The Effect of Sudden Drop in Partial Pressure of Oxygen During Ascent on Heart Function

by

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Abstract

Background: Cardiovascular disease is the second leading cause of diving deaths. Scarcity of 12 lead ECG recordings during dives leaves many questions unanswered about cardiac function during ascent. I hypothesized that decreased oxygen partial pressure (PpO_2) initiates cardiac arrhythmia on ascent. I examined heart rate variability (HRV), rhythm and circulating markers of cardiac damage in the blood in response to submersion, increased pressure and reduction in the partial pressure of oxygen during the ascent.

Methods: Experiments were performed in the wet pot of the hyperbaric chamber. Participants (N=19) were occupational and scientific divers, age 39.3 years, BMI 26.5 kg/m^2, 3 females. Each completed two dives in a drysuit while swimming in 8^oC water outfitted with a 12 lead ECG holter recorder. A 30-minute swim was performed at ambient pressure followed by a dive to 5 atmospheres absolute (ATA) with a direct ascent to surface pressure. The experimental exposure held the PpO_2 at 1.0 ATA for the ascent. Blood samples were drawn at baseline, immediately after the dive and one-hour post dive. ECG analysis was performed for 5 epochs of 5 minutes each.

Results: Diving increased heart rate and decreased HRV ($p<0.05$). The change in heart rate variability time domain was increased on ascent with oxygen clamping over the control ($P=<0.004$). Diving increased markers of cardiac vagal tone ($P=<0.02$) and decreased markers of sympathetic tone ($P=<0.003$). Diving caused QTc prolongation, particularly in the control ($P=0.021$) on ascent. No ST depression was observed, and ST elevation was present in the anterior leads with no differences between epochs or conditions. Diving increased the number of atrial ectopics (PAC) particularly with oxygen clamped on ascent ($P=0.002$). There was no troponin (cTnI) or significant change in pH or Lactate however there was a significant increase in B-Type natriuretic peptide (BNP) production with the oxygen clamped on ascent ($P=<0.0001$).

Discussion: This is the first study to examine the effect of submersion and diving on HRV using 12 lead ECG while exercising in a controlled study, and unlike previous studies without exercise I saw an increase in HR and a significant decrease in heart rate variability. This agrees with the effect of exercise alone. The effect of clamping oxygen on the ascent eliminated the reduction of HRV from control. Submersion and diving both

increase markers of cardiac vagal tone unlike the effect of exercise. Markers of sympathetic tone were decreased during submersion but not during the 5 ATA dive. This suggests an autonomic conflict not observed when no exercise is present during a dive. The ST segment elevation showed the typical “early repolarization syndrome” of young, athletic, healthy, males with physically demanding jobs. Under conditions of high oxygen pressure an increase in the QT interval from baseline was observed along with a significant increase in PACs and BNP levels. Its relation to the observed PAC’s and QTc is unclear.

Keywords: Diving, Sudden Cardiac Death, ECG, Transient Ischemia, Drop in O_2

Dedication

“Sometimes the lights all shining on me

Other times I can barely see

Lately it occurs to me

What a long strange trip it’s been” - Grateful Dead, Trucking

I am so lucky to have so many people have faith in me, and allow me the chance to try.

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List of Acronyms

ACh	Acetylcholine
ANP	Anti-diuretic peptide
ATA	Atmospheres Absolute
BNP	B-Type natruetic peptide
CO	Cardiac Output
CO_2	Carbon Dioxide
cTnI	Cardiac Troponin I
DAN	Divers Alert Network
FSW	Feet of Seawater
HBOT	Hyperbaric Oxygen Therapy
HF	High Frequency
HR	Heart Rate
HRV	Heart Rate Variability
LF	Low Frequency
LQT	Long QT syndrome
LVH	Left Ventricular Hypertrophy
MET	Metabolic Equivalent
MSW	Metres of Seawater
N_2	Nitrogen
O_2	Oxygen
PAC	Premature Atrial Contraction
$PaCO_2$	Pressure of Arterial Carbon Dioxide
PiO_2	Pressurre of inspired Oxygen
PNS	Parsympathetic Nervous System
Pp	Partial pressure
PpO_2	Partial Pressure of Oxygen
PVC	Premature Ventricular Contractionn
RMSSD	Root Men Square of Successive Differences of RR Interval
SA	Sino-Atrial
SCD	Sudden Cardiac Death
SCUBA	Self Containted Breathing Apparatus
SDNN	Standard Deviation of Normal R to R Intervals
SDIPE	SCUBA Immersion Pulmonary Oedema

SNS	Sympathetic Nervous System
Vfib	Ventricular fribulation
VLF	Very Low Frequency

Chapter 1.

Introduction

1.1. The advancing age of divers

Diving with self-contained breathing apparatus (SCUBA) has become an increasingly popular sport since the inception of the Aqualung, a commercially available demand regulator introduced in 1942 by Cousteau and Gagnan. In the early years, participation in SCUBA required a high degree of fitness and a demanding training regime based on Navy diver training, often with strenuous exercises to eliminate those not suited to the environment. Around the mid-1980s, the development of buoyancy control devices made diving easier. A buoyancy control device is a vest that serves two purposes: to secure the cylinder of compressed air to the diver and to assist the diver in achieving neutral buoyancy. This is a state where the diver neither sinks nor floats but is suspended without effort, like an astronaut in zero gravity. This can be achieved at any given depth by varying the volume of gas in the vest supplied by the cylinder. As a result, dive-training agencies have promoted diving as an easy activity almost anyone can enjoy.

The average age of the recreational diver has progressively increased since the 1960s, with a notable increase in the number of divers beyond 50 years of age. The British Sub Aqua Club reports that the percentage of divers over the age of 50 increased from 10% in 1998 to 30% in 2013 (1).. A report published in 2015 by the Sports and Fitness Industry Association determined that 8% of casual divers, defined as less than 7 dives per year, and 22% of core divers, defined as 8 or more dives per year were over the age of 54 years.(2). Overall, those over 54 years of age made up 11% of the total divers. This is slightly higher than the overall number of other watersports participants over 54 years of age, at 8.5% of the total participants between 2011-2016 (3–6). The Divers Alert Network (DAN) reported that the mean age of insured DAN divers worldwide steadily increased from 41.0 in 2000 to 44.3 in 2007 (7).

1.2. Cardiovascular events are the leading cause of diving fatalities

The DAN 2017 report on diving fatalities, like other reports from around the world, determined that drowning was the most common cause of fatalities (1,8–11)and cardiac events was the second leading cause (10). The actual number of cardiac fatalities may be higher, with a substantial number of deaths recorded as unexplained sudden drowning due to loss of consciousness, particularly in middle-aged males which maybe due to a cardiac event leading to drowning. When reviewing the circumstances surrounding these events, autopsy reports, and previous health records, the combined evidence suggests cardiac arrhythmias and arrest may be their underlying cause (12).. This theory is supported by the DAN report showing that cardiac events are the leading disabling events contributing to the cause of death. The British Sub Aqua Club reported that, in many of the drowning cases at the surface, there is a growing body of experts that suspect SCUBA diving immersion pulmonary oedema (SDIPE). The relationship between cardiovascular control and SDIPE is current area of interest (1,10). More than 90% of diving-related fatalities are in people over 40 years of age, and more than 70% are in people over 50 years of age (10).

