressure was measured on the patient's calf due to a history of bilateral mastectomies. The *Anesthesia Patient Safety Foundation Newsletter* has now reported 11 more cases and is currently conducting a poll to evaluate the actual number of cases as this just seems to be the tip of the iceberg. It is apparent that a more thorough understanding of the physiological changes associated with the upright position is crucial to prevent catastrophic brain injury.

The catastrophic outcome in all of the above cases was a cerebral vascular accident. A stroke or cerebral vascular accident is the rapidly developing loss of brain function due to a disturbance in blood supply to the brain. This can be the result of bleeding/hemorrhage, ischemia from a clot, or hypoperfusion. Eighty percent of strokes

are ischemic in nature. This is the leading cause of adult disability in the United States and Europe and the number two cause of death worldwide (28). Risk factors for stroke include advanced age, hypertension, previous stroke or transient ischemic attack, diabetes, high cholesterol, cigarette smoking, and atrial fibrillation. Since all documented strokes in the sitting position were ischemic in nature, our focus will be on ischemic pathophysiology. Ischemic strokes may occur due to one of the following reasons; thrombosis, embolism, systemic hypoperfusion, or venous thrombosis (28).

Thrombotic strokes are blood clots which usually form around atherosclerotic plaques. These account for 50% of all strokes. Thrombus may occlude the vessel itself or lead to an embolic stroke when a piece of the plaque breaks off. Thrombotic strokes can be from large vessels like the common and internal carotid arteries, vertebral, or branches of the Circle of Willis. Small vessel disease usually involves smaller arteries in the brain such as branches of the Circle of Willis or middle cerebral artery (28).

Embolic strokes happen when an artery is blocked by an embolus. It is most frequently a thrombus but can be from fat, air, bacteria and/or cancer cells. Emboli can come from the heart in atrial fibrillation or from the leg when a deep vein thrombosis is present. Brain tissue although auto regulated, ceases to function if deprived of oxygen for more than 60 to 90 seconds. After 3 hours, there is irreversible injury and death of tissue. This is why stroke protocols require tissue plasminogen activator (TPA) treatment within 3 hours of onset of symptoms. When adequate blood supply is not delivered to the brain, it resorts to anaerobic metabolism. The brain is especially vulnerable to ischemia since it has little respiratory reserve and is completely dependent on aerobic metabolism. The ischemic cascade as it is referred to, starts with less adenosine tri phosphate (ATP) being produced and a buildup of lactic acid byproducts.

This disrupts the normal acid base balance and results in the destruction of cells. Once oxygen and glucose are depleted, ATP can no longer be made, and energy dependent ion pumps fail. These pumps are necessary for tissue cell survival and there-fore tissue dies in their absence. The excitatory neurotransmitter Glutamate is also given off during ischemia and causes neuronal injury. Extracellular levels are normally kept low by uptake carriers powered by ion pumps. When in this anaerobic state, Glutamate transporters reverse their direction and send glutamate into the extracellular space. Here it acts on NMDA receptors in nerve cells producing an influx of calcium which activates enzymes to digest the cells proteins, lipids, and nuclear material. This calcium influx can also lead to mitochondria failure, energy depletion and trigger apoptosis. This is compounded by free radicals which damage blood vessel endothelium and also initiate apoptosis. This cycle repeats itself resulting in increased cellular death unless adequate perfusion is restored. Maintaining constant cerebral perfusion is critical for maintaining healthy brain tissue and normal brain function.

The Physiology of Cerebral Perfusion

The Brain

The human brain is the center of the nervous system and is a highly complex organ. It is estimated to have 50-100 billion neurons and 1000 trillion synaptic connections (27). This vital organ monitors and regulates the entire body. It receives sensory information which is rapidly analyzed and a response sent out to control actions and functions. Highly proficient and organized, the brain is divided into several areas. In general, the brainstem controls breathing, heart rate, and other autonomic functions. The neocortex is responsible for higher order thinking, learning, and memory, and the cerebellum controls the body's balance, posture, and the coordination of movement.

The dominant feature in the human brain is corticalization. The cerebral cortex is so big it overshadows every other part of the brain. For research purposes it is divided into three regions: the primary sensory region, the primary motor region, and lastly the association areas. The two hemispheres of the brain are identical bilaterally and each one controls the contra lateral side of the body. That is, the left side of the brain controls the right side of the body and vice versa. These two cerebral hemispheres are connected by a very large nerve bundle called the corpus callosum which acts as the primary communication between the two sides (27).

Cerebral Blood Flow

The brain is the least tolerant of ischemia of all of our organs and although it only accounts for about 2% of the body's weight it receives 15% of the cardiac output. (4). Interruption of cerebral blood flow for just a few seconds causes unconsciousness and a few minutes can cause irreversible cellular damage (4). Blood leaves the heart and flows to the brain via two internal carotid arteries and the two vertebral arteries. The major source of flow however is from the internal carotid arteries. It is common to auscultate the neck during preoperative physicals for the presence of bruits indicating alteration to flow in the carotid arteries. The vertebral arteries branch off the subclavian artery and come together to form the basilar arteries. They then split to form two posterior cerebral arteries. The posterior cerebral arteries become part of the circle of Willis. This circle gives rise to three pairs of distributing arteries on each side of the brain. These arteries then lead to further branches that eventually lead to capillaries. Leptomeningeal arteries are also an important collateral circulation in the brain. They provide alternative flow when a distributing artery or one of its branches becomes occluded (4). The leptomeningeal pathways have been shown to be the cornerstone of

cerebral blood flow during ischemia (41). The veins of the brain drain the blood into dural sinuses and out the internal jugular vein.

The skull as we know is a rigid structure enclosing and protecting the brain and vasculature inside. Because if its rigidity the three compartments; brain tissue (80%), blood (12%), and cerebral spinal fluid (8%) are fixed (78). In essence, the skull then is a rigid, fluid filled, fixed box and any change in one compartment will lead to a change in the other. Therefore, it is critical that cerebral blood volume be tightly controlled. As either, brain, blood or cerebral spinal fluid (CSF) increase, intracranial pressure (ICP) rises only slightly until compensatory mechanisms are overcome and then there is a steep rise in ICP with only small changes in volume (77). The formula CPP= MAP-ICP verifies that as ICP rises, higher perfusion pressures are required to prevent ischemia. Thus blood pressure (BP) regulation is essential.

Blood Pressure Regulation

Neural Control

The topic of vascular resistance is highly complicated with many variables and is thought to be controlled by three main mechanisms. The first is by neural control of the sympathetic nervous system. Cerebral blood flow averages 50ml/min/100g of brain tissue. The brainstem controls autonomic function. Sympathetic nerve fibers from the cervical ganglia (superior, middle, and inferior) innervate the brain vasculature. The chain ganglia are located on both sides of the vertebrae. They are postganglionic neurons which release norepinephrine in order to contract vascular smooth muscle cells. It is here that blood pressure is regulated via vascular tone. The brainstem neurons involved are the nTS (*nucleus Tractus Solitarius*) and the ventrolateral medulla (VLM). The *n*TS neurons are responsible for afferent baroreceptor and chemoreceptor activity. The

sensory fibers from the aortic arch baroreceptors travel through the nodose ganglion X, and fibers from the carotid sinus baroreceptors travel through petrosal ganglion IX, to terminate in specific *n*TSsubnuclei. Afferent stimulation causes hypotension and bradycardia. nTS neurons excite cardiac vagal motoneurons to decrease heart rate and cardiac output (CO). nTS neurons also make indirect inhibitory connections with sympathetic pre-motor neurons in the VLM. The ventrolateral medulla premotor neurons connect to sympathetic neurons in the intermediolateral cell column. The hypothalamus, cerebellum, and cortex all mediate cardiovascular adjustments but structures above the medulla cannot maintain blood pressure. The motor cortex controls vasodilatation during exercise and the amygdala during defensive behaviors. The cerebellum controls vasoconstriction pathways and mediates homeostasis during postural changes. Parasympathetic innervation is also present from the vagus nerve; however cerebral vasodilation is very small when activated. A schematic of blood pressure regulation is below.
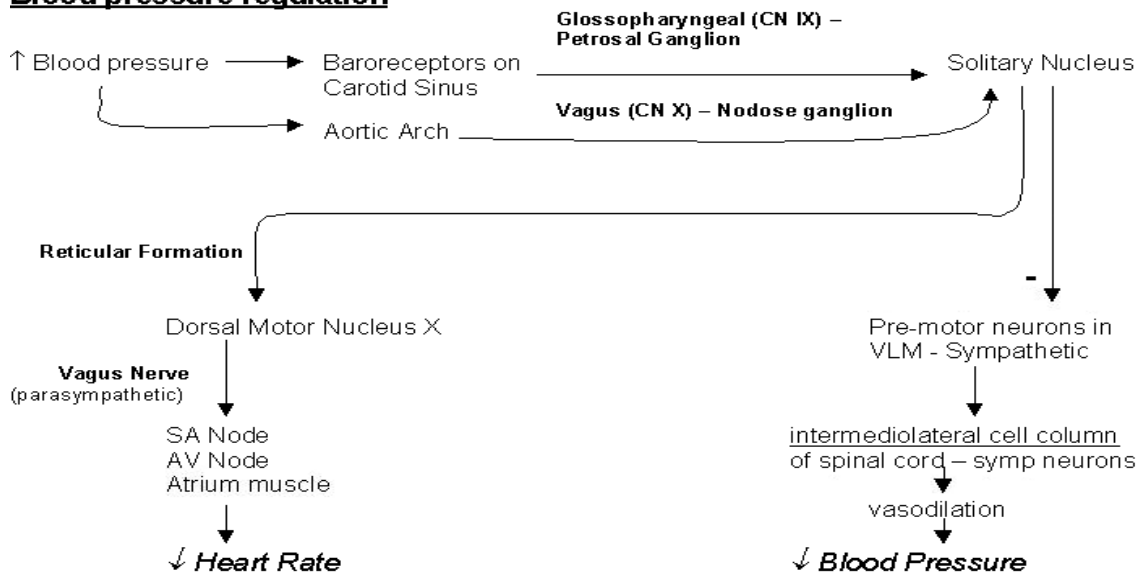
Figure 1.1 Diagram of neural control of blood pressure regulation taken from Clinical Neuroscience online Journal (26).

Although neural control is important, the main control of cerebral vasculature is by metabolic means. Metabolic control is when brain metabolism increases, the partial pressure of oxygen (PO_2) in the extracellular fluid is decreased, which causes an increase in partial pressure of carbon dioxide (PCO_2) and a concomitant decrease in pH. Carbon dioxide is a powerful modulator of cerebrovascular resistance. Cerebral blood flow is directly related to $PaCO_2$. Carbon dioxide reactivity refers to the ability of the brain vessels to vasoconstrict in the presence of hypocapnia and to vasodilate in the presence of hypercapnia. This important physiological regulatory response is not impaired by anesthetics (14). In severe hypotensive states, the cerebral vessels are maximally dilated and fail to constrict when $PaCO_2$ decreases (55). The cerebral blood flow (CBF) changes 1-2ml/100g/min for every 1 mmHg change in $PaCO_2$ within the range of 20-80 torr (45). PaO_2 on the other hand does not affect CBF unless levels fall below 50 torr resulting in vasodilation. When hypoxia, hypercarbia, and acidity are present, this results in vasodilation to increase blood flow to the tissue. It is important to understand that systemically this effect is different. If the pH is lowered and PCO_2 kept constant as in metabolic acidosis, there is very little effect on the brain vasculature because hydrogen ions in the blood cannot easily pass through the blood brain barrier. If pH is lowered and PCO_2 increased as in respiratory acidosis in systemic blood, CO_2 can readily cross the blood brain barrier and will lead to a decrease in pH causing pronounced vasodilation in cerebral vessels and an immediate increase in blood flow (4). In opposition, hyperventilating will cause a decreased PCO_2 and an increase pH producing vasoconstriction and a decrease in blood flow. In addition, vasodilation can result from hypoxia or a decreased cardiac output but the effects are far less than are seen from arterial hypercapnia and then may be mediated by other factors such as nitric

oxide, potassium, and adenosine (3). Lastly, cerebral vasculature can have changes due to myogenic control which respond to changes in transmural pressures, causing vasoconstriction (4).

Blood flow to each tissue is delivered with the goal of providing nutrients to each cell in that tissue. Blood flow to the brain must be flexible to meet changing demands. The brain is considered a special circulation in that blood flow is preserved. Consider exercise for example, increased perfusion is directed to active muscle and skin, decreasing flow to splanchnic and renal circulations but conserving flow to the brain (4). Normal cerebral perfusion pressure (CPP) is 80 mmHg, but when reduced to less than 50 mmHg there is metabolic evidence of ischemia and reduced electrical activity. CPP decreases by 15% simply by sitting in an awake patient (43). There have been a number of studies on patients with severe head injuries which have shown an increase in mortality and poor outcome when CPP falls to less than 70 mmHg for a sustained period (45). If blood flow to the brain is reduced below a critical point, there is a fall in venous saturation. As the flow of blood and delivery of oxygen is reduced, the brain, in order to maintain its oxygen supply, extracts more oxygen from blood, leading to a fall in venous oxygen saturation. Hence the potential need for monitoring cerebral oxygenation.

The main regulator of cerebral perfusion is pressure - dependent activation of smooth muscle in brain arterioles and the physiologic cascade is pictured below. When perfusion to the brain is increased, arteriolar muscle is stretched. This stretch activates Phospholipase C (PLC) resulting in diacylglycerol (DAG) production and arachidonic acid release. Cytochrome P450 4A2 then converts the arachidonic acid to 20-hydroxy eicosatertraenoic (20-HETE) acid which then activates protein kinase C. Protein kinase

C inhibits potassium channels, with special affinity for calcium-activated potassium channels (K_{ca}) which results in a lower membrane potential of the vascular smooth muscle. When vascular smooth muscle is activated, vasoconstriction occurs (24).
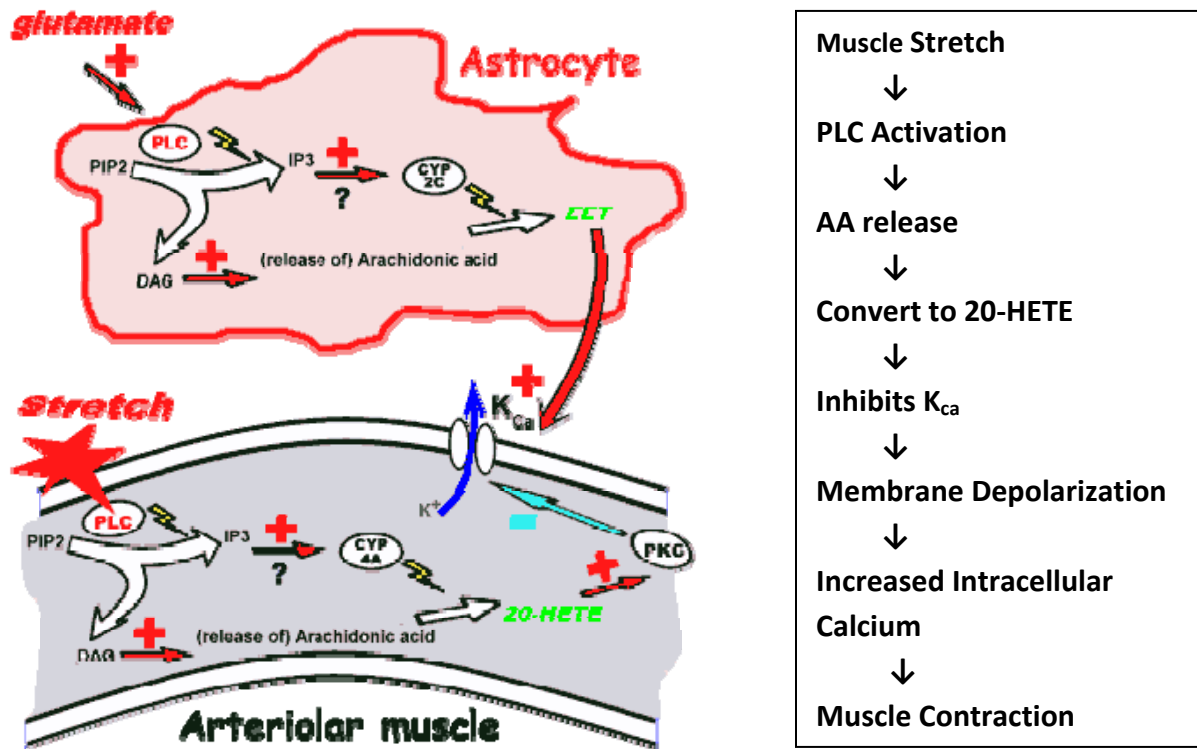
Figure 1.2 Illustration of pressure-dependent activation of smooth muscle taken from anesthetist.com (24)

This pressure dependent activation will maintain blood flow over a wide range of pressures. However, when local cellular metabolic activity increases, glutamic acid spills over from the neuron, causing astrocyte membranes to release arachidonic acid. The arachidonic acid is then converted by cytochrome p450 2C11 (in rats) to epoxyeicosattrienoic acid (EET). EET diffuses to nearby smooth muscle and stimulates K_{ca}, antagonizing the effect of HETE. Thus cerebral autoregulation is a balance between HETE which causes vasoconstriction and ETE which vasodilates. Other metabolites may also be released from astrocytes such as thromboxane A2, PgE, PgF

and prostacycline (24). Lastly, metabolic mediators and chemoregulation have a role in modulating cerebral blood flow (CBF). Mediators such as H^+, K^+, adenosine, phospholipids, angiotensin II, and most recently nitrous oxide (NO) have been described in the literature (45). NO cause's vasodilation increasing CBF (38). NO, adenosine and prostacycline have been shown to affect K_{ca} channels. Angiotensin II may also play a role.

In addition to all of the above regulators of perfusion, several studies suggest CBF can be compromised by mechanical obstruction and injury to major veins and arteries during head positioning in the sitting position. Blood flow reduction in the vertebral artery caused by extension and rotation or tilt of the head may result in posterior brain circulation infarcts. Specific blood flow obstruction of the internal jugular veins in the sitting position can also impede cerebral venous drainage (10). Finally, hypotension and generalized circulatory instability can be caused by gas embolism. This rare complication has been reported with air and CO_2 distension of the joint capsule followed by pressurized injection of irrigation fluid (10).

Autoregulation

The brain has a precise regulatory system where CBF and metabolism are coupled. Cerebrovascular autoregulation refers to the ability of brain vessels to vasoconstrict and vasodilate within a wide range of cerebral perfusion pressure (CPP). Cerebral autoregulation has been thought to maintain cerebral blood flow constant between a mean arterial pressure (MAP) of 50-150 mmHg. Beyond these limits, CBF becomes blood pressure dependent. A common concern among anesthesia personnel is that the uncontrolled hypertensive patient's autoregulation is shifted to the right requiring a higher CPP to ensure adequate perfusion.

In recent years, Drummond *et al* (10) suggested that the 50 mmHg for the lower limit of autoregulation should be modified upward to reflect a range of values from 70-93 mmHg. If CPP increases, cerebrovascular constriction occurs with the effect of decreasing cerebral blood volume and maintaining a constant cerebral blood flow. Similarly, decreases in CPP induce autoregulatory vasodilation, an increase in cerebral blood volume, and maintenance of a constant cerebral flow. In cases of impaired cerebral blood flow, autoregulation changes and cerebral blood flow occurs in a pressure passive fashion with an inverse effect on cerebral volume. That is, with increases in CPP, cerebral blood volume increases because the vessels get passively dilated, and with decreasing CPP there is a vascular collapse and a decreased flow and blood volume. Intravenous anesthetic agents (hypnotics, ketamine, and opioids) maintain cerebral blood flow autoregulation. In contrast, drugs with vasodilating potential such as desflurane and high dose sevoflurane impair dynamic and static autoregulatory responses (14).

Anesthetic Influence on Physiological Factors in the Sitting Position

The term sitting position refers to any position where the torso is elevated above the legs. Depending on the surgical procedure, this position can range from a true 90 degree sitting position to a modified 45 degree position. The advantages of this position are usually surgeon preference based on technique and anatomy. Complications of this position under anesthesia include; eye injury, jugular venous obstruction, endobronchial intubation from flexion of the neck, pressure necrosis of the skin, cervical spine injury, stroke, and even death (55).

In the upright position under a general anesthetic there are several complicating factors altering the normal physiological processes. Cardiovascular changes are

minimal in the 45 degree head up position but cardiac output decreases 20% when the head is raised to 90 degrees (49).

Figure 1.3 Diagram of sitting position for shoulder surgery taken from www.pitt.edu-sitting-general

This decrease in cardiac output is primarily due to a decrease in venous return and is exaggerated by the vasodilatory properties of the anesthetics. Other significant changes in the upright position include; a decrease in the mean arterial pressure (MAP), central venous pressure (CVP), pulmonary artery occlusion pressure, stroke volume, cardiac output (CO), and PaO_2. Factors that are increased include: Alveolar-arterial oxygen concentration gradient (PAO_2-PaO_2), pulmonary vascular resistance and total peripheral resistance. SVR and HR general increase 50-80% under normal physiologic, non-anesthetized conditions to offset the above effects. However, this autonomic

response is blocked by vasodilating anesthetics, which further exacerbate and compromise cardiac output. In addition, blood pressure and cerebral perfusion pressure decrease due to vasodilation and impaired venous return. In the awake patient, venous return from the cerebral circulation is usually increased by inspiratory subatmospheric pressure during spontaneous ventilation, but this mechanism is nullified by positive pressure ventilation.

Cerebral Steal refers to the stealing of blood from one area of the brain to give to another. When there is an ischemic area of the brain, vessels are already maximally dilated and therefore do not receive an increase in CPP. Adjacent brain regions do however respond with an increase in flow to healthy tissues. Inverse Steal or the Robin Hood phenomenon as it is called is the opposite in that blood is taken from rich, healthy tissues and directed to ischemic or poor areas. This effect is due to vasoconstriction secondary to hypocapnia or an anesthetic agent such as Pentothal (45).

Cerebral Perfusion pressure is determined by the difference between the MAP and intracranial pressure (ICP). In general, anesthetic agents (Propofol, barbiturates, benzodiazepines, opiods, and inhalation agents) all decrease MAP in a dose dependent fashion. Their potential to decrease systemic hemodynamics is related to the speed of application and pre-existing volume status of the patient. The only drug with stimulating potential on hemodynamics is ketamine. In contrast, barbiturates and Propofol decrease ICP, with benzodiazepines, ketamine, and sevoflurane <1 minimum alveolar concentration having little to no impact on ICP. Due to their potent vasodilating stimulation, desflurane, isoflurane and nitrous oxide increase ICP due to increases in cerebral blood volume. Therefore, barbiturates and propofol may increase CPP if the administration is not associated with the decrease in MAP but only with an increase in

ICP. While benzodiazepines and narcotic agents have little or no effect on CPP because their net zero effects on MAP and ICP.

Anesthetic Agents and their Effects on Cerebral Perfusion

The effects of anesthetic agents on cerebral perfusion are of utmost importance when administering to a patient in the upright position. Propofol is the number one induction agent used in anesthesia today. Because it has favorable kinetics with a rapid redistribution, patients wake up fast decreasing hospital stays and costs. It has a GABA mimetic action resulting in dose dependent sedation or anesthesia. It significantly reduces cerebral blood flow, the cerebral metabolic rate of oxygen consumption ($CMRO_2$), ICP, and cerebral perfusion pressure. These effects are due to a decrease in MAP and cerebral vasoconstriction (49). Engelhard summarizes the implications in a 2009 review. He states that in regards to anesthetic implications on vasodilation and vasoconstriction, Propofol and thiopental produce vasoconstriction in brain vessels. Propofol vasoconstricts more frontal and brain stem territories while thiopental is predominantly vasoconstricting in occipital brain territory (14). Propofol has been shown to vasodilate by blocking sodium and calcium channels in in- vitro bovine arterial segments. However, *in vivo* preparations are shown to be vasoconstrictive. This vasoconstriction decreases cerebral metabolism and cerebral blood flow. This is likely caused by a combination of CNS, cardiac, and baroreceptor depression along with systemic vasodilation (49). Propofol is also the most cardiac depressing induction agent used in anesthesia, more so than Etomidate and thiopental.

Thiopental used as an induction agent has a profound effect on cerebral metabolism. There is a dose dependent decrease in $CMRO_2$ and cerebral blood flow due to cerebral vasoconstriction (45, 49). This is due to an influx of calcium into

vascular smooth muscle cells (45). In addition, its cardiac effects are dose dependent decreasing cardiac output, contractility, and SNS outflow which results in vasodilation (49). It minimally depresses baroreceptor activity so these changes result in an increase in heart rate. Hypovolemic patients can have a 69% reduction in cardiac output and a significant decrease in blood pressure from Pentothal (49).

Etomidate, also used as an induction agent in anesthesia, decreases cerebral blood flow (34%) and $CMRO_2$ (45%) respectively. A major advantage of this drug is its ability to maintain hemodynamic stability. There are minimal changes in heart rate and blood pressure keeping cerebral autoregulation intact and eliminating the possibility of pressure dependent cerebral flow (47). A disadvantage is the high incidence of myoclonus and adrenal cortical suppression (45).

Ketamine, a non-competitive NMDA receptor antagonist, induces regional specific vasodilation and increases and decreases cerebral metabolism in distinct brain regions. Ketamine is a direct cerebral vasodilator irrespective of cerebral metabolic demands (14). It has been shown to increase CBF 60-80% and return to normal in 20-30 minutes. This is attributed to its excitatory effects and increase in $CMRO_2$ (49). Cardiovascular effects include increased blood pressure, heart rate, cardiac output and central venous pressures with an increase in myocardial oxygen consumption. Therefore, it is used cautiously in cardiac patients. However, the main complaints by patients are hallucinations and nightmares under anesthesia thus, is used less frequently because of this undesirable effect.
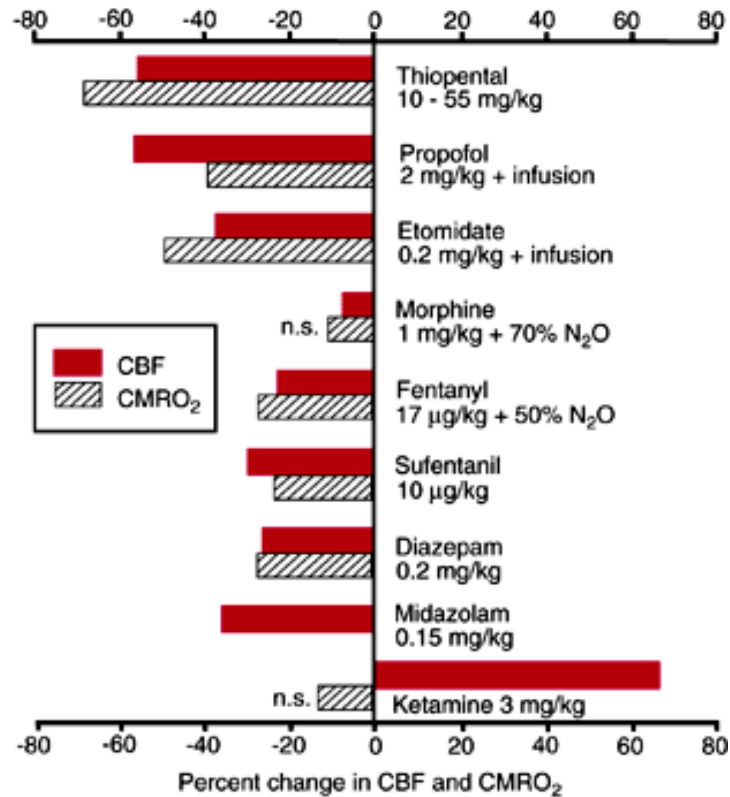
Table 1.4. Changes in cerebral blood flow (CBF) and cerebral metabolic rate for oxygen ($CMRO_2$) caused by intravenous anesthetic agents. The data are derived from human investigations and are presented as a percentage of change from unanesthetized control values. Taken from Pharmacology and Physiology for Anesthesia: Foundations and clinical applications ISBN :978-1-4377-1679-5. Chapter 19

Benzodiazepines also cause a decrease in CBF due to a decrease in CVR and $CMRO_2$ but is less than that observed with other anesthetics. Foster *et al* found a 30-34% decrease in CBF with 0.15mg/kg of midazolam in healthy volunteers (45).