In 60% of the fatalities, there were personal accounts of the incident reported by the diving partner which revealed death occurring almost as often underwater as it did at the surface post dive (10).. Those deaths that were determined to be cardiac-related occurred at the end of the dive when the diver ascended to shallower depths (12)..Based on autopsy findings, the victims' profiles, and the sequence of events as reported by witnesses, together with analyzing the victims' equipment, and expert opinions of the DAN reviewers,(9) the most common cause of death was drowning with the leading cause of disabling injury being an acute cardiac event.

Similarly, The British Sub Aqua Club has collected data on diving fatalities. The average age in 2017 of fatalities was 55 years (1). In 45% of these deaths, SCUBA diving immersion pulmonary oedema (SDIPE) was viewed to be a contributory factor. Similar to terrestrial pulmonary oedema caused by the failure of the left ventricle to contract sufficiently to eject blood and most often observed with congestive heart failure. With SDIPE it is not due to heart failure and many are fit young divers. The exact mechanism of why some are prone is still a topic of investigation. DAN South Africa

reported the mean age for divers of 43.5 years and that 33% of diving fatalities are cardiac-related. Brazil reports a much lower prevalence of cardiac deaths at 9%; however, they report that over 40% are due to drowning, which, in some cases may have been triggered by a cardiac event or SDIPE (13). In Australia, a study examining diving fatalities from 1992 to 2005 included 24 cases where a coroner's report was available. The mean age was 39.2 years and 66% were male.(14). This is similar to the demographic of current divers in the USA.(2). Drowning was the most common cause of death in the Australian report at 58%, followed by cardiac-related deaths at 17%. However, when the cases of drowning caused by a cardiac event were included with the cardiac group, the percentage of cardiac-related fatalities increased to 33%. The mean age for this group was 50.3 years. Similar to the DAN report, 29% of fatalities happened at depth, 25% on ascent, and 33% at the surface (14). In the general population, cardiac-related deaths account for 23.5% of all deaths in the United States,(15) and approximately 50% of these are due to sudden cardiac death.(16). The probable rate of cardiac related deaths during diving is seemingly higher than the general population cause of death terrestrially.

1.3. Modifiable and environmental risk factors for cardiovascular related diving fatalities

One risk factor for cardiovascular disease is obesity. Obesity is related to fitness, although not mutually exclusive. The obesity rate in diving fatalities matches the US obesity rate of 36.5% (10,17) demonstrating that, unlike some other sports, diving is not only for those who are fit but is now a sport enjoyed by everyone. Increased age is correlated with an increase in the percentage of the population with hypertension, another risk factor for sudden cardiac death (SCD). Similarly, SCD risk increases with age.(18). Key differences between the general public and the mortality statistics of divers with cardiac-related disease is that the divers are generally younger at the time of the event,(19) and while cardiac-related deaths decreased in North America between 2000-2014, they increased in divers over the same period. Another risk factor for sudden cardiac death is left ventricular hypertrophy (LVH). LVH is often associated with hypertension and is seen in some athletes. Divers were observed to have a higher incidence of LVH and to have LVH occurring at a younger age than the general public,

so it is possible that this represents another pertinent risk factor for dive-related cardiovascular events (20).

Diving off a boat in warm tropical waters can be done with little physical expenditure. The Metabolic Equivalent (MET) refers to the ratio of the metabolic rate during physical activity in comparison to the resting metabolic rate. One MET is the approximate energy cost roughly of sitting quietly. The workload of SCUBA has been estimated to range from 5 METs (8) to 7 METs.(21). However, the cardiovascular impact of this relatively low workload may not be comparable to land-based activity of the same intensity on land (such as jogging at 4.5 mph or shovelling snow at a moderate intensity) due to the additional environmental factors that comprise the underwater experience. Despite the increased cardiovascular demand there is less perceived exertion than the equivalent land-based MET. Gross capacity, the total output one is capable of, decreases by 50% when using a bicycle stress test in water compared to in air (22). Unlike terrestrial activities, diving exposes the body to the effects of immersion. When the body is immersed in fluid, there is a blood shift of approximately 700ml from the extremities to the core. This increased central blood volume increases cardiac filling pressure. The water temperature, when lower than body temperature, will conduct heat away from the body four times faster than air causing the body to respond to the cold with vasoconstriction at temperatures which, in air, would not trigger vasoconstriction.

When a diver descends, the ambient pressure rises by one atmosphere for every 33 feet or 10 meters of sea water. According to Dalton's law, the partial pressure of each gas that comprises the breathing mix will rise in proportion to the total ambient pressure. For example, breathing air at sea level or one atmosphere has a partial pressure of oxygen (PpO_2) of 0.21 ATA and of nitrogen and other gasses of 0.79 ATA, which comprise the total atmosphere (of 1 ATA at sea level). When a diver reaches 2 atmospheres, the partial pressure of these gasses increases proportionately so that the partial pressure of oxygen is 0.42 ATA and the partial pressure of nitrogen and other inert gasses is 1.68 ATA. Oxygen is a powerful vasoconstrictor, so as divers descend, they will experience increases in vascular resistance as a result of rising PpO_2. According to Boyle's law, as a diver descends and pressure increases, the density of gas proportionately increases. This increased gas density increases breathing resistance which requires a greater inspiratory pressure than when breathing air at 1 atm. Each of the effects of diving listed above (cold-induced vasoconstriction, oxygen

induced vasoconstriction, increased breathing resistance, and the effect of immersion) all contribute to the increased hydrostatic pressure gradient in the lungs (between the pulmonary capillaries and the alveoli which is theorized to contribute to the risk of SDIPE) (23). Recent evidence suggests that SDIPE may be more common than previously thought and could potentially be the most common cause of sudden death during diving (1). While it has been shown that excessive hydration prior to a dive may contribute to SDIPE, changes in heart function, in particular ventricular relaxation and contraction, along with ventricular arrhythmias brought on by the diving environment could be a contributing factor. The contribution of the high oxygen pressure has been studied in a clinical setting during hyperbaric oxygen therapy. During treatment in a dry chamber environment when patients breathe high-pressure oxygen, the risk of flash pulmonary oedema is present, in particular for those patients with reduced left ventricular function. Flash pulmonary oedema is sudden onset of fluid in the lung interstitium, secondary to elevated cardiac filling pressure. Congestive heart failure or reduced cardiac ejection fraction is often contraindication for treatment (24).