Narcotics show a minimal to modest decrease in CBF and $CMRO_2$ but in general do not induce any major changes in cerebral hemodynamics and are therefore used to provide analgesia in neurological patients. In a comparison of fentanyl, alfentanil and sufentanil on CPP and ICP, fentanyl was found to be the ideal narcotic as it had no significant effect on ICP and decreased CPP by 28% for brain tumor patients (45).

Cholinergic agonists such as neostigmine, used to reverse neuromuscular blockade, can mimic REM sleep as natural sleep is maintained by acetylcholine. The

agonists are then thought to increase CBF. However, anticholinergics like robinul and atropine are given during general anesthetics along with cholinergic agonists to offset the profound cardiac effects and they themselves decrease CBF (45). Local anesthetics rapidly cross the blood brain barrier and modestly decrease $CMRO_2$ (20%) and CBF (24%) (45).

Unlike local anesthetics, muscle relaxants do not cross the blood brain barrier but can release histamine resulting in vasodilation. Succinylcholine which is a depolarizing muscle relaxant, and commonly used in anesthesia, causes fasciculation's or increased muscle spindle activity increasing CBF and ICP. Its use is controversial when ICP is a concern. Vecuronium, a commonly used non-depolarizing muscle relaxant, appears to be without any cerebral effects and is becoming a muscle relaxant of choice in neuroanesthesia. Pancuronium, although cost effective, causes a rise in MAP and heart rate. This has not proven to be a problem in canine CBF, $CMRO_2$, or ICP, but in patients where autoregulation is defective, CBF and ICP are increased. Atracurium, is without histamine release but its metabolite laudanosine crosses the blood brain barrier (BBB) and can cause seizures in large doses. However, at clinically relevant doses it appears to maintain CBF, $CMRO_2$, and ICP (45).

Volatile anesthetics used in the operating room today include isoflurane, sevoflurane and desflurane. The conventional understanding of most anesthetics is that they reduce neuronal function and therefore depress metabolic demands. The requirement for less oxygen then reduces cerebral blood flow. Inhalation agents on the other hand are well recognized to cause cerebral vasodilation and increased CBF. Cerebral autoregulation is preserved at concentrations of 1 minimum alveolar concentration (MAC) of almost all volatile anesthetic agents however, when

administering higher doses, there is an uncoupling of the normal metabolism and blood flow relationship (45). Physiologically, when $CMRO_2$ decreases, blood flow is decreased due to a reduced requirement for oxygen delivery and carbon dioxide removal. The anesthetics uncouple this relationship in a dose dependent way. As autoregulation is abolished, CBF becomes pressure dependent. As blood pressure increases, CBF and vasodilation occur. When blood pressure decreases, cerebral blood flow is not sustained because autoregulation was abolished. The effect of anesthesia on CBF autoregulation is seen below.
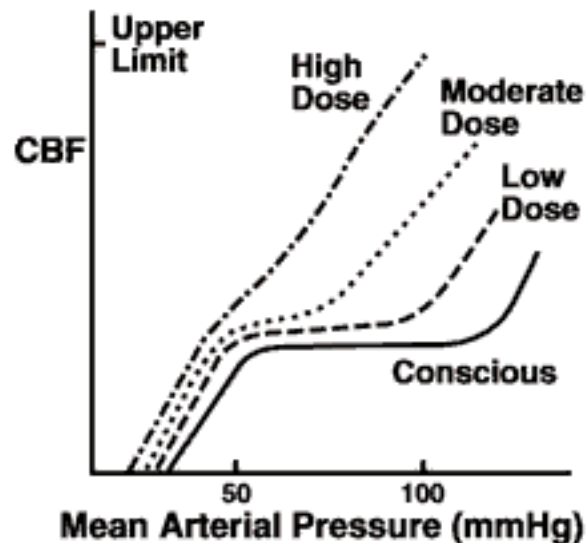
Figure 1.5. The effects of increasing concentrations of volatile anesthetics on CBF autoregulation. Both upper and lower thresholds are shifted to the left. Taken from FJM Walters(78)

The important consequence of this uncoupling with higher doses of agents is that there is a rapid rise in CBF when MAP is increased under anesthesia versus staying at a more constant flow when autoregulation is present.

Volatile anesthetics also shift the CO_2-CBF relationship to the left. That is to say that hypocapnia reduces cerebral blood flow and prevents vasodilation as is physiologically normal, however, if CO_2 rises, a rapid increase in CBF will follow (76).

Sevoflurane has been shown to decrease CBF secondary to a decrease in cerebral metabolism at concentrations less than 1 MAC. This effect is unique as desflurane, and isoflurane have all shown to be potent vasodilators which increase CBF despite the fact that they decrease cerebral metabolism. Because CBF and metabolism are reduced in the presence of Propofol, barbiturates, and sevoflurane, coupling between CBF and metabolism is intact. However, since halothane, isoflurane, and desflurane increase flow but decrease metabolism, the classical approach of flow metabolism coupling is impaired. Similar to the vasodilating volatile anesthetics, nitrous oxide is a potent cerebral vasodilator. The vasodilating properties of nitrous oxide are profound and cannot be entirely antagonized by concomitant hypocapnia. Desflurane, and isoflurane decrease CPP because they decrease MAP or both decrease MAP and increase ICP (11).

In addition to the anesthetics, deliberate hypothermia may be used for cerebral protection. Under anesthesia patients cannot regulate body temperature and become poikilothermic. This decrease in body temperature reduces $CMRO_2$ and therefore CBF. The decreased metabolism is most apparent in the cerebral and cerebellar cortex, less in the thalamus, and minimal in the hypothalamus and brainstem. Neurons are 25-30% more tolerant of hypoxia with a 2-3 degrees centigrade decrease (45). Severe hypothermia on the other hand is harmful as it leads to metabolic acidosis and abolishes autoregulation.

Lastly, intravascular volume must be maintained perioperatively to prevent cerebral ischemia. Hypovolemia is detrimental and can lead to cell death. Optimal perfusion pressures, viscosity, and oxygen delivery are essential in preventing adverse outcomes. Induced hypotension should not be considered in the sitting position as well

as induced hypertension which may increase surgical bleeding and obscure the surgeons view and prolong anesthesia time.

Bezold-Jarisch Reflex

A phenomenon of note in the sitting position has been described in the literature as the Bezold-Jarisch reflex (BJR). This cardio inhibitory reflex occurs in the sitting position when stretch receptors located in the ventricles (mainly the inferoposterior wall of left ventricle) are triggered, increasing parasympathetic nervous system activity and inhibiting sympathetic activity resulting in a triad of bradycardia, hypotension, and peripheral vasodilation (8). These receptors are both mechano (pressure, volume) and chemosensitive (veratrum alkaloids, adenosine, amidine derivatives, and venom). They relay afferent signals via the unmyelinated C fibers of the vagus nerve tonically inhibiting vasomotor centers. Studies suggest the BJR is independent of heart rate modulation (8). Hypotension and bradycardia occur in the presence of other intact reflexes like the baroreceptor reflex, implying that it may inhibit it in either the afferent or efferent pathway (8).
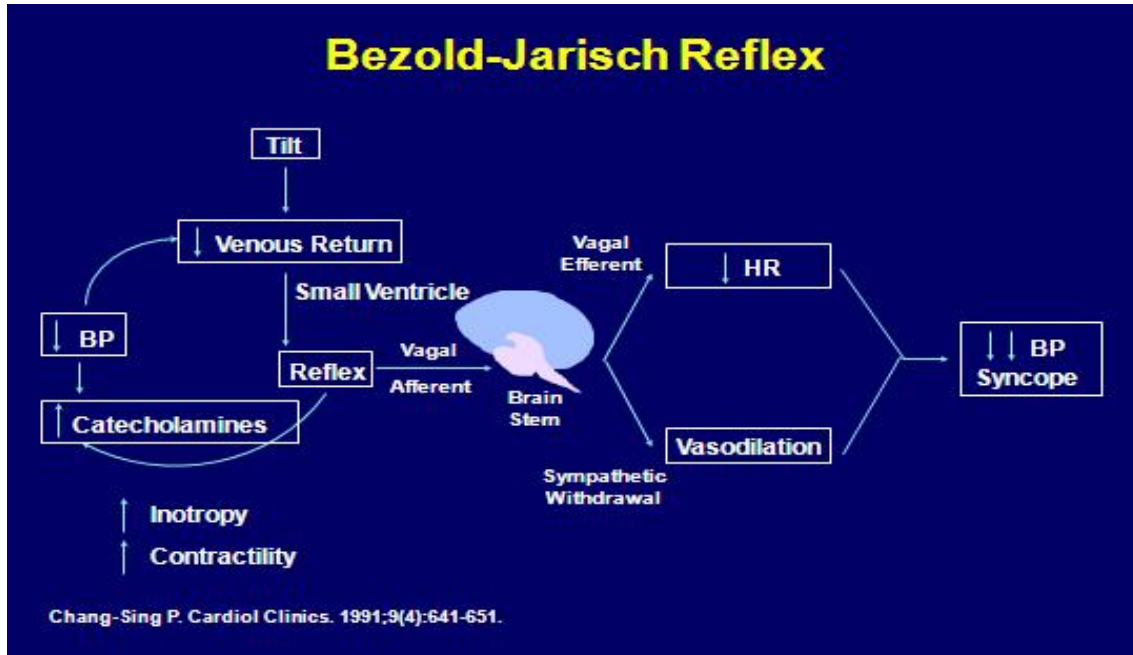
Figure 1.6 Diagram of the Bezold-Jarisch reflex taken from Chang-Sing P. Cardiol Clinics. 1991;9(4):641-651

The regulation of blood pressure is complex with involvement of multiple systems. The vasomotor center under normal physiological conditions keeps blood vessels partially constricted via sympathetic outflow hence the underlying vasomotor tone. It is evident that the BJR works in conjunction with the baroreceptor reflex to control blood pressure. As seen in the diagram above, when there is a decrease in firing from the afferent fibers of the BJR, vasomotor centers are no longer inhibited and there is an increase in blood pressure. However, with an intact baroreceptor reflex, the blood pressure response is attenuated (8).

When both systems are intact, that baroreceptor reflex appears to be the dominant regulator of blood pressure. However, the fact that "vertrum alkaloids can produce such a dramatic blood pressure response in the presence of an intact baroreceptor reflex suggests that this relationship can be uncoupled, and the BJR can be dominant" (8). The response is somewhat different between the two reflexes as the

sympathoinhibitory response of the BJR is more active in renal vasculature versus skeletal vascular beds for carotid baroreceptors.

Literature suggests that shoulder surgeries performed under interscalene block with the patient in the sitting position is associated with an increased incidence of hypotension and bradycardia (13-28%) (65) due to the BJR. It is thought that the combination of peripheral vasodilation, increased contractility from absorbed epinephrine, and vigorous contraction of an empty ventricle activates the BJR. Studies show epinephrine added to the local anesthetic for interscalene blocks significantly increased the incidence of the BJR, 11% versus 29% respectively (65), and metoprolol can decrease the incidence if given prophylactically from 28% to 5% (36). Due to the increased incidence of this reflex with the use of epinephrine in interscalene blocks, all pre-operative blocks in this study will be straight ropivicaine local anesthetic. Interestingly, alpha agonist drugs such as phenylephrine can activate cardioinhibitory receptors (8). This drug is a commonly used to treat hypotension under anesthesia. It is clear from the literature that whatever factors are present during an anesthetic to allow the BJR to become dominant, negates other important homeostatic mechanisms (8).

Thus, the knowledge of anesthetic effects on the physiological variables is essential in the choice of drug for the individual patient. Despite the fairly low incidence of .38%, perioperative stroke is a devastating complication for patients, families, as well as for the health care providers involved. In addition, perioperative stroke has a 60% morbidity compared to 15-46% for stroke in general (49). With all the available perioperative neuro-monitoring techniques available it may well become an integral part of prevention of adverse neurological events.

Monitoring

The choice of monitors for patients in the sitting position under general anesthesia remains controversial. It is interesting that the brain is one of the least monitored organs during anesthesia. Standard monitors used in operating rooms today include the measurement of heart rate, EKG, blood pressure, temperature, oxygen saturation, and end tidal CO_2. There are an increasing number of monitors being introduced to measure other physiological parameters during the perioperative period. Some important considerations for surgery in the sitting position should include; cardiac output, cerebral perfusion and or cerebral blood flow monitoring.

Blood Pressure

Standard blood pressure (BP) measurements are generally taken from the brachial artery of the arm in the sitting position. The issue of concern is that the MAP at the brain is very different when compared to the site where the BP is actually measured in the arm. "*The BP difference will be equal to the hydrostatic pressure gradient between the heart/arm and the brain. If the auditory meatus (used to reflect the base of brain) is 20cm above the level of the heart, the difference will be 15 mmHg. Even accounting for the hydrostatic pressure gradient between the base of the brain and the arm does not take into account the added distance from the base of the brain at the Circle Of Willis, to the most cephalic portion of the cerebral cortex, an additional distance of 10-12 cm depending on the persons height, which represents a further gradient of about 9 mmHg*" (10). To quantitate the hydrostatic gradient, there is a 0.77 mmHg decrease for every centimeter gradient (1mmHg for each 1.2 cm). In general, the approximate distance between the brain and the site of the BP cuff on the arm in the seated position will be 30 cm depending on the angle of the sitting position and the

height of the patient; hence the brain MAP will be 8-24 mmHg lower than the measured mean brachial artery pressure. If the beach chair position is combined with deliberate hypotension, cerebral perfusion will be severely compromised. An even more exaggerated occurrence may develop when the BP cuff must be placed on the leg (in a mastectomy for example). The legs are considerably lower than the brain, thus the gradient will be even greater (10).

Cardiac Output

The pulmonary artery catheter has been in use for decades and has provided valuable clinical information on patient hemodynamics. Today, many more cardiac output (CO) monitors are available which use a wide range of methods to calculate the same values. They include arterial waveform analysis, Partial Fick principle, Bioimpedance, or Esophageal Doppler. Bioimpedence monitoring was developed in 1965 by NASA to estimate CO non-invasively in astronauts. It is one of the few truly noninvasive CO monitors. Impedance is the resistance to alternating current. A small 3mA high frequency current is applied to the thorax and electrodes placed on the thorax measure resulting changes to a given impedance time, mainly from changing aortic volume. In a review of literature of cardiac output monitors, Modeflow had the lowest mean squared error suggesting the best performance (13). CardioQ P, Aesculon, and USCOM showed poor agreement with thermodilution techniques which has been the Gold standard (56), Kuper also reviewed nine available CO monitors and found the BioZ, a bioimpedance monitors accuracy to be rated as reasonable. The advantages of this monitor are that it is noninvasive, easy to use and set up, and provides continuous data; the disadvantage is it becomes highly inaccurate in edematous patients (31). The BioZ diagnostic system uses disposable sensors that transmit a small electrical signal

through the patient's thorax to measure changes in the aortic blood volume and velocity with each heartbeat.   Parameters reported are cardiac output, systemic vascular resistance, contractility, and fluid status.   It then displays the patients impedance cardiography report (ICG) on a screen to identify whether heart function has changed. The machine utilizes Signal processing: AERIS (Adaptive extraction and recognition of Impedance Signals) and the Z MARC (modulating aortic compliance) algorithm to calculate cardiac output.   There are 4 dual skin sensors with 8 lead wires which are placed on the patient's neck and chest.   Depicted below are the sensors, leads and BioZ machine.

Figure 1.7 The Cardiodynamic Bio Z machine and sensors pictured above used in this study to monitor cardiac output taken from Cardiodynamics brochure

Figure 1.8 The Cardiodynamic Bio Z display screen and sensor placement are pictured above taken from Cardiodynamics brochure

Leads are placed as seen in the above right diagram and in the event of a cable,

sensor disconnect or malfunction, a warning screens presents to identify the problem. A status report can then be printed providing each patient's individual data.

Cerebral Oximetry

Cerebral oxygenation has not been routinely monitored in patients undergoing surgery because it required a sampling of blood from the jugular vein by way of a central venous catheter. The technique was also flawed in that it missed regional malperfusion. Cerebral oximetry monitoring is an upcoming technique used intraoperatively to measure cerebral oxygenation. It is non-invasive and may prevent devastating outcomes (16). A study by Tobias comparing the pulse oximeter to the cerebral oximeter showed that in all 42 cases studied, the cerebral oximeter was more sensitive and detected a drop in rSO_2 before a drop in SaO_2 (71). The cerebral oximeter estimates regional tissue oxygenation by transcutaneous measurements of the frontal cerebral cortex which is most vulnerable to ischemia due to a limited oxygen reserve (67). It determines oxygenation by the amount of light absorbed by hemoglobin. There are two photo detectors one deep, and one shallow for each light source to allow the selective sampling of tissues.
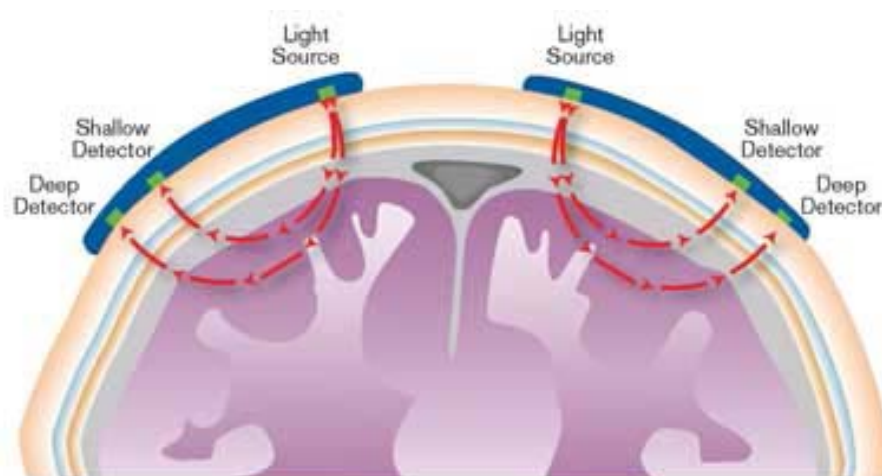
Figure 1.9 The cerebral oximeter works via two detectors that detect deep and shallow light on right and left hemispheres. Taken from www.apsf.org website

It is not dependent on pulsatile flow like a pulse oximeter. Many articles have published the benefits of cerebral oximetry. Rubio et al and others confirmed the use of near infrared spectroscopy (NIRS) as a feasible technique to avoid complications and optimize clinical outcomes related to cerebral malperfusion (63). The Nonin Oximeter has proven a valuable device in this arena and its usefulness is depicted in the schematic below of a patient undergoing surgery in the sitting position.
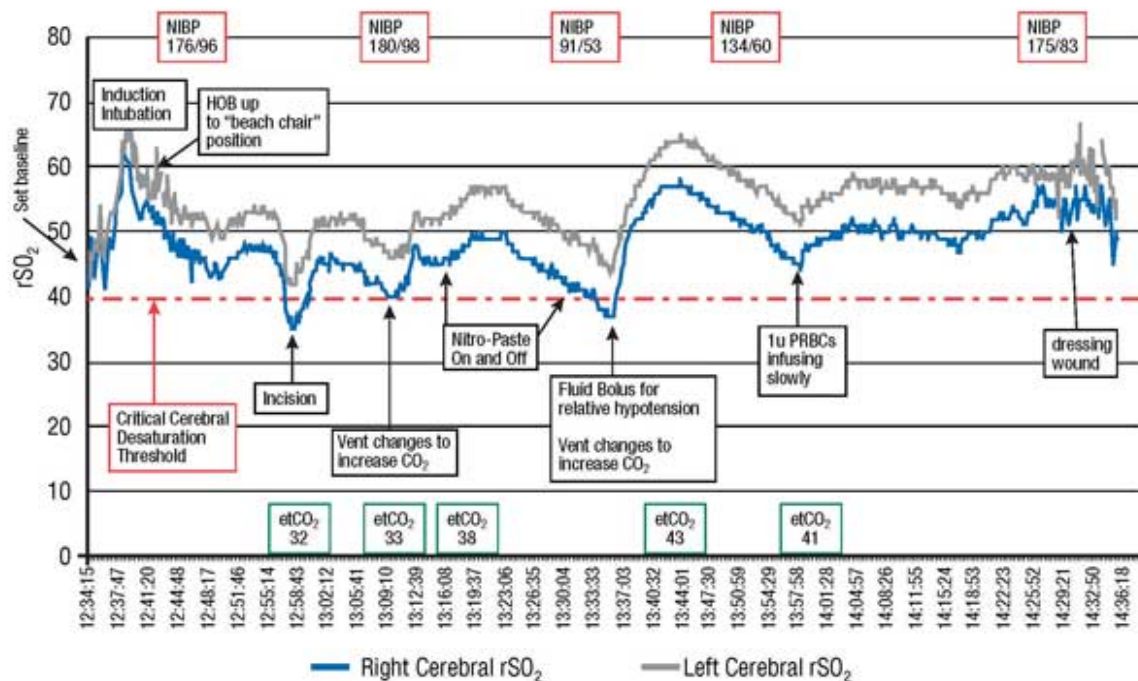
Figure 1.10 Graph of cerebral perfusion data during surgery taken from Fischer (16). The cerebral perfusion (rSO2) correlates with changes in MAP under anesthesia

As seen in the data above, a drop in blood pressure correlates with a drop in cerebral oxygenation and provides real time information on anesthesia management during the surgical procedure. Everything from oxygen demand and supply, to the need for fluid resuscitation are apparent. In a review by Casati et el (9), due to the wide variability in baseline cerebral oxygen saturation (rSO_2) measurements from patient to patient, baseline values need to be determined prior to anesthesia as cerebral ischemia

is considered a reduction of 20% from baseline. They also note that if baseline rSO_2 is less than 50% to start, the critical threshold of 20% should be reduced to 15% for that patient. Routine use of this monitor in anesthesia has been shown to improve patient outcome and shorten hospital stay (9). The value of this monitor under anesthesia is again reported by Fischer which depicts the direct correlation of blood pressure to cerebral perfusion in the data shown in the graph to the right. As MAP drops, S_cO_2 drops. When phenylephrine is given in boluses, MAP and S_cO_2 rise. Not only was the oximeter helpful in correlating MAP to S_cO_2 but also to end tidal carbon dioxide levels shown below
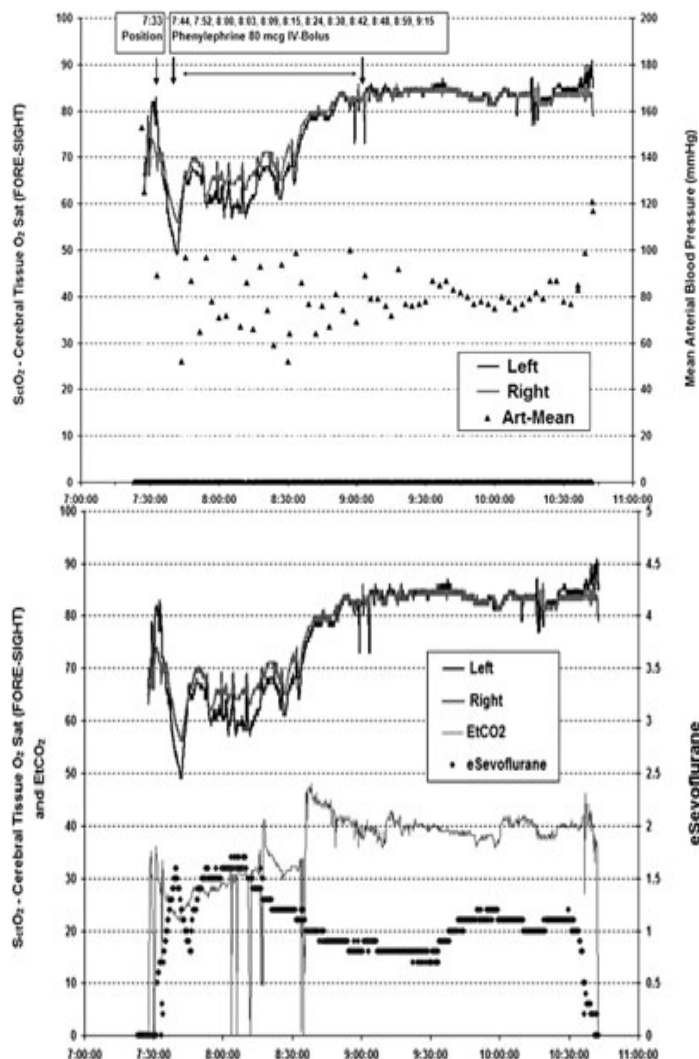
Figure 1.11 Graphs showing correlation of MAP and $EtCO_2$ with S_cO_2. Here we see a direct correlation between $EtCO_2$ and S_cO_2. in a patient under sevoflurane general anesthesia. When spontaneous respirations resume and $EtCO_2$ levels rise, there is an improvement in hemodynamics and cerebral perfusion improves also, Taken from Fischer (16). As MAP drops, ScO2 drops. When phenylephrine is given in boluses, MAP and ScO2 rise. Not only was the oximeter helpful in correlating MAP to ScO_2 but also to end tidal carbon dioxide levels shown below. Taken from GW. Fischer (16)

Arterial $PaCO_2$ has a near linear relationship with cerebral blood flow. For every 1mmHg increase in $PaCO_2$, there is a 2%-4% increase in CBF (15). The author also suggests normal or slightly elevated $etCO_2$ should be maintained for ventilated patient is in the sitting position or if a sedation case, spontaneous respirations may be protective.

S-100B - A Biomarker

A neuropsychological component was included in this study which requires a blood draw for S-100 data pre-operatively, post operatively, at again one day post-op. This is a member of highly homologous Ca^{2+} binding proteins family and well documented peripheral marker of glial injury. Glial cells are non-neuronal cells that provide support and nutrition, maintain homeostasis, from myelin, and participate in signal transmission in the nervous system. Studies indicate that S-100 proteins are involved in the inhibition of protein phosphorylation, inhibition of cytoskeletal constituent assembly, regulation of Ca^{2+} homeostasis, stimulation of enzyme activities, and interaction with transcription factors. Otherwise known as the glue of the nervous system, there are ten times more glial cells than neurons. S-100 belongs to a family of calcium binding proteins. The isoform $S-100B_2$ is a 21kDa two beta chain protein that is normally present in serum at very low concentrations of 0.03-0.12 µg/l, but very high concentrations in the brain (32). Although found in glial cells and Schwann cells, it is believed to be synthesized by glial cells alone. S-100a is present in glial cells alone and S-100ao is found in neurons (53). Its primary role is that of healing and maturation processes as listed above, but it is also a trigger for apoptosis by stimulating nitric oxide synthase and lipid peroxidation pathways. It is analyzed in serum via luminescence immunoassay (32). Research has shown that serum S-100 levels are indicative of the volume of cellular damage and outcome after stroke, trauma or subarachnoid

hemorrhage. High (micromolar) concentrations of S-100B have shown to be neurotoxic, participating in the physiology of neurodegenerative disorders. The clinical values have been demonstrated in stroke, cerebral complications associated with cardiac arrest and in patients with severe as well as minor head injuries. Peak serum concentrations occur at 1-3 days depending on the heterogeneity of cell damage in focal brain lesions. It is unclear whether cellular damage is sufficient to cause the release of S-100 into serum, or an impaired blood brain barrier (BBB) is needed. It has been shown that patients who have elevated s-100 levels 2 days after surgery even without any known cerebral complications have a shorter life expectancy. The question remains in some reported incidences of irregular peak concentration levels as to whether its specificity is truly to brain tissue alone. Literature suggests it may be also be released from fat, melanocytes, and T-lymphocytes as well (32,53). In addition, it is important to note that S-100 levels will be elevated in patients with severe neurological deficits on admission and prior to any surgical complications.