1.4. Knowledge gaps

Although the effects of hyperbaric air and oxygen on heart rate, rhythm and variability have been previously reported in a dry hyperbaric chamber, these effects have not been investigated during an immersed dive with continious comprehensive cardiac monitoring in a controlled study. This is important because there are a number of features of immersed diving that might increase the risk of adverse cardiovascur events. For example, at the end of a dive, when a diver ascends, there is a rapid drop in oxygen pressure. This sudden drop in the inspired pressure of oxygen (PiO_2) from hyperoxic levels during the dive to normoxic levels at the surface may result in transient ischemia due to an imbalance in supply and demand. At the same time the inspired pressure of carbon dioxide ($PiCO_2$) also decreases, causing the coronary arteries to constrict reducing coronary blood flow (25). This occurs during dry hyperbaric therapy treatment, however studies have only examined the period of high PiO_2 and not the effect of the drop that occurs at the end of a treatment or during an air break. Along with the increased preload during hyperoxia, immersion and cold may result in transient ischemia to subendocardial tissue. As noted earlier there is a positive relationship with diving and left ventricular hypertrophy that, in times of decreased flow during ventricular diastole

and coupled with an increase in demand from increased preload, can cause an imbalance and produce transient ischemic events. Furthermore, exercise-induced transient ischemia can occur earlier in a cold environment, particularly in an older population (26,27) and this has important implications for cold-water immersion. Myocardial ischemia is associated with a rapid increase in electrical instability and often fatal ventricular arrhythmias. With most events of cardiac related fatalities being reported at the end of the dive, and occasionally in young fit divers, knowing how the cardiovascular system responds to the channge in gas pressure and total pressure is important. In addition how the body responds to the prolonged exercise during submersion and prolonged exposure to cold in combination with the change in pressure is important too as they both put demands on the body independently. Sudden cardiac death can be triggered by vigorous exercise, decrease in pH, and increase in body temperature in those with channelopathies such as long QT and Brugada syndrome. SCD from these rhythm disorders occurs more often in younger people and 50% do not know they have a disorder Unlike SCD caused by atherosclerotic coronary artery disease, which is almost exclusively related to age and is more prevalent in men,(28). Examining the response to the drop in pressure, drop in PpO_2 along with exercise while immersed in cold water in healthy participants may shed some light on the stress the end of the dive creates.

1.5. Implications of research

Given the paucity of data on the cardiac effects of cold-water immersion at depth, and prompted by the many reports of divers experiencing sudden loss of consciousness during ascent or shortly after surfacing, the goals of my research are to determine whether the drop in PiO_2 and $PiCO_2$ upon ascent from immersion at depth is sufficient to impact myocardial perfusion, using electrocardiographic markers as proxies for myocardial ischemia. I will also examine the impact of ascent-related physiological changes on autonomic regulation of the heart via analysis of heart rate variability and rhythm. Cardiac markers of B-type naturietic peptide (BNP) and cardiac troponin I (cTnI) will be examined. Blood gas analysis for lactate and pH will be performed to understand if there could be a contribution from channelopathies to the pathophysiology of SCD. A change in pH can affect gating properties of sodium channels in the case of Brugada and LQT (Peters).

Current recreational SCUBA diving screening guidelines for divers, dive masters, and instructors intended to detect potentially lethal cardiovascular abnormalities is through personal and family history and a physical exam alone. No cardiac testing such as a stress test or 24 hour Holter recording are done to look for anomalies or cardiac disorders such as an occupational diver would be screened for after the age of 40. Although a family history of drowning, unexplained syncope or SCD is correlated with the presence of channelopathies, use of medical questionnaire alone has a limited sensitivity of <10% to detect genetic disorders and diseases (28). Furthermore, in occupational divers, only those over the age of 50 are screened for the presence of coronary circulatory abnormalities or exercise-induced arrhythmia by a cardiac stress test and this is not required for recreational divers or instructors. A better understanding of the impact of environmental factors on cardiac function may lead to better screening requirements for divers, and a better understanding of the underlying factors that may trigger SCD during diving activities. Ultimately, with a better understanding and screening process, the number of diving fatalities could be reduced.

1.6. Hypothesis and specific aims

I hypothesise that the drop in inspired pressure of oxygen during the ascent of a dive will result in transient cardiac ischemia manifested by ST depression, increases in troponins, increased BNP and an increased incidence of electrocardiographic markers of cardiac arrhythmia. Furthermore, SCUBA diving will produce signs of ventricular dysfunction that may contribute to pulmonary oedema or sudden cardiac death due to rhythm disorders, particularly during ascent.

To evaluate the specific role of the decrease in the inspired pressure of oxygen (PiO_2) upon ascent, I compared cardiovascular responses between a control dive in which the inspired pressure of oxygen is permitted to decrease as normal, and an oxygen-clamped condition, in which the decrease in inspired pressure of oxygen during ascent is prevented by oxygen supplementation.

Aim 1

To investigate electrocardiogram (ECG) recordings for ST depression as an indication of transient ischemia in response to a sudden drop in the PiO_2.

Aim 2

To describe heart rate variability and rhythm during wet dives and with the PiO_2 drop during ascent and when clamped.

Aim 3

To examine the cardiac stress markers BNP and cTnI, along with lactate production and pH during wet submersed dives with exercise.

I examined heart rate variability (HRV), rhythm and circulating markers of cardiac damage in the blood in response to submersion, increased pressure and reduction in the partial pressure of oxygen during the ascent.

Chapter 2.

Background

This chapter will start with a review of cardiovascular physiology to set the framework of the physiological systems that will be examined. A review of gas laws that pertain to diving; Boyle's Henry's and Dalton's will follow. Lastly, the environmental factors of immersion/submersion, increased pressure, and cold and their effect on human physiology will be reviewed with a focus on the various measures examined in this study. Together this will provide the rationale for how these measures may address the aims of this study. The chapter will end with a review of current research in cardiovascular responses to diving.

2.1. Cardiovascular physiology review

2.1.1. Control

The cardiovascular system is under the control of the autonomic nervous system. It is divided into the sympathetic (SNS), often referred to as the ‘fight or flight' system and the parasympathetic (PNS), referred to as the ‘rest and digest’ system. These systems control heart rate, rhythm and force of contraction along with blood pressure and cerebral blood flow by vasoconstriction or vasodilatation of blood vessels. The internal process of determining if the sympathetic or parasympathetic system should respond is initiated by stretch receptors called baroreceptors that sense pressure. Pressure is determined by stroke volume, heart rate, circulating blood volume and vascular resistance. An increase in any of these three will increase pressure. The aortic baroreceptor is located at the aortic arch where blood is leaving the left ventricle of the heart. This receptor sends an afferent signal to the medulla oblongata found in the brain stem which controls the set point for the heart and ensures homeostasis. The other receptor, the carotid baroreceptor, located on either side of the neck, is found on the carotid sinus of the carotid artery. It sends afferent signals to the medulla oblongata via the glossopharyngeal nerve.