Neuro-Cognitive Testing

An additional measure of pre and post-operative neuropsychological tests were performed. These are scientifically validated objective tests to evaluate brain function. MRI, CT scans etc.., although able to diagnose disease processes and abnormalities, are unable to assess brain function. These tests cover a range from simple motor performance to complex reasoning and problem solving. Each is composed of quantitative and qualitative assessments. Quantitative results are compared with a normative standard and qualitative results are analyzed as a pattern of performance among a number of tests. Therefore, to assess neurocognitive function a wide range of tests need to be used to examine a wide range of functional domains (25). In this study,

the following tests were used to evaluate neurocognitive function pre-operatively and at 6 weeks post-operatively. The value of the 6 week post-operative test was used to trend differences as most patients were on prescription pain medication altering performance.

Seven neurocognitive tests were used in this study. The first is the Wechsler Test of Adult Reading (WTAR).

1. *Wechsler Test of Adult Reading*-This test provides an estimate of pre-morbid intellectual function in persons 18-89 years old. It takes less than 10 minutes to complete. It is normed with the Wechsler Adult Intelligence Scale (WAIS-III). It is composed of a list of 50 words that have atypical grapheme to phoneme translations (25).

2. Wechsler Adult Intellectual Scale-III Digit Span (WAIS-III)-This is a set of 13 subtests which measure memory, knowledge, problem solving, calculation, abstract thinking, spatial orientation, planning, and speed of mental processing. It was published in 1997 and provides scores for Verbal IQ, Performance IQ, and Full Scale IQ.

3. Oral Symbol Digit Modalities Test-This test detects cognitive impairment. The examinee has 90 seconds to pair specific numbers. It has a remarkable sensitivity to detect brain damage and cognitive impairment.

4. Judgment of Line Orientation-A test widely used to assess visuo-spatial processing.

5. California Verbal Learning Test-II (CVLT)-A popular clinical and research test that measures repetition learning, serial position effects, semantic organization, intrusion, and protective interference.

6. Controlled Oral Word Association Test-These tests measure the speed and flexibility of verbal thought processes

7. Trailmaking Test-This test measures attention, visual searching, mental processing speed, and the ability to mentally control simultaneous stimulus patterns (25).

CHAPTER 2

Methods

Patients age 18 to 65 years undergoing general anesthesia for a shoulder arthroscopy at the Detroit Medical Center Surgery Hospital in lateral or beach chair position were asked to participate in the study.

Inclusion Criteria:

1. Patients undergoing shoulder surgery with the Principal Investigator or one of the co-investigators

2. Willing to give informed Consent

3. Willing to have a blood draw in PACU and one day post and participate in neurocognitive test at 6 week follow up visit

Exclusion Criteria:

1. Patient refusal

2. Known Carotid stenosis >80%.

3. History of CVA or other significant cerebral event

4. Diagnosis of multiple sclerosis, dementia, or traumatic brain injury

5. History of developmental or learning disorder

6. Cardiomyopathy or atrial fibrillation

The proposed research plan will evaluate the cerebral perfusion of 100 patients receiving a general anesthetic in the beach chair or lateral decubitus position with several non-invasive monitors. The research was introduced by Dr. Stephen Lemos and an informed consent obtained by a research assistant. A full pre-operative history and physical exam was performed by the anesthesia care team. Upon start of the intravenous line, standard labs were drawn in addition to a S-100B serum marker. A

standard anesthetic outline was followed to ensure consistency in protocols. The anesthetic protocol was as follow:

An informed consent was obtained to participate in the study which included consent to a general anesthetic. The cerebral oximetry monitor was then applied and baseline measurements were recorded. A S-100B lab was drawn with the IV start pre-operatively in a red top tube. The patient was then transferred to a room equipped for local anesthetic blocks, monitors were applied, surgical site time out was done and midazolam sedation given. The ultrasound guided interscalene block was performed by the anesthesiologist with plain ropivicaine. When the operating room was ready the patient was transported to the room, transferred to the OR table and monitors applied. The blood pressure cuff was placed on the upper non-surgical arm. Anesthesia was Induced with 2mg/kg Propofol unless contraindicated then Etomidate 0.2mg/kg was used. Neuromuscular blockade and opioids were used as needed. Data was recorded every 5 minutes on data collection tool until extubation. The time of induction and time of position change were noted on a data collection tool. After intubation the patient was placed on the volume control with settings to maintain $EtCO_2$ at 32 mmHg. One hundred percent oxygen was used for induction and then decrease to 50% as tolerated for the remainder of the case. Isoflurane was used for the maintenance of anesthesia. Patients may then be positioned in lateral or sitting position and the degree of sitting recorded on the data collection tool. Patients could receive reversal of neuromuscular blockade as indicated and 100% oxygen at the end of the case. All monitors were removed after extubation and prior to transfer to PACU. A second S-100B lab draw was repeated in PACU by a PACU RN. A third S-100B was drawn the following day by a

visiting RN at the patient's home. Any concerns or variances from protocol were documented.

Next, the Nonin Cerebral/somatic oximeter was applied pre-operatively to obtain baseline cerebral venous oxygenation levels prior to sedation in the sitting and supine positions. This monitoring modality was maintained continuously throughout the operative procedure until emergence from anesthesia. This device recorded and saved continuous data. The last monitor applied was the BioZ noninvasive cardiac output monitor to evaluate changes in cardiac output as they pertain or related to position changes and/or perfusion changes. Sedation of midazolam and or opioids were used for regional blocks as needed after the above baseline measurements are obtained. All regional blocks were done with Ropivicaine without epinephrine.

Upon arrival to the operating room, standard monitors were placed with the blood pressure cuff on the non-surgical arm. All patient's received a general anesthetic with Propofol 2mg/kg unless contraindicated, (then they received Etomidate 0.2 mg/kg), along with neuromuscular blockade and opioids as indicated. Patients were placed on positive pressure ventilation with oxygen concentrations of 100% for induction of anesthesia as is standard and then 50% FiO_2 as tolerated for the remainder of the case. Ventilation was adjusted to maintain an end tidal CO_2 measurement of 32 mmHg. Patients were then positioned in the standard lateral or beach chair position. The degree of sitting was recorded for each patient. Right and left sided brain venous oxygen saturation, brachial artery non- invasive blood pressure, heart rate, temperature, cardiac output, end tidal CO_2, and CO were recorded every 5 minutes. Patients received reversal of neuromuscular blockade as indicated at the end of the procedure and 100% oxygen for emergence from anesthesia. All monitors were removed prior to

transport to the post anesthesia care unit. The S-100B lab draw was repeated in the PACU. A follow up S-100B lab draw was done by home nurses at 24 hours in addition to repeat neurocognitive testing at 6 weeks. Serum was collected for assays of complement function in sterile plain red top glass vacutainer tubes from Becton Dickinson. Blood was allowed to clot and then centrifuged for 20 minutes at 1250 X g to pellet the clots and cells. The serum was stored at -70 degrees until the assay was performed. The assay was completed by BioVendor Human S-100B ELISA standards. The procedure was that quality controls and samples were incubated in microplate wells pre-coated with polyclonal anti-cow S-100B antibody. Biotin labelled monoclonal anti-human S-100B antibody was added to the wells after 120 minutes and incubated for 60 minutes with captured S-100B. Streptavidin-HRP Conjugate was added after a second washing. After 30 minutes incubation and the last washing step, the remaining conjugate was allowed to react with the Substrate Solution (TMB). The addition of acidic solution stopped the reaction and absorbance of the resulting yellow product was measured. Data was compiled at the conclusion of the project.

Statistics

An analysis of covariance (ANCOVA) was performed to compare the post-surgery scores of certain neurocognitive tests between the two body positions (beach chair position and lateral decubitus), using the pre-surgery neurocognitive test scores as the covariate (the pre-surgery score was taken into account when evaluating the relationship between post-surgery score and group).

Repeated measures analysis of variance (ANOVA) tests were used to ascertain if there were any statistical significant interactions over time between patient positions (lateral decubitus and beach chair) and continuous variables (S-100B readings, Cardiac

Output Mean Arterial pressure, Cerebral Perfusion – Left and right sides). For post hoc tests the Pair-Wise Bonferroni tests were used where appropriate. Statistical significance was defined as $p<0.05$.

CHAPTER 3

Results

Results of all measurements in the study were analyzed and correlations between lateral decubitus and beach chair position amongst cerebral perfusion, blood pressure, cardiac output, S-100B and neurocognitive testing measurements were sought for significance.

Neurocognitive Testing: ANCOVA Interpretation

An analysis of covariance (ANCOVA) was performed to compare the post-surgery scores of certain neurocognitive tests between the two body positions (beach chair position and lateral decubitus), using the pre-surgery neurocognitive test scores as the covariate (the pre-surgery score was taken into account when evaluating the relationship between post-surgery score and group).

Data from 25 patients were analyzed, 7 of which had the surgery done in the beach chair position and 18 in the lateral decubitus position. The neurocognitive tests included in the analysis were: Symbol Digits Modalities Tests (oral and written scores), FAS total score, Estimated Full Scale IQ, Judgement of Line Orientation score, Trail-Making Parts A and B times, and the Rey Auditory Verbal Learning Test (RAVLT) (Trials 1-5) scores.

For the Symbol Digits Modalities Oral Test, there was not a significant difference in post-surgery score between the two groups ($p = 0.937$). For the Symbol Digits Modalities Written Test, there was also no significant difference in post-surgery score between the two groups ($p = 0.635$).

There was no significant difference in FAS total score between the two groups ($p=0.774$). There was also no significant difference in estimated full scale IQ (FSIQ)

between the two positions (p = 0.913). There was no significant difference in the Judgment of Line Orientation score between the two groups (p = 0.932). There was no significant difference in the time to complete the Trail-Making Part A test between the two groups (p = 0.695). Also, there was no significant difference in the time to complete the Trail-Making Part B test between the two groups (p = .461). Lastly, there was no significant difference in the Rey Auditory Verbal Learning Test (RAVLT) score between the two groups (p = 0.687). Overall, there were no significant differences in post-surgery neurological testing scores between the two body positions. This gives evidence that body position during shoulder surgery may not have an effect on neurocognitive function after surgery.

When comparing the post-surgery scores to the pre-surgery scores (without taking body position group into account), many significant differences became apparent. For the Symbol Digits Modalities Oral Test, there was a significant difference in score between the pre-surgery test and the post-surgery test (p < 0.001). Along with this, there was a significant difference in the Symbol Digits Modalities Written Test score between the pre-surgery test and the post-surgery test (p < 0.001). There was also a significant difference in FAS total score between the pre-surgery test and the post-surgery test (p < 0.001). There was a significant difference in FSIQ between the pre-surgery test and post-surgery test as well (p < 0.001). For the Judgment of Line Orientation Test, there was a significant difference between pre-surgery score and post-surgery score (p < 0.001). There was no significant difference in the Trail-Making Part A test score between the pre-surgery test and the post-surgery test (p = .051). However, there was a significant difference in the Trail-Making Part B test score between the pre-surgery test and post-surgery test (p < 0.001). Also, there was a

significant difference in the RAVLT score between the pre-surgery test and the post-surgery test (p = 0.003). Overall, in all but one of the neurocognitive tests analyzed, there was a significant difference between the pre-surgery and post-surgery scores (not taking body position into account). These differences are attributed to a slight learning curve which was to be expected.

S-100B ANOVA Results

The data were analyzed using repeated measures analysis of variance (ANOVA). In the event that the ANOVA showed a significant result, pair-wise Bonferroni post hoc tests were conducted to evaluate where the significant differences occurred.
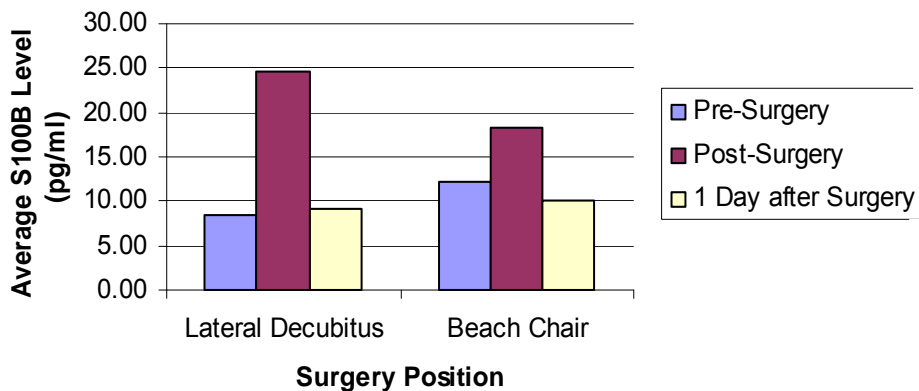
Figure 3.1 Average S100B Level Before and After Surgery. There is a significant rise in S100B levels post-operatively in both sitting and beach chair positions which returns to near normal 1 day post –operatively.

Lateral Decubitus Position Sheet Data

Repeated Measures *ANOVA*-There was a significant difference in average S-100B Level among the three blood draws (p < 0.001).Post Hoc Analysis:Pair-Wise Bonferroni tests showed that the S-100B level at Draw 2 was significantly higher than that of Draw 1 (mean difference = 16.281, p = 0.001). The S-100B level at Draw 2 was also significantly higher than that of Draw 3 (mean difference = 15.574, p = 0.002).

There was not a significant difference in S-100B level at Draw 1 and S-100B level at Draw 3 (mean difference = 0.707, p > 0.999).

Beach Chair Position Sheet Data

Repeated Measures *ANOVA*-There is a significant difference in average S-100B levels among the three blood draws (p = 0.001). Post Hoc Analysis*:* Pair-Wise Bonferroni tests showed that the *S-100B level at* Draw 2 was significantly higher than that of Draw 1 (mean difference = 7.677, p = 0.018). The S-100B level at Draw 2 was also significantly higher than that of Draw 3 (mean difference = 4.567, p = 0.012). There was not a significant difference in S-100B level at Draw 1 and S-100B level at Draw 3 (mean difference = 3.110, p = .369).

Mean Arterial Pressure

Mean arterial blood pressure results measured on 22 lateral decubitus patients and 11 beach chair position patients were analyzed using repeated measures of ANOVA and showed no difference between overall position (p= 0.57). There was a statistically significant interaction between both positions (lateral decubitus and beach chair) and time (p<0.001), regardless of position MAP decreased over time under anesthesia.
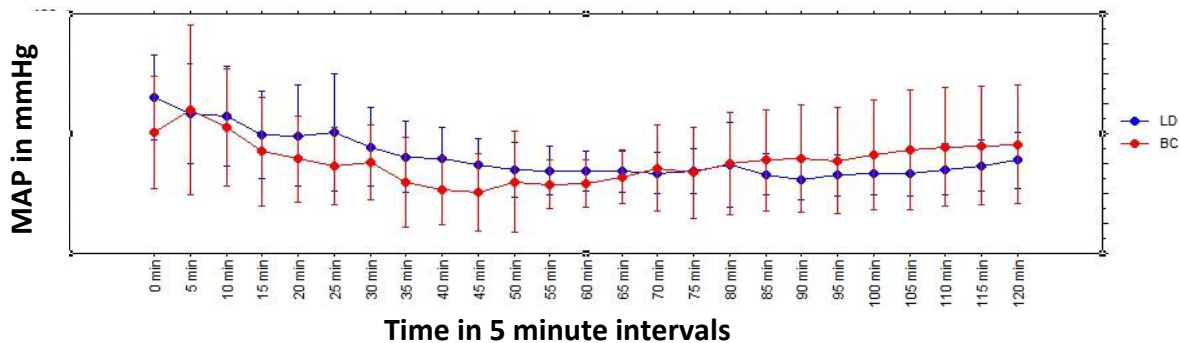
Figure 3.2. MAP results - Mean arterial blood pressures measured in beach chair (BC) and lateral decubitus (LD) positions every five minutes under general anesthesia showed no difference between positions (p=0.58) but a significant decrease in both positions over time (p<0.0001).

Table 3.1. Anova for Mean Arterial Pressure

	DF	Sum of Squares	Mean Square	F-Value	P-Value	Lambda	Power
Position	1	651.789	651.789	.319	.5782	.319	.084
Subject(Group)	33	67467.673	2044.476				
Category for Time	24	30163.995	1256.416	12.419	<.0001	298.061	1.000
Category for Time * Position	24	6232.679	259.695	2.567	<.0001	61.606	1.000
Category for Time * Subject(Group)	792	80127.017	101.170				

Cardiac Output

Cardiac output was analyzed on seven patients, five in the lateral decubitus position and two in the beach chair position, by repeated measure of ANOVA. Results showed a significant decrease over time in both lateral decubitus (position 1) and beach chair (position 2) (p=0.0001). There was no significant difference noted between positions over time (p=0.804).
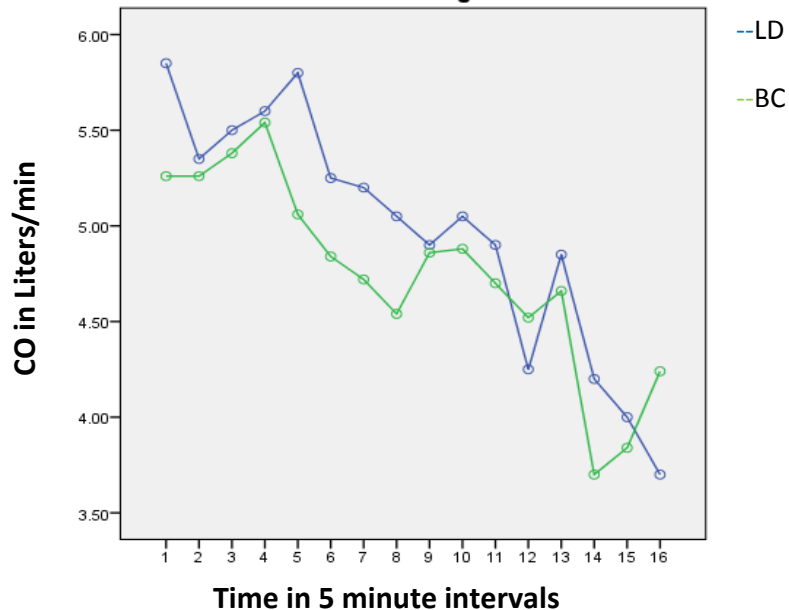
Figure 3.3 Estimated Marginal Means of CO over time. There was a significant decrease in CO over time in both positions (1= lateral decubitus, 2= beach chair) (P=0.001) and no significant difference between positions(p=0.804).

Table 3.2. Test of Between-Subjects Effects

Measure: CO

Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	2157.563	1	2157.563	139.754	.000
VAR00089	1.063	1	1.063	.069	.804
Error	77.192	5	15.438		

Table 3.3. Between-Subjects Factors

		N
Position	1.00	2
	2.00	5

Cerebral Oximetry

Cerebral oximetry data of 35 patients, 24 in LD position and 11 in BC position, were reported. Under general anesthesia there was a statistically significant interaction between both positions (lateral decubitus and beach chair) and rSO_2 levels over time (p<0.001). There was no overall significant difference between the two positions (p= 0.8257). In addition, although there were short periods of decreased cerebral oxygenation values recorded intra-operatively on patients, there was no adverse outcome for the patients.
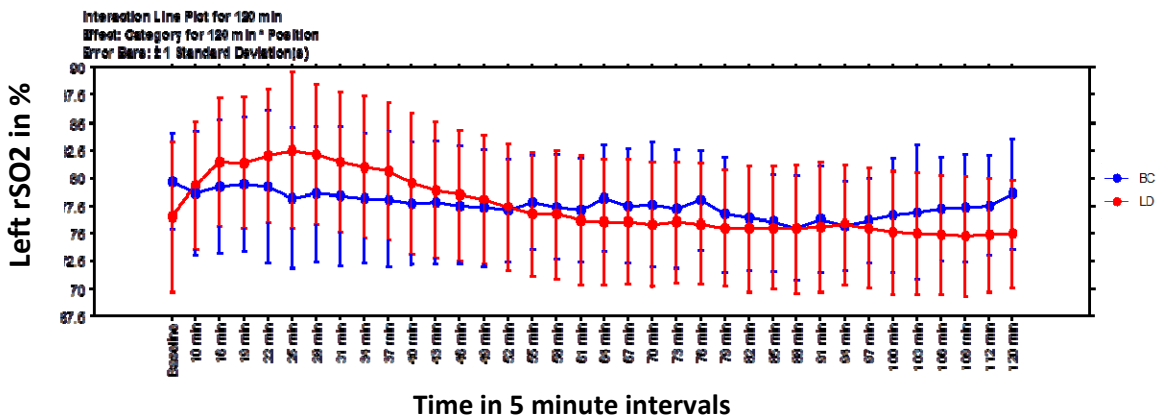
Figure 3.4 Cerebral Perfusion Results (Left rSO2) in beach chair (blue) and lateral decubitus (red) positions showed a significant change between positions over time (P 0.0001) and no significance between positions(p=0.9450)

Table 3.4. ANOVA for Left rSO2

	DF	Sum of Squares	Mean Square	F-Value	P-Value	Lambda	Power
Position	1	3.667	3.667	.005	.9466	.005	.050
Subject(Group)	29	23272.233	802.491				
Category for 120 min	35	2609.166	74.548	7.588	<.0001	265.596	1.000
Category for 120 min * Position	35	1008.200	28.806	2.932	<.0001	102.628	1.000
Category for 120 min * Subject(Group)	1015	9971.191	9.824				
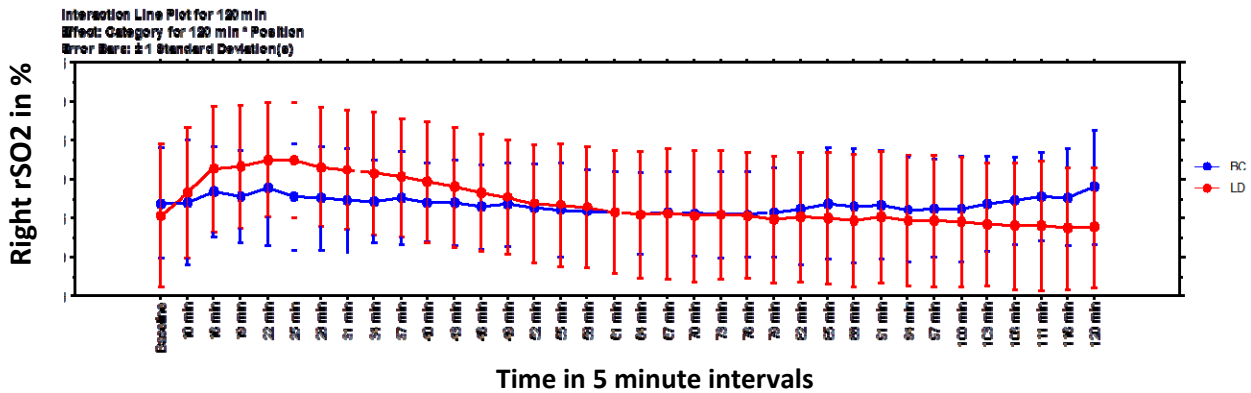
Figure 3.5 Cerebral Perfusion Results (Right rSO2) in beach chair (blue) and lateral decubitus (red) positions showed a significant change between positions over time (P 0.0001) and no significance between positions(p=0.9450)

Table 3.5. ANOVA for Right rSO2

	DF	Sum of Squares	Mean Square	F-Value	P-Value	Lambda	Power
Position	1	7.706	7.706	.005	.9450	.005	.051
Subject(Group)	29	46147.400	1591.290				
Category for 120 min	35	2691.024	76.886	6.100	<.0001	213.515	1.000
Category for 120 min * Position	35	1485.604	42.446	3.368	<.0001	117.873	1.000
Category for 120 min * Subject(Group)	1015	12792.514	12.603				

Two of the 32 patients enrolled had a significant cerebral desaturation event (CDE) seen below with no adverse clinical outcome noted.   Both CDE's were in the beach chair position and none were noted in the LD position
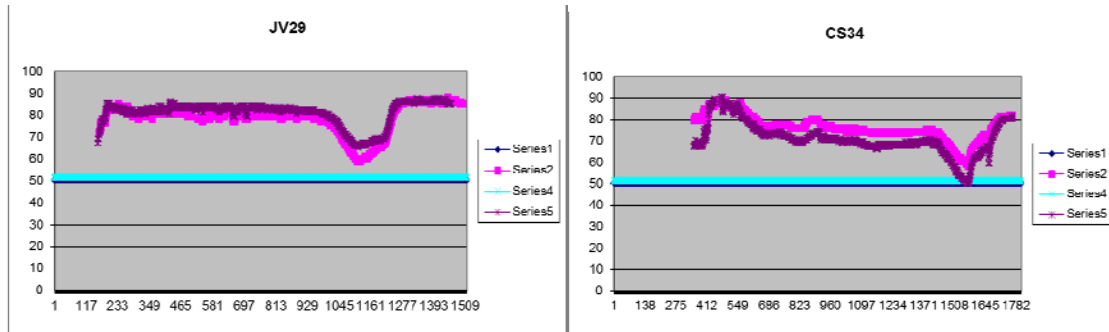
Figure 3.6 Clinical Desaturation Event- The graph above is of right and left cerebral oxygenation measurements recorded intra-operatively. Both of these patients were in beach chair position. No CDE's were noted in LD position.

CHAPTER 4

Discussion

As anesthesia providers around the country, Nurse Anesthetists are responsible for ensuring a safe anesthetic plan and delivery. This requires not only knowledge of the appropriate pharmaceuticals administered to patients but also to provide the best care possible.   When evidence is published citing multiple morbidities related to positioning under general anesthesia, it is the clinician's responsibility to evaluate the cause of those morbidities and change or adapt practice as appropriate. The increase in strokes has resulted in a myriad of new research. The risks of anesthesia are real and the physiology behind it remains unknown. Several studies show a correlation of anesthesia and memory deficits along with cognitive dysfunction. Specifically, postoperative cognitive impairment after anesthesia has been associated with cognitive decline and neurotoxicity. In a previous study, Isoflurane was shown to increase cytokine expression and cell injury in brain areas such as the hippocampus, causing cognitive dysfunction in rats (22). Spatial memory and learning was also impaired after anesthesia and surgery. High mobility group box-1 (HMGB1) was released into the systemic circulation, showing a leak in BBB and resulting in neuronal deficits and inflammation accounting for memory dysfunction. Lunardi et al (39) found that a midazolam, isoflurane, nitrous oxide anesthetic in young rats led to permanent neuronal loss later in life. The degeneration was manifested by acute substantial neuroapoptotic damage and permanent neuronal loss in later stages of synaptogenesis and that the morphological disturbances contributed to learning and memory deficits. However, a limited study of 438 patients by Rasmussen *et al* (59) showed no significant changes in cognitive function.   Our results compared to Rasmussen's in that overall there is no

significant difference in post-surgery cognitive function based on neurological testing between beach chair and lateral positions under anesthesia. This gives rise to evidence that body position during shoulder surgery may not have an effect on neurocognitive function.   The significant difference noted overall in neurocognitive tests pre-operatively and post-operatively, regardless of position can be attributed to a slight learning curve which was expected.

Several recent studies have used cerebral oximetry as a guide to monitor cerebral perfusion intra-operatively. In a review by Shear and Murphy (64) one study evaluated 124 patients having shoulder arthroscopies under general anesthesia and found that the incidence of cerebral desaturation events in the beach chair position (BCP) was significantly higher (80.3%) versus 0% in lateral decubitus position (LDP). Patients with CDE's also had an increased incidence of post op nausea and vomiting. Moerman (64) in the same review article also found an 80% incidence of CDE in beach chair position. Tange (64) on the other hand found no significant change in rSO_2 or MAP in the BCP (64). In a comparison of rSO_2 with jugular venous bulb saturations in 56 patients under anesthesia by Joeng (64), the cerebral oximeter showed only a 30% sensitivity in detecting a jugular venous bulb saturation of a critical value < 50%. Forty one percent of the patients suffered a desaturation (64). The reason for no decrease in rSO2 may be that CPP is preserved by autoregulation

Our results showed no significant difference in rSO_2 between positions under general anesthesia but a significant change in position over time. Thus the use of the cerebral oximetry remains controversial as a reliable monitor of ischemia during surgery. The anesthetic technique used in this study was a combination of regional anesthesia (RA) and general anesthesia (GA). Two recent studies show that there may

be less incidence of CDE under RA. Yadeau (64) looked at cerebral perfusion in 99 patients in BCP, only 0.77% of patients had a cerebral desaturation despite a 77% incidence of hypotension. Murphy (64) evaluated 60 patients and found a 57.6% incidence of CDE in the BCP versus 0 in the RA group. Our results showed 2 out of 35 patients had a CDE and both were in the beach chair position. Thus it appears that RA may a safer choice for surgeries in the beach chair position (64).