When the medulla oblongata senses high blood pressure via glossopharyngeal nerves, it sends a parasympathetic efferent signal via the vagus nerve to the sinoatrial (SA) node in the heart by a release of acetylcholine. Muscarinic acetylcholine receptors respond to the acetylcholine release with a decrease in intracellular cAMP and an increase in cell membrane K^+ conductance. At the AV node this decreases the slope of phase 0 of the nodal action potentials. This leads to slower depolarization of adjacent cells and reduced velocity on conduction. Acetylcholine is an inhibitory signal to slow the heart rate and decrease stroke volume. In addition sympathetic activity is reduced with less norepinephrine release on the α-receptors on arteriolar smooth muscle causing vasodilation. The reduced norepinephrine is also sensed by the β_1-receptors in the SA node and in ventricular myocardium reducing the force of contraction

If blood pressure is too low, the medulla oblongata sends signals via sympathetic nerves to exert their actions on the SA and AV node by releasing the neurotransmitter norepinephrine that binds to β-adrenoreceptors. This will increase intracellular cAMP and cause an increase heart rate and stroke volume. The increase in norepinephrine will also act on the α-receptors on arteriolar smooth muscle cells causing vasoconstriction. The adrenal glad releases epinephrine during exercise and stress which acts primarily on β_2-adrenergic receptors found on smooth muscle cells or arterioles supplying skeletal muscles, heart and liver. B_2-adrenergic receptors are coupled to Gs proteins which increase cAMP release inhibiting myosin light chain kinase and causes smooth muscle relaxation to increase blood flow to the heart, lungs, muscles and liver...

Under resting conditions, PNS predominates and vagal tone prevails, and variations are dependent on vagal modulations (29). Later when environmental factors are discussed, an examination of how diving may cause a rise in vagal activity and a decrease in cardiac sympathetic activity, will be presented although there is a lack of consensus.

The contribution of the PNS and SNS to the autonomic control is not one or the other; they can both contribute at the same time. When slow breathing, both PNS and SNS are increased. Immediately following aerobic exercise, both the PNS and SNS are elevated while heart rate recovers. The SNS can increase or decrease PNS activity (30).

The autonomic system responds quickly; the PNS reflex is faster at <1s while the SNS reflex is >5s.(30) When a change is prolonged, control of the cardiovascular system occurs through changes in blood pressure by the kidneys and hormonal release through the renin-angiotensin-aldosterone system (RAAS). In the kidneys, the juxtaglomerular cells in the smooth muscles sense if the blood pressure is low and release the enzyme renin. This can also happen if neighbouring sympathetic nerves are activated. When renin is released, it cleaves angiotensinogen present in the blood. Angiotensinogen then becomes angiotensin I which is converted to angiotensin II by the lungs and endothelial cells in the blood vessels. Angiotensin II will cause smooth muscle cells to contract and increase resistance. It will also create increased plasma volume via the kidneys causing an increase in stroke volume. The pituitary gland releases anti-diuretic hormone and the adrenal gland releases aldosterone which have much the same result as Angiotensin II in increasing stroke volume and resistance.

When there is an increase mean arterial pressure, it will cause an increase in the glomerular filtration rate which refers to the amount of blood filtered by the glomerulus over time. When the pressure in the Bowman's space and glomerulus increases, it will cause a larger filtration volume resulting in an increased excretion of fluid causing a decrease in plasma volume and a decrease in venous return, cardiac output and thus reducing mean arterial pressure due to the Frank-Starling mechanism discussed later.

Another mechanism to reduce mean arterial pressure is the release of the hormones atrial natriuretic peptide (ANP) primarily produced by cardiomyocytes of the atria and brain-type natriuretic peptide (BNP) produced mainly in the cardiomyocytes of the ventricles in the heart in response to stretch. Both ANP and BNP bind to the same natriuretic peptide receptor. The physiological actions are similar, and the binding to the natriuretic peptide receptor causes intracellular production of cGMP resulting in natriuresis and diuresis, peripheral vasodilation, inhibition of the renin-angiotensin-aldosterone system, and inhibition of the sympathetic nervous system from activating vasoconstriction.

BNP is a hormone first identified in 1988 from extracts of porcine brain. It was soon discovered to originate from cardiomyocytes in the ventricles in response to stretch from volume or pressure overload. There is a suggestion of release in response to

myocardial ischemia independent of ventricular wall stress (31) and that the immediate release is proportional to the level of ischemia (32).

The prehormone N-terminal fragment proBNP (NT-proBNP) is the precursor to BNP and comprised of 108 amino acids. Once released into the circulation it is cleaved in equal parts into the biologically active 32 amino acid hormone BNP. Both BNP and NT-proBNP are directly correlated. However, BNP is cleared from plasma by binding to natriuretic peptide receptors and through proteolysis by neutral endopeptidases. NT-proBNP is primarily cleared by renal excretion. Due to the different mechanisms of clearance, BNP has a much shorter half-life of 20 minutes where NT-proBNP has a half-life of 120 minutes. Due to the shorter half-life, the circulating concentrations are six-fold higher in BNP than NT-proBNP despite being released in equal proportions. This shorter half-life makes using BNP a more relevant marker for acute stress.

A normal value for BNP is <100 pg/ml. Between 100-400 pg/ml is a grey area and above 400 pg/ml is a clinically significant indication that heart failure is imminent. Factors such as female sex and increased age are associated with higher levels of BNP, while obesity is associated with lower levels (33).

The Frank-Starling mechanism explains the relationship between end-diastolic volume and stroke volume. It states that stroke volume, which is determined by the force of contraction, will increase with a larger volume of blood in the ventricles. Preload is the wall stress or stretch in the left ventricle at end-diastole, the period of relaxation just before the ventricles contract. When the ventricles stretch due to high preload the force of contraction increases with more actin able to bind with myosin. The end-diastolic volume will increase with exercise, increased central blood volume, venous constriction, as well as when the heart rate is decreased allowing more time for filling, resulting in an increased stretch and therefore a higher force in contraction. Atrial and ventricular distension resulting from a sudden increase in preload may promote arrhythmias.(34). Arrhythmias will be explored later in this chapter along with the environmental factors that would increase preload.

Cardiac output (CO) is typically around 5 l/min, measured by the total amount of blood that the heart can pump per minute comprised of stroke volume multiplied by heart rate. When stroke volume or heart rate increase, CO increases.

Afterload is the left ventricular wall stress during ejection, which is proportional to pressure during ejection and determines the force against which the cardiomyocytes must contract. For most people, aortic pressure at ejection is equal to afterload. When afterload rises, this results in an increase aortic pressure and activation of the parasympathetic system. As discussed earlier this will decrease heart rate and vasodilate blood vessels.