To determine if there were ischemic events intra-operatively, we looked at S-100B levels. Our results showed a statistically significant increased S-100B level in PACU which suggests an impaired blood brain barrier (BBB). This brain specific protein released into systemic circulation depends on astroglial cell disintegration. The fact that it is in the systemic circulation indicates damage to brain tissue and the BBB. The difference from this study and other studies is that the S-100B continued to increase over 2- 3 days in other studies. The S-100B returned to near normal levels on post op day one in our study. Suhrida *et al* (70) found that increased S-100B levels were associated with poor cognitive function in neurologically healthy older adults and was inversely related to performance in multiple cognitive domains, including memory, psychomotor speed and visual attention, and working memory. The reason is unclear, however it could suggest that any ischemic process was decelerated. The mechanism may be that neurons rely on aerobic metabolism and have a high energy demand compared to other cell types. In ischemia, oxidative phosphorylation in the mitochondria ceases. This triggers a series of events such as Na/K ATPase pump failure, cell membrane dysfunction and edema, and degradative enzymes which erode the BBB.

Previous studies have demonstrated that anesthesia and surgery impair the

blood brain barrier of aged rats on post op day 1 with transmission electron microscopy by evidence of swollen vessel, expanded perivascular space, enlarged astrocyte feet and detachment of the end-feet plasma membrane from the basal lamina (22). Although extra-cranial sources of S-100B have been discussed in the literature such as white and brown fat, skin and skeletal muscle, melanocytes studies now show that extra-cranial sources of S-100B do not affect serum levels (54,20). It is interesting that only one of the two patients that had a CDE had an increase in S-100 B levels in PACU (6.16 pg/ml to 12.58 pg/ml). The results of S-100B testing can be available within one hour of blood sampling and the cost is approximately $20 (81). Because the S-100B is a relatively new biomarker for stroke, more research needs to be done in this area to evaluate its use and correlation with anesthesia and outcomes.

Cerebral perfusion pressure is dependent on MAP. Mean arterial blood pressure and cardiac output measured in this study showed no significant difference between BCP and LDP however there was a significant decrease over time under anesthesia in both positions. This can be attributed to the vasodilating effects of the anesthetic gas. The concern is what MAP is too low to cause injury and for what period of time can hypotension be tolerated without neurologic involvement? Surgeons may request controlled hypotension for better visualization during arthroscopic procedures. Lee *et al* (64) noted that while maintaining a MAP of 60-65 mmHg on 28 patients under GA, there was a significant decrease in rSO_2. No change in CBF occurred when MAP was maintained > 70 mmHg. An accepted standard has not been identified and limitations in this study include small sample size and variable degrees of sitting for measurements.

Several other methods are available to monitor cerebral perfusion under anesthesia. The Trans cranial Doppler ultra sound and electroencephalogram (EEG)

are two. A study of 40 patients using Doppler ultrasound showed a significant decrease in MAP in BCP under GA compared to RA (64). McCullough (64) also showed a decrease in cerebral artery blood flow of 22% by ultra sound when the systolic BP dropped from 142 mmHg to 96 mmHg. A study using EEG monitoring by Gillespie (64) showed ischemic changes in 3 of 52 patients in the BCP under GA with induced hypotension.

The recent literature on BCP surgeries suggests that cerebral malperfusion occurs and is a concern. The incidence is increased under GA as compared to RA which may better maintain cerebral autoregulation. With non-invasive monitors being introduced into the perioperative arena, and having been proven to show CDE's, it is clear that further research needs to be done to perhaps include these monitors as a standard of care in various patients prone to devastating outcomes. In addition, further research on basic monitoring such as the location of the blood pressure cuff can be crucial to patient outcomes under anesthesia in the sitting position. Baseline blood pressure measurements should be obtained and clinicians should be aware that blood pressure measurements on the arm of a patient in BCP likely overestimate CPP. In addition, the increased use of antihypertensive medications is a concern. Trentman (64) showed an increased incidence of hypotension and vasopressor use in a retrospective chart review of 384 patients in the BCP. Solid evidence based research on these patients is needed to clarify future trends in monitoring in the sitting position to avoid catastrophic injuries.

In summary, it appears that beach chair position and lateral decubitus position for shoulder surgery under general anesthesia have similar decreases in blood pressure and cardiac output over time without any adverse clinical outcome based on

neurocognitive testing. In addition, despite occasional decreases in cerebral oximetry, during surgery, and the altered BBB, no residual adverse neurological outcome was noted. The clinical significance of an elevated neuro biomarker S-100B has yet to be determined.
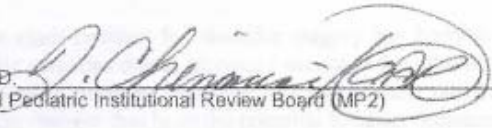
APPENDIX A

WAYNE STATE UNIVERSITY

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Full
AAHRPP

NOTICE OF FULL BOARD APPROVAL

To: Stephen Lemos
Orthopedic Surgery

From: James Chinarian, M.D.
Chairperson, Medical Pediatric Institutional Review Board (MP2)

Date: March 08, 2010

RE: HIC #: 021810MP2F

Protocol Title: The Effect of Body Position on Changes in Cerebral Blood Flow, Cognition, and Motor Function in Patients Undergoing Shoulder Surgery: Lateral Decubitus versus Beach Chair Position

Sponsor: ° Anesthesia Patient Safety Foundation

Protocol #: 1002008022

Expiration Date: February 10, 2011

Risk Level / Category: Adult: Research not involving greater than minimal risk

The above-referenced protocol and items listed below (if applicable) were **APPROVED** following *Full Board Review* by the Wayne State University Institutional Review Board (MP2) for the period of 03/08/2010 through 02/10/2011. This approval does not replace any departmental or other approvals that may be required.

- Protocol (version dated 1/19/2010) and Revised Protocol Summary Form (revision received in the HIC office 2/26/2010)
- Revised HIPAA Summary Form and Revised HIPAA Authorization Form with Consent (revisions received in the HIC office 2/26/2010)
- Medical Research Informed Consent Form (revision dated 2/26/2010)
- Psychological Testing Materials

° Federal regulations require that all research be reviewed at least annually. You *may* receive a *"Continuation Renewal Reminder"* approximately two months prior to the expiration date; however, it is the Principal Investigator's responsibility to obtain review and continued approval *before* the expiration date. Data collected during a period of lapsed approval is unapproved research and can never be reported or published as research data.

° All changes or amendments to the above-referenced protocol require review and approval by the HIC **BEFORE** implementation.

° Adverse Reactions/Unexpected Events (AR/UE) must be submitted on the appropriate form within the timeframe specified in the HIC Policy (http://www.hic.wayne.edu/hicpol.html).

NOTE:

1. Upon notification of an impending regulatory site visit, hold notification, and/or external audit the HIC office must be contacted immediately.
2. Forms should be downloaded from the HIC website at **each** use.

APPENDIX B

Case Presentations by Cullen and Kirby (10)

Case 1

A 47-year-old woman underwent shoulder arthroscopy. Preoperative blood pressure (BP) was 125/83 mm Hg; heart rate (HR), 98 beats per minute (bpm); and weight, 89 kg. After premedication with 50 mg meperidine, 40 mg hydroxyzine, and 0.2 mg glycopyrrolate intramuscularly, anesthesia was induced with 200 mg propofol, 100 mg succinylcholine, 30 mg lidocaine, and also 50 mg labetalol because she was hypertensive just before induction. Anesthesia was maintained with 2% isoflurane, 60% nitrous oxide, and oxygen. Twenty minutes into the case, her BP decreased to 100/60 mm Hg and then remained in the 80 to 90 mm Hg systolic range for the remainder of the case. Oxygen saturation (Spo_2) levels were 100%, and end-tidal CO_2 ($ETco_2$) values were in the low 30%s throughout the case. The patient was placed in the "barbershop" position. Upon arrival to the postanesthesia care unit (PACU), her BP was 113/60 mm Hg but she did not awaken. Naloxone, 0.1 mg intravenously, was given but she remained unresponsive and not moving her extremities. Another 0.1 mg of naloxone was given 35 minutes after arrival in the PACU followed by 3 more doses of naloxone and 2 doses of physostigmine. During this time, her trachea remained intubated and she was well oxygenated. Neurologic evaluation suggested a diencephalic syndrome, possibly brain infarction. She was unresponsive to voice commands or painful stimuli, and reflexes were decreased bilaterally. A computed axial tomographic (CAT) scan of the head was normal initially but suggested brain swelling and obliteration of the cistern 5 days later. Magnetic resonance imaging 1 week later showed changes in both cerebral hemispheres suggesting cortical infarcts, involvement

of the anterior and medial temporal lobe bilaterally, no significant edema, and no significant herniation. At no time was there any evidence of an intracranial bleed. After 2 weeks, her Glasgow Coma Scale was 3; her fundi were clear and crisp. She had corneal reflexes, a positive gag, and negative doll's eyes; she was hyperreflexic with increased tone and was unresponsive to noxious stimuli in all 4 extremities. She is projected to remain in a vegetative state.

Case 2

A 57-year-old, 190-cm, 107.7-kg white man in excellent health underwent shoulder surgery for a torn rotator cuff. In the accident that caused the torn rotator cuff, he also had compressed cervical vertebrae that caused some weakness of his arms. Anesthesia was induced with 200 mg propofol, 40 mg rocuronium, 30 mg lidocaine, and 100 µg fentanyl. Intubation was uneventful, and anesthesia was maintained with isoflurane 2.5% to 1.5% with 67% nitrous oxide in O_2. Oxygen saturation remained in the high 90% range, $ETco_2$ was normal, and temperature was 35.8°C throughout the case. The patient was placed in the beach chair position for the surgery. Blood pressure started around 125/60 mm Hg, early in the case, drifted down to 100/55 mm Hg and then to 95/65 briefly before increasing up to 110 mm Hg systolic. Heart rate remained 70 to 80 bpm. Near the end of the case, his BP again drifted down to 90/55 mm Hg for the last 10 minutes of the procedure. On arrival to the PACU, BP was 165/75 mm Hg; HR, 90 bpm; respiration rate, 16 breaths per min; initial Spo_2, 80%, which increased to 100% for the remainder of his PACU course with supplemental O_2; and he was comatose. Although he received 0.1 mg naloxone and 0.1 mg flumazenil, he remained unarousable and unresponsive for the entire time he was in the PACU. There were no focal neurologic deficits, but he did respond to noxious stimuli and moved all 4

extremities. Neurology consults suggested a posterior circulation infarct involving the midbrain and the cortical thalamic region.

Case 3

A 53-year-old, 174-cm, 84-kg man underwent left shoulder surgery. His past medical history included a workup for chest pain, which demonstrated an abnormal exercise stress test, abnormal thallium stress test, a normal coronary catheterization, and a normal echocardiogram. The patient had hyperlipidemia and a positive family history for coronary artery disease (CAD) and stroke. However, the patient was in excellent health. After premedication with 7 mg morphine and 0.6 mg droperidol intramuscularly, anesthesia was induced with 200 mg propofol and 100 mg succinylcholine followed by a nondepolarizing muscle relaxant. Anesthesia was maintained with isoflurane, nitrous oxide, and oxygen. The patient was placed in the beach chair position at almost 90° for the surgery. There were no problems with intubation, and Spo_2 and $ETco_2$ values were normal throughout the procedure. He received 2000 mL of crystalloid, no urine output was recorded, and no blood loss occurred. Blood pressure started at 130/70 mm Hg, and after induction of anesthesia, it was purposely allowed to decrease to the 90/50 mm Hg range at the request of the surgeon. Blood pressure remained in the 90/50 mm Hg range for most of the case, although in the last half hour, BPs were in the 80/50 mm Hg range. Heart rate was about 60 bpm for most of the case. On arrival to the PACU, BP was 95/50 mm Hg and HR was 60 bpm, but he did not awaken. He was given naloxone and flumazenil twice but remained unresponsive. He moved his extremities spontaneously but not on command. Additional naloxone and flumazenil were not effective, and he was transferred to the intensive care unit. A CAT scan, carotid Doppler study, and

echocardiogram were all normal. Neurologists' opinion was that he had a left hemispheric watershed infarct. Significant neurologic dysfunction remains permanent.

Case 4

A 54-year-old woman underwent left shoulder replacement surgery in the beach chair position. The patient had no history of hypertension. Two years previously, she ruled out for a myocardial infarction. Preoperative electrocardiography, echocardiogram, thallium scan, and exercise tolerance test were normal. The patient received an interscalene block with 40 mL of 0.5% bupivacaine with epinephrine (1:200 000). Because of a previous mastectomy, a 20-gauge intravenous catheter was placed on the right foot and a noninvasive BP cuff was placed on the calf. There was no documentation that the calf BP value was compared with a left arm BP value before the patient was anesthetized and the left arm became unavailable. No arterial catheter was placed although deliberate hypotension was used. Anesthesia was induced with 100 mg propofol, 250 mg thiopental sodium, 50 mg rocuronium, and 250 μg fentanyl. Anesthesia was maintained with 3.5% sevoflurane and 67% nitrous oxide in O_2. Nitroglycerin, 3 doses of 50 μg each, and 5 mg labetalol times 4 doses were used to produce deliberate hypotension. One hour after induction, her BP was between 85 and 100 systolic mm Hg. Two hours later, her BP was 70/40 mm Hg and then remained around 90/60 mm Hg for the next 40 minutes, when it decreased to 50/25 and was treated with phenylephrine. Electrocardiography showed sinus rhythm throughout, Spo_2 was always high, and $ETco_2$ was in the high 20s range for most of the case. In the PACU, her emergence was delayed and she did not breathe spontaneously. A radial artery catheter was finally placed while she was in the PACU, and BPs were normal. Apnea persisted, and her pupils were fixed and dilated. A blood gas analysis on

controlled ventilation showed a Pao_2 of 236 mm Hg, $Paco_2$ of 35 mm Hg, and pH of 7.4, with a glucose of 92 mg/dL. Neurologic evaluation revealed brain death with no cerebral blood flow (CBF), a flat electroencephalogram, no reflexes, no response to pain, and no lesions on the CAT scan. At autopsy, the upper spinal cord and medulla were infarcted. The anesthesia equipment was impounded, and after testing, it was found to be functional and without problem.