2.1.2. Heart rate variability (HRV).

There is a significant relationship between the autonomic nervous system and sudden cardiac death. There is a correlation between low variability of heart rate in patients who experience SCD and high variability in healthy young subjects (29). The physiological variation in the time interval between heartbeats, the R-to-R wave usually fluctuates with inspiration and expiration. During normal respiration, vagal tone is decreased inhibiting the release of acetylcholine on inspiration causing the heart rate (HR) to increase, and then it stops inhibiting during expiration causing it to decrease as a result. These fluctuations are called physiological sinus arrhythmia and are normal. The autonomic nervous system is primarily controlled by the parasympathetic system during rest. The sympathetic system will increase with exercise or with mental exertion. Overall there is a greater variability when one is more well rested than when overtrained.

There are two domains used to calculate HRV: time and frequency. Various spectral methods can be used to determine frequency domain. Power spectral density analysis provides information on how variance (power) distributes as a function of frequency (29). Mathematical algorithms can provide an estimate of the power spectral density. Methods are generally non-parametric or parametric, with parametric having having a fixed number of parameters. The main spectral components are low frequency (LF) and high frequency (HF) and are measured in ms^2 for power and Hz for frequency. The HF band (0.15-0.4 Hz) reflects the respiratory sinus arrhythmia described above and directly reflects cardiac vagal activity, thus parasympathetic activity. HF will decrease with stress. The LF band (0.04-0.15 Hz) is related to the baroreceptor control and mediated by both vagal and sympathetic systems (35). Very low frequency (VLF) band (0.0033-0.04 Hz) is more commonly used in longer duration recordings due to the oscillation time occuring only once per minute, making short term measures not as useful. VLF is influenced by exercise and not a predictor of mortality; however, a

decrease in VLF can have an association with arrythmias. It is a large contributor to the Total Power.

It is common practice to present the power spectral density measures with normalized units (nu). This is the relative value of each power component in proportion to the total power minus the VLF (although sometimes the VLF is included). This minimizes the effect of the changes in Total Power on the value of the LF and HF measure and removes most of the large variability within and across subjects, therefore tending to be more normally distributed over the raw measure (36). HFnu reflects the modulation of the PNS and influences the SA node. LFnu may reflect SNS modulation, however many say it reflects both SNS and PNS modulations. There is a linear relationship due to the mathmatical formula used to derive the value, eg. HFnu = HF/(HF+LF) and LFnu = LF/(HF=LF). As previously mentioned some researchers will use the VLF in the formula (HF+LF+VLF) as the denominator; therefore, comparing results knowing how the normalized units were computed is important, as is the calculation for power of the frequency bands. Another measure of sympathovagal balance is the LF/HF index.

Time domain is calculated by variability of the interval between consecutive beats as measured by the R to R wave. It is not the heart rate *per se*, but the interval that is analyzed. This R to R interval is called the normal-to-normal (NN) intervals when ectopic beats are removed. It most often is calculated by the standard deviation (the square root of the variance) of the NN interval (SDNN) and the square root of the mean squared difference between NN intervals (RMSSD). Short term RMSSD directly reflects parasympathetic activity (37).(16). It is highly correlated to the HF domain, and a decrease is related to electrical instability. The influence of breathing is uncertain (38). The SDNN measure is influenced by both PNS and SNS contributions and highly correlated with VLF and LF and TP when greater than HF. SDNN reflects change in breathing and will decrease with exercise. Because longer recordings will show an increase in the total variance of HRV, it is inappropriate to compare SDNN of different recording lengths. Due to this, it is generally calculated on short-term (5-minute) and long-term (24-hour) recordings.

2.1.3. The ECG trace

Heart rate and rhythm are initiated in pacemaker cells or conduction cells that do not contract but work by spreading action potentials via gap junctions to cardiomyocytes that are contractile. Action potentials are due to the passage of ions in and out of the cell through ion channels in the cell membrane that changes the polarization of the cell. The contraction of the heart begins with the depolarization of conduction cells in the SA node. The conduction cells have HCN channels (hyperpolarisation-activated cyclic nucleotide-gated) leaky channel that allows the passage of potassium (K^+) and sodium (Na^+) ions, known as the “funny” current. When activated it will slowly. during the resting phase, referred to as pacemaker potential, which causes the membrane to become more positive and depolarize. The HCN channels are directly affected by sympathetic nerves resulting in an increase in heart rate when the SNS is activated. When the membrane potential reaches -40 mV voltage-gated calcium (Ca^{2+}) channels open, and the influx of Ca^{2+} depolarizes the cell. Voltage-gated K^+ channels open shortly after and cause K^+ to leave the cell and return the membrane potential to its pacemaker-resting phase or the pacemaker potential. This spontaneous depolarization of the pacemaker cells spreads from the SA node to the atrial myocardium through gap junctions. The contractile cells, unlike the pacemaker cells, do not spontaneously depolarize and sit at a much lower resting membrane potential of around -90 mV due to the high K^+ concentration in the cell due to leaky K^+ channels being open. When a neighbouring cell depolarizes it will pass some Na^+ and Ca^{2+} through the gap junctions, and this will drive the membrane potential to a more positive value.

The heart, comprised of four chambers, consists of the upper chambers called the atria, and the lower chambers called the ventricles. Each chamber is electrically isolated from each other. In the top of the right atrium is the SA node while the AV node is between the atrium and ventricle and conducts the electrical signal between the two. With an ECG, the electrical signals of depolarization and repolarization of the cardiomyocytes can be recorded. The depolarization of the SA node sets the rate of the heart, innervated by the vagus nerve, and as discussed earlier is under the control of the autonomic nervous system via the medulla oblongata. The ventricles have Purkinje cells that conduct faster through a higher number of gap junctions. During one cardiac cycle, when the SA node is depolarized, it sends the signal to the neighbouring cells to depolarize, and this signal passes through the gap junctions to contract the atrium in

synchrony in a caudal and leftward direction. Because the atrium wall is thin, it is a smaller signal amplitude than the ventricles, and it also is void of Purkinje fibers, so it produces a slower electrical signal. When the signal meets the fibers between the atrium and ventricle, it cannot pass except through the AV node. The AV node has slow conduction due to a higher resting membrane potential and lack of sodium channels requiring calcium to depolarize the cell. Because it takes longer to depolarize, it allows the ventricles to fill and not contract until the atrium is finished contracting. The ventricles will depolarize very quickly due to the Purkinje fibers in the subendocardium causing the ventricles to contract almost simultaneous despite being larger than the atrium. Due to the left ventricle myocardium being thicker than the right ventricle myocardium, the current travels towards the left on the ECG.

The 12-lead ECG consists of 10 electrodes that record the electrical activity created by the cardiac action potential by generating an electrical vector that is recorded by an ECG lead. These 12 leads each consist of two sets of ECG leads, the six limb leads (I, II, III, aVF, aVR, aVL), and the six precordial leads (V1-V6). The recording is done with two electrodes; one positive called the exploring electrode and one negative the reference electrode. The vector denoting the direction and magnitude of the impulse is represented on the ECG lead as a positive or negative deflection. All recordings at any given instant during the cardiac cycle show the same electrical event but from different angles.

The ECG trace has distinct waveforms with corresponding letters that correlate to the action of the heart. The first wave is the P wave. It represents the depolarization of the atrium. The beginning of the P wave is when the SA node depolarizes, the peak of the P wave is when the signal reaches the AV node, and the end of the P wave is where the current is passing through the bundle of His. The P wave is followed by a short iso-electrical period when the current passes to the bundle branches (the flat line between the P wave and Q wave), leading to depolarization of the ventricle starting with septal depolarization. The QRS segment represents the depolarization of the ventricle. The beginning of the Q wave represents the current passing through the Purkinje fibers followed by significant ventricle depolarization (R wave) and basal ventricular depolarization (S wave). At the end of the QRS when the ventricles entirely depolarize, they are in systole, and there is another iso-electrical period called the ST segment. Finally, there is the repolarization of the ventricles (T wave). The repolarization of the

atrium masked by the depolarization of the ventricle is not present on the ECG trace. Examination of the various segments of the ECG trace are useful to detect ischemia, arrhythmias, and both acquired and inherited channelopathies that can lead to SCD.

2.2. Cardiovascular disease

The leading cause of natural death worldwide is cardiovascular disease. SCD is an unexpected death caused by cardiovascular disease that occurs suddenly, usually less than an hour from the onset of symptoms. In Canada, there are 30,000-40,000 cases of SCD per year. SCD accounts for approximately 50% of the mortality from cardiovascular (16) which includes heart failure and ischemic heart disease.

Heart failure is when the heart cannot pump enough blood to meet the demand of the body. It can be either systolic heart failure where there is a reduced contractility and ejection fraction, or diastolic heart failure, when there is less blood in the ventricles due to hypertrophy of the ventricle wall. Either type can happen on either side of the heart but usually starts with the left side. Left-sided failure leads to pulmonary oedema, the build-up of fluid in the lungs. When heart failure is on the right side it leads to oedema in the extremities particularly the legs, ankles and feet.

Myocardial ischemia is lack of oxygen to the heart muscle. It can result in myocardial infarction, arrhythmias, heart failure, and SCD. There are two types of myocardial ischemia. Type one is a blockage of blood flow due to a rupture of plaque in an artery providing blood and oxygen to cardiomyocytes. Before the plaque ruptures, there can be a period of coronary artery disease where blood flow is reduced but not cut off depending on the degree of blockage. When a complete blockage occurs and cell death results, it is referred to as myocardial infarction (MI) often called a heart attack. A transmural infarction affects the entire wall from the endocardium to the epicardium, and will result in an elevation of the ST segment of the ECG trace and referred to as an ST-segment elevation myocardial infarction. Should the infarction affect only the subendocardium, a depression in the ST segment is observed and is referred to as a non-ST segment elevation myocardial infarction.

Type 2 ischemia, usually caused by an imbalance of supply and demand, is associated with conditions that lead to elevated myocardial oxygen demand or

decreased subendocardial oxygen delivery. Decreased delivery can occur with LVH, microvascular disease, tachycardia, and increased preload, all which decreases maximum flow during ventricular diastole. Demand for resting coronary flow increases with tachycardia, increases systolic blood pressure, increases contractility and reduces haemoglobin. Type 2, often seen on stress tests, can be caused by coronary spasm or endothelial dysfunction where the artery occludes without a thrombosis. When there is insufficient oxygen supply for aerobic metabolism to produce ATP, the cardiomyocytes will switch to anaerobic metabolism using limited amounts of glycogen to produce ATP. The cardiomyocytes will slow and eventually cease contractions during anaerobic metabolism to survive for up to 20-30 minutes before cell death (39).

Myocardial ischemia can be seen on the ECG trace with a change in amplitude of the ST segment. The lack of oxygen can cause ventricular fibrillation (Vfib) or sinus bradycardia if the ischemia is located in the inferior wall of the left ventricle, which will be discussed later in this chapter.

As discussed earlier, the ST segment represents Phase 2 of the action potential where both K^+ is leaving the cell and Ca^{2+} is entering the cell, creating a balance of ions entering and leaving the cell and therefore no net change in the charge of the cell membrane. This balance is the plateau stage of depolarization when the ventricles are in systole. This segment in the ECG trace, when used as an objective diagnostic tool, reflects transient ischemia or subendocardial ischemia observed as a depression in the ST segment or transmural ischemia and myocardial infarction found with an elevation in the ST segment.

There are several other causes of a change in the ST segment. With the net neutral charge during this segment in the ECG trace, a flat line will appear representing the isoelectric period and will be at the same amplitude as the PR segment or the TP segment in a normal healthy recording. If, when referencing the ST segment in comparison to the PR segment, there is a deviation to the height of the isoelectric line, further investigation is required. While the use of the PR segment is defined in textbooks (40) and many consensus documents and studies, some recommend using the TP segment for the baseline isoelectric comparison (41,42).

With the hypothesis that a sudden drop in the PiO_2 may cause a transient ischemic event, there should be an observable depression below the PR segment. Other causes of ST depression are hypertrophy that may be present in this population. However, the diagnosis of hypertrophy requires echocardiogram imaging. Hyperventilating, hypothermia, Brugada syndrome, exercise, tachycardia, and non ST elevated myocardial ischemia may all cause an ST depression (43). The criterion set out by the American Heart Association in a consensus guideline with the American College of Cardiology Foundation and the Heart Rhythm Society for detecting depression in the ST segment requires a minimum of 2 or more anatomically contiguous leads with a depression of ≥0.1 mV except for V2 and V3 depression of ≥0.05 mV regardless of age or sex. When the ECG software detects a depression, further investigation must be done to determine the characteristics of the depression. A depression accompanied by an upslope towards the T wave is a normal finding during exercise except when accompanied by a prominent T wave in the majority of the precordial leads known as de Winter's sign, an acute ischemia caused by a proximal occlusion of the left anterior descending artery. When the depression is horizontal or down sloping it is typical of ischemia. Other repolarization abnormalities that can cause a depression in the ST segment left or right bundle branch block and Wolff-Parkinson-White syndrome, both accompanied by changes in the T wave amplitude. It is the ST-deviation without the T wave change with the exception described above of de Winter's sign that indicates acute ischemia.

Elevation in the ST segment would be an indicator of ischemia with myocardial infarction and should not happen in a healthy subject population. The leads can determine the location of the ischemia, with leads V1-V4 anterior, I, V5-V6, aVL lateral, and II, aVF, III inferior. There is usually a depression in the electrically opposite leads. In ST depression, the location is not detectable by the limb leads.