APPENDIX C

Case Discussion by Cullen and Kirby (10)

Cerebrovascular Risk Factors

In the absence of any known cerebrovascular disease on preoperative and postoperative evaluation, as well as a very minimal number of cerebrovascular risk factors, a major ischemic event occurred in these patients. Risk factors for stroke in general are listed in. None of our patients had a history of tobacco use or hypertension. All patients had normal electrocardiographs, the patient in case 3 had a normal carotid Doppler, and the patient in case 1 had a negative exercise stress test. The only risk factors for stroke identified in this series were male sex for cases 2 and 3, and hyperlipidemia and positive family history for CAD and stroke in case 3. One patient (case 1) presented with a single instance of elevated BP just before induction that could be attributed to nervousness, a common and frequently encountered phenomenon. Although the patient in case 3 was known to have hyperlipidemia, a positive family history for CAD, stroke, and a positive stress test, cardiac catheterization, considered the gold standard for detecting CAD, was normal, thus ruling out CAD. It seems unlikely that these risk factors, which are not specific to patients undergoing shoulder surgery and are very common in the general population undergoing minor risk surgery, accounted for the ischemic events. Asymptomatic carotid artery stenosis (50%-90%, as well as carotid occlusion) is not associated with an increased risk for stroke during high-risk coronary artery bypass grafts. Furthermore, age, sex, diabetes, CAD, peripheral vascular disease, prior history of multiple cerebrovascular accidents, and post stroke transitory ischemic attacks have not been shown to have predictive value in identifying patients at higher risk for a second stroke during anesthesia. Risk stratification relying

solely on history of hypertension, diabetes, cardiac disease, hypercholesterolemia, prior stroke, or heart attack has low sensitivity and is inadequate to predict perioperative stroke. Weintraub and Khoury suggest that it might be time to abandon surrogate markers of atherosclerotic disease as predictors of perioperative stroke.

APPENDIX D

Letter to the editor: Labetalol May Decrease Cerebral Perfusion in Beach Chair Position by Ann Lofsky MD (37)

To the Editor:

I read with interest the 2 case reports and discussion by Drs. Cullen and Kirby of central nervous system (CNS) catastrophes that occurred in patients undergoing shoulder procedures in the beach chair position. I noticed that the 2 cases had another common factor that was not discussed in their article; both patients had received labetalol while in the operating room. According to the original article, the first patient was given 50 mg of labetalol to treat high blood pressure readings obtained immediately prior to inductionwhile the second patient received 20 mg of labetalol in divided doses as part of a deliberate hypotensive technique. Interestingly, neither patient had a history of hypertension.

Labetalol is marketed for control of blood pressure in severe hypertension. It combines selective alpha1 blocking action with non-selective beta1 and beta2 blockade. The ratio of alpha to beta blockade is 1:7 when used intravenously. Relatively weak alpha1 blockade causes vasodilation, while stronger beta1 blocking decreases heart rate and contractility. Beta2 blocking prevents sympathetically mediated vasodilation and bronchodilation. Labetalol itself produces postural hypotension. The package inserts report a 58% incidence of "symptomatic postural hypotension" in awake patients when tilted or placed upright following labetalol injection, presumably referring to complaints of lightheadedness or dizziness. This is a sufficiently concerning effect that the administration guideline reads: "Patients should always be kept in a supine position during the period of intravenous drug administration." Manufacturers' recommendations

do not constitute a legal standard of care, and the fact remains that many anesthesiologists do administer labetalol intravenously in patients in beach chair positions without complications. I personally question, however, whether this could be a contributing factor to some instances of CNS infarcts, such as the 2 presented in the Newsletter article.

Despite autoregulation, in the standing position, cerebral blood flow (CBF) in healthy individuals falls by 14-21% of supine values..Only with tilts up to 20 degrees does CBF remain constant. There is evidence that in the upright position, CBF is more dependent on the arterial-venous pressure gradient than it is on mean arterial pressure, so extra caution might be advisable when using drugs that alter hemodynamics under these circumstances, especially when measuring cuff pressures alone. Labetalol injection has already been shown to act synergistically with at least 2 potent inhalational anesthetics in producing hypotension, reducing cardiac output, and increasing CVP. Since 1996, package inserts for the drug have included the following warning: "Several deaths have occurred when Labetalol HCl injection was used during surgery (including when used in cases to control bleeding).

I first became interested in the clinical pharmacology of labetalol after reviewing a number of anesthesiology malpractice claims in which otherwise healthy patients became bradycardic and arrested within 20 minutes of being given the drug to treat epinephrine-induced hypertension. I was surprised to find that literature regarding the physiologic explanation for this is available, although it remains a rather underappreciated phenomenon in much of the anesthesia community. In the presence of epinephrine, norepinephrine, or phenylephrine, the weak alpha-adrenergic blockade of labetalol, in addition to strong combined beta-blockade, allows for unopposed

adrenergic stimulation. This can result in severe increases in systemic vascular resistance along with declines in cardiac output, and has been associated with cases of pulmonary edema and death—even in healthy adults and children. In the current article, while discussing patient safety in the beach chair position, the authors suggest using "vasopressor infusion, as needed during the time of the procedure when the patient is upright and at risk." I am concerned that the infusion of phenylephrine or epinephrine in a patient who has already received labetalol (or another beta-blocker) might potentially produce the life-threatening complication described above.

Labetalol is not a short-acting drug, and its effects would likely have lasted the duration of both surgeries described in the article—and substantially into the postoperative periods. Its elimination half-life after IV administration is estimated at 5.5 hours. In drug company studies, it took an average of 16 to 18 hours for blood pressure to return to pretreatment values. Accordingly, the not uncommon practice of using labetalol to treat transient episodes of high blood pressure and tachycardia in otherwise non-hypertensive patients that result from preoperative anxiety, intubation stimuli, or surgical stress, strikes me as odd, considering its pharmacology. There are certainly other means available to treat temporarily high heart rates and vasoconstriction.

"While the beach chair position has now become standard of care for shoulder procedures in many orthopedic practices, the addition of labetalol to general anesthesia adds another layer of complexity to physiology in the upright position, with implications that have yet to be fully determined. I agree with the authors that the use of the beach chair position combined with deliberate hypotension will likely compromise cerebral perfusion. But using labetalol for any reason—thereby blocking all of the body's usual responses to postural change: vasoconstriction, increased heart rate, and increased

contractility—might also affect cerebral perfusion in patients who are positioned head-up. I applaud Drs. Cullen and Kirby for spotlighting many of the potential problems with this situation and for advocating caution whenever one is positioning a patient in beach chair. Let us hope we can continue to identify ways of decreasing the anesthesia risk for a patient position that improves surgical technique.: Ann S. Lofsky, MD

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ABSTRACT

THE EFFECT OF BODY POSITION ON CEREBRAL BLOOD FLOW, COGNITION, CARDIAC OUTPUT, MAP, AND MOTOR FUNCTION IN PATIENTS UNDERGOING SHOULDER SURGERY: LATERAL VERSUS BEACH CHAIR POSITION UNDER GENERAL ANESTHESIA

by

KELLEY LABONTY

August 2014

Advisor: Dr. Steven Cala

Major: Physiology

Degree: Doctor of Philosophy

This study aims to determine if there are alterations in cerebral perfusion in patients undergoing general anesthesia in the sitting position. With the reporting of 15 catastrophic cerebral vascular accidents recently being published during shoulder surgery in the sitting position, an increase of 90 times from previously reported data, there has become a clear need for immediate research in this area. A peri-operative stroke has a 60% incidence of morbidity versus 15-46% for strokes in general. This is a devastating outcome for families, physicians and all involved. Current literature points to the sitting position as being a significant risk factor for decreasing cerebral perfusion. Surgeons utilize this position for ease of surgery and may request deliberate hypotension to decrease bleeding and increase visualization at the surgical site. It is unclear whether deliberate hypotension, inadvertent hypotension, air embolus, spinal cord stretching, or neck vessel stretching are key factors involved. An area of concern is that the blood pressure recorded in the arm of the patient in the sitting position is significantly less than that in the brain, this in addition to the decrease in cardiac output

while sitting, and vasodilation of the general anesthetics all create the perfect storm to offset normal autoregulatory responses.

Interestingly, the brain is the least monitored organ under anesthesia. It is evident that this practice requires re-evaluation. With the invent of numerous non-invasive cerebral perfusion devices being cited in the literature as very useful in monitoring cerebral perfusion, it is important that we utilize this technology to provide safe patient care and improved outcomes. Devices such as the Cerebral Oximeter and non-invasive cardiac output monitor can provide relevant information and may aid in preventing these catastrophic events. It is our goal to implement these monitors in patients undergoing general anesthesia in the sitting and lateral decubitus position to evaluate their effectiveness in alerting the anesthesia provider to decreases in cerebral perfusion and improving patient outcomes. Secondly, with the concomitant use of these two devices, we may be better able to understand the physiological role of cerebral perfusion in the sitting position and gain insight as to the cause of the cerebral vascular events and patients at risk. In addition, the S-100 lab test is a peripheral marker of glial injury and has been shown to correlate well with brain injury. It is our belief that this lab test is underutilized and may be very beneficial in these cases. Research shows elevation of this marker two days post operatively is indicative of a shorter life expectancy regardless of any known cerebral complications. Lastly, although MRI's and CT Scans can detect brain abnormalities, they cannot assess brain function. Neuro-cognitive testing on the other hand has been shown to reliably evaluate brain function and will be implemented at three different times in this study to correlate with monitoring and lab data obtained peri-operatively.

Methods: 100 patients age 18-65 years old will be included in the study. They

will receive a general anesthetic in the beach chair or lateral decubitus position for shoulder surgery. Baseline neurocognitive testing will be done along with cardiac output, cerebral oxygenation, and S-100 lab values. A standard anesthetic protocol will be followed for all patients. Continuous monitoring of CO and cerebral oximetry will be utilized throughout each case. Post-operatively the S-100 lab will be repeated and again at 24 hours followed by neurocognitive testing. The final neuro-cognitive test will be completed at the 6 week post-operative follow up visit.

The goal of this study is to determine whether conducting shoulder surgery in the beach chair position causes neurocognitive changes in patients when compared with those undergoing surgery in the lateral decubitus position.

Specific aims

1. To determine whether the regional oxygen saturation in the brain is diminished during shoulder surgery in the beach chair position using near infrared spectroscopy.

2. To determine whether there is a significant change in cardiac output and MAP in the beach chair position versus the lateral decubitus position using a non-invasive cardiac output monitor.

3. To determine if there are neurocognitive injuries associated with sitting and lateral positions by examining the S-100 Beta levels and neurocognitive evaluations of patients before and after surgery.

We hypothesize that cerebral perfusion is decreased in patients undergoing surgery in the sitting position due to a combination of decreased cardiac output, vasodilation and higher lower limits of cerebral autoregulation. We believe this decrease in cerebral perfusion will be seen by the cerebral oximeter. We also predict

that the S-100 B lab test will be sensitive enough to pick up significant changes in cerebral perfusion.

AUTOBIOGRAPHICAL STATEMENT

KELLEY LABONTY

EDUCATION:

Bachelor of Science in Nursing (1991)   Wayne State University
Master of Science in Anesthesia (1997)   Wayne State University
Ph.D. in Physiology (2014)   Wayne State University

LICENSURE & CERTIFICATION

1991-present   Registered Nurse, State of Michigan
1997- present   Nurse Anesthesia Specialty Certification
1991- present   Advanced Cardiac Life Support
1984- present   Basic Cardiac Life Support
2003 - 2005   ACLS Instructor

WORK EXPERIENCE

10/12- present   University of Michigan, Flint, MI.
                                         Anesthesia Program Coordinator
                                         Faculty
                                         Hurley Medical Center Clinical Instructor, Flint, MI
01/99- present   Detroit Receiving Hospital, Detroit, MI.
                                         Clinical and Didactic Instructor WSU Nurse Anesthesia Program
                                         Board Runner, Specialize in Trauma Anesthesia
08/04- present   Wayne State University, Detroit, MI.
                                         Adjunct Faculty;
06/98-01/99   St. John Hospital, Detroit, MI
                                         Staff CRNA, Heart, OB and Pediatric experience
09/97-06/98   Genesys Regional Medical Center, Grand Blanc, MI
                                         Staff CRNA. Regional anesthesia and central line placement

PUBLICATIONS
          AANA Journal 1997- East Meets West; Anesthesia in the Baltic States

RESEARCH

10/09- present   The Effect of Body position on Changes in Cerebral Blood Flow,
                                         Cognition, and Motor Function in patients undergoing shoulder Surgery-
                                         Lateral versus Beach Chair position
06/08-present   Tear IGa Levels in Trauma Patients and the Correlation to Pneumonia
                                         and Organ Failure PI- Lawrence Diebel MD, Detroit Receiving Hospital
03/09-12/09   Anesthetic effects on Cardiac Conduction
                                         PI-Sony Jacobs MD, Harper University Hospital

AWARDS

2011   AANA New York Life Doctoral Fellowship Award
2010   AANA Foundation Doctoral Fellowship Award
2008   WSU Graduate Professional Scholarship
2006   Clinical Instructor of the Year, Detroit Receiving Hospital
2005   Clinical Instructor of the Year, Detroit Receiving Hospital
1997   Agatha Hodgins Award - Most outstanding anesthesia student
1997   WSU Graduate Professional Scholarship