Elevation in leads V1-V3 can be caused by several other factors. A myocardial transient outward potassium current (I_{to}) which can occur in human ventricular myocytes can play a pivotal role in the action potential and repolarization. When I_{to} occurs, a transmural voltage gradient during ventricular activation takes place due to differences in the action potential between the epicardium and endocardium. This can result in phase 2 re-entries and close coupled premature ventricular contractions and may lead to ventricular fibrillation. The cause of I_{to} can be either acquired or inherited. These include

remodelling due to hypertrophy in particular left ventricular hypertrophy, long QT syndrome, Brugada syndrome and early repolarization syndrome. In addition, testosterone has shown to increase I_{to} in what is referred to as “male pattern” ST elevation (44). Approximately 10% of SCD is caused primarily by electrical disorders or ion channel diseases and up to 13% of the healthy population has early repolarization syndrome (45) and 75% of those are male. It is higher in athletes. In a study by Haïssagurre et al. (46), 31% of patients with idiopathic ventricular fibrillation had ERS vs. 5% in healthy controls. The risk of SCD from ERS is higher in people over the age of 50 (45). On ECG the ST elevation associated with ERS disappears when the HR is increased (44,45). ST elevation can also be seen without ERS with hypothermia and with bradycardia. Hypothermia can also induce long QT syndrome (LQT), discussed later in this chapter.

While the criterion for the deviation from the PR segment isoelectric line in the measurement of the ST segment amplitude is generally agreed upon, the time point for where to make this measure in reference to the J point, the junction between the termination of the QRS complex and the beginning of the ST segment, lacks consensus.(47,48) The ST segment is typically between 5 ms to 120 ms with 80 ms the average. There are recommendations to use from the J-6 (J point plus 6 ms) (42) to J-80. The American Heart Association and American College of Cardiology (43) and several emergency medicine societies and groups (48) recommend using the J-40 to J-80 time point. When considering where after the J point to choose the time point for automated measures, both specificity (the number of false positives reported), and sensitivity (the ability to detect true positives) are factors. While measures made at the J-10 time point have the highest specificity, measures at the J-80 have the greatest sensitivity (48). Another consideration will be if the recording takes place while the subject is at rest or exercising. With exercise increasing sympathetic tone, and sinus tachycardia, exercise stress tests will often use the J-60 to J-80 time point,(41) and in one study the J-80 was found to be superior;(47) however, it will also produce many more false positives than the J-10.

In response to ischemia, cardiomyocytes release troponin. Muscle contraction occurs when actin binds to myosin and forms a cross-bridge allowing actin to move the filaments closer together. During this process, Ca^{2+} is taken up by Troponin C (cTnC), triggering Troponin T (cTnT) to bind with and displace Tropomyosin and exposing the

myosin-binding site for actin. Troponin I (cTnI) is responsible for deactivating the binding of the myosin head. cTnT and cTnI are more present in cardiac cells, and both are used as biomarkers of myocardial injury. Troponin is found free in the cytosol of the cardiomyocyte and shuttles back and forth with the myofibril. It is released due to injury through large fenestrations in the membrane of the cardiomyocyte. The cTnI is released in a higher concentration than cTnT and will rise with ischemia 60 minutes to 4 hours after an ischemic event and peaks at 12-16 hours. For this reason, cTnI is used in the emergency room setting as a diagnostic tool for MI. In addition, a generation from MI, troponin has been seen to elevate with stress tests and in marathon runners (39).

Lactate is another indicator of ischemia and may also be an indicator of hypoxemia. Lactate accumulation is a typical response to exertion when the body switches to glycolysis to provide additional ATP and the excess pyruvate produced is converted to lactate. In response to exercise, lactate increases gradually then more rapidly as the activity becomes more intense. At the same time, glycolysis will cause a decrease in pH due to the hydrogen cations that result from ATP hydrolysis causing the concentration to rise and causing acidosis. Although lactate production does not cause pH to decrease, it occurs together. Because lactate increases with exercise intensity, its concentration can be used to verify workload. Lactate concentration is one of the most used measures during clinical exercise testing and during performance testing for athletes. A decrease in pH can trigger long QT in some subtypes (49).

2.2.1. Left Ventricular Hypertrophy

The left ventricle naturally has the thickest wall in the heart. Hypertrophy refers to when the myocardium is thicker than average. Left ventricular hypertrophy (LVH) is frequently asymptomatic, yet it is an independent predictor of sudden cardiac death. Repolarization changes can be caused by LVH (44). It is known to cause lethal arrhythmias and ventricular ectopic beats. Divers have been observed to have a greater left ventricular wall thickness and greater overall heart mass post mortem than the general public who have died in traffic fatalities when age-matched.(20) In comparing recreational divers to occupational divers, the occupational divers with greater dive frequency had significantly a greater overall heart mass and a left ventricular wall (50).

LVH is common in hypertension. Generally, elevated left ventricular pressure, elevated systolic arterial blood pressure of considerable duration, or a long-lasting increase in contractility in the heart, or both, will cause of an increase in myocardial mass (50). LVH is present in 48% of SCD in competitive athletes.(16) It is a common risk factor for the development of torsades de pointes, which presents as ventricles beating quickly and chaotically making the waves look twisted, and less blood is pumped from the heart due to this action. Torsades de pointes can cause syncope or lead to Vfib. Other conditions that can trigger torsades de pointes bradycardia, hypothermia and long QT syndrome, discussed in the next section.

2.2.2. Arrhythmias

Normal cardiac rhythm is between 60-100 beats per minute (bpm) with the average being 75 bpm and dominated by the PNS. It will be higher during exercise or times of stress and lower at rest. The determination of a normal rhythm is with three consecutive beats on the ECG with identical waveforms. The SA node should generate every heartbeat, and cardiac impulse should propagate through the normal conduction pathway with normal velocities which pass through the atrium slower than through the ventricles. If it does not follow this pattern, then we consider it to be an arrhythmia. If any structure other than the SA node initiates depolarization of the heart, it is referred to as an ectopic beat. Ectopic means it is out of place or not normal. If there are 3 or more ectopic beats, then it is referred to as an ectopic rhythm. Ectopic arrhythmias are regular in older populations but not younger. Ectopic beats can be either atrial or ventricular. A premature atrial contraction (PAC) can happen with a regular rhythm. The PAC event appears when there is a short RR wave with a normal rhythm and P wave. A premature junctional contraction is not due to heart rate but will create an event that is not regular during normal rhythm. It may not have a P wave; it can be antegrade or retrograde. Neither of these requires treatment. A premature ventricular contraction (PVC) is different and occurs with a compensatory pause because the atrial depolarization still happens on time. The QRS will be wider than 12 ms, will change the rhythm, and the RR will be very wide. Delay of the QT with a prolonged refractory period can lead to fibrillation. If these PVCs occur every other beat, it is termed bigeminy, while trigeminy occurs every third beat, and quadrigeminy every fourth.

Heart rates that are slower than 60 bpm are considered minor bradycardia. Less than 40 bpm would be moderate bradycardia. Supraventricular tachyarrhythmias are when the origin is from the SA node, the atrial myocardial tissue or the AV node. Ventricular tachyarrythmias are when the impulses emanate from the ventricles.

Bradyarrythmias are typically due to dysfunctional automaticity in pacemaker cells or a block in the impulse somewhere in the conduction system. There are three mechanisms for arrhythmias. Automaticity refers to when tissue produces depolarization independently such as when the sympathetic nervous system releases NE via the vagus nerve on the SA node and sinus tachycardia occurs. Junctional arrhythmias occur in the AV node, an area specialized in slow conduction between the atria and the ventricles. The slow conduction allows the atria to empty into the ventricles. If the current travels too quickly then junctional tachyarrhythmia occurs.

Ventricular fibrillation is a key cause of sudden cardiac death. It is the lack of coordinated muscle contraction of the ventricles to produce an ejection of blood from the ventricles. Frequently caused by oxygen deprivation from ruptured atherosclerotic plaque, it can also be the result of other causes. When coronary artery disease is present and reduces blood flow providing less oxygen to the ventricular cardiomyocytes, over time it causes irritability to the cardiomyocytes which can induce the cardiomyocytes to over fire or fire abnormally. Scar tissue from previous MI, cardiomyopathy, genetic disorders or years of coronary artery disease can disrupt conduction. Electrolyte abnormalities can also cause Vfib due to disruption in electrical conduction. There are also genetic mutations that can lead to changes in rhythm and lead to Vfib, some of which are discussed here.

Atrial tachycardia can occur when the atrial myocardium is acting as the pacemaker at rates between 125-150 bpm. Atrial tachycardia is observed on the ECG trace with multiple P waves before the QRS complex and happens much faster than the QRS complex. When the P waves become unrecognizable and occur multiple times very quickly before the QRS complex, with the HR 250-350 bpm it is due to atrial flutters. Atrial fibrillation above 350bpm is much like ventricular fibrillation but takes place in the atrium. When the signal for the atria to contract is disorganized, the myocardium of the atria will not contract effectively. With atrial fibrillation there is a change in the RR intervals and a lack of P-waves. Causes include atrial enlargement from lung disease,

high blood pressure, valve disease, hormonal abnormalities or alcohol abuse. This can lead to stroke when blood pools in the atrium; clots can occur that later embolize and may lead to stroke.

The QT segment is the span of depolarization of the ventricles from the beginning of systole to the end of the repolarization of the ventricles when diastole begins. The duration is inversely related to heart rate. To determine if the QT segment is elongated, it must be corrected by adjusting for heart rate (QTc). There are several methods for computing the QTc. The traditional approach is the Bazett's formula. However, it has been shown to not perform well at very low and very high heart rates. Another method is the Fidericia method. Prolongation of this segment is called a long QT (LQT) and may trigger ventricular tachycardia and arrhythmias which can lead to ventricular fibrillation and sudden cardiac death. LQT is caused by prolongation of repolarization due to abnormal movement of either Na^+ or K^+ ions. It can be caused by genetic mutations in the genes encoding cardiac ion channels or acquired from medications, health and environmental conditions. LQT is associated with mutants in 17 genes (51) with 3 of these genes accounting for over 90% of inherited LQT cases. Type 1 is a mutation in the KCNQ1 channel incited by exercise, in particular, swimming along with other situations with high sympathetic activity. Type 2 is a mutation in the KCHN2 channel and is known to be predominantly triggered by a sudden startle along with exercise and during sleep. Type 3 is a mutation in the SCN5A and mainly seen during sleep and bradycardia (52). However, it is also seen during exercise, fever, ischemia, drug use, and acidosis (51,53).Mutations in Na^+ genes cause a gain of function where the K^+ gene mutations cause a loss in function; both will create a prolongation of ventricular repolarization. Triggered prolongation of the repolarization in LQT can lead to the development of early after-depolarization, resulting in the ventricular tachyarrhythmia such as torsades de pointes. If this lasts longer than 30 seconds, it may progress to ventricular fibrillation leading to SCD.

Brugada syndrome is another inherited arrhythmogenic disorder. It is associated with sudden loss of consciousness resulting from torsades de pointes and Vfib. Brugada syndrome arrhythmias often were seen during periods of high vagal tone such as a sudden decrease in heart rate or bradycardia. One of the genetic variations of Brugada syndrome, BrS1 is associated with the SCN5A gene and accounts for approximately 20% of the cases (51).Like LQT3 it causes a loss in function triggered by the same

environmental factors such as a drop in pH or an increase in temperature (49). An elevation distinguishes Brugada syndrome in the ST segment in leads V1-V3 and with right bundle branch block. Often changes in the T-wave are present (54).

Prolongation in the peak of the T wave towards the end of the T wave (T peak to T end, Tp-Te) correlates with abnormal dispersion of ventricular repolarization which increases the likelihood of ventricular arrhythmogenesis and tachycardia. It is significantly associated with increased risk of sudden cardiac death.(13,55).

To measure Tp-Te it is debated if it is rate-dependent and if a correction should be made in the same manner as the QT segment. Increasingly we are seeing the values reported this way. Values associated with risk are >100ms for acute MI and >113 ms in bradyarrhythmias. There is a high risk of ventricular arrhythmias with a reentry current. The value to indicate risk of SCD in the community is still debatable, between 74-100 ms as cut off minimum (56).

2.2.3. Changes with age

The Framingham Heart Study began in 1948 in Framingham, Massachusetts with a total of 5,209 men and women between the ages of 28 and 62. They underwent biennial examinations that included an extensive cardiovascular history and examination, including 12-lead ECG and blood analysis. It is the most extensive longitudinal study of cardiovascular epidemiology.

From this data, many studies have been published examining the changes that occur with age. These studies have shown that after age 50-60, pulse pressure increases, diastolic blood pressure drops and systolic pressure rises. The explanation for the fall in diastolic blood pressure is most likely due to large artery stiffness (57). Decreased compliance of the aorta will increase pulsatility and impair the baroreflex, leading to hypertension and increased afterload causing left ventricular hypertrophy. The development of coronary artery disease is directly correlated with age.

2.3. Gas Laws

2.3.1. Boyle's Law

Boyle's law states that the volume of a gas will vary inversely with pressure ($P_1V_1=P_2V_2$). When we increase the pressure from 1 ATA to 2 ATA (two times), the volume must decrease by one half. Density is inversely proportionate, when the volume of gas decreases two fold (to ½) then the density would increase two fold. This results in a diver at 2 ATA breathing air that is twice as dense as at sea level. As pressure increases the density of the gas will increase proportionately, so that at 3 ATA the density is three times that of the surface. At 4 ATA the density is four times that of the surface and so on.. Boyles law not only affects the air spaces in a divers body but it explains the increased density of the air the diver breathes.

2.3.2. Daltons Law

Dalton's law states that the total pressure (Pt) is equal to the sum of the partial pressures (Pp) of each gas that comprises the atmosphere ($Pt=Pp_1+Pp_2+Pp_3+Pp_4\ldots$). Air is composed of approximately 21% oxygen (O_2) and 78% nitrogen (N_2) with about 1% other gases such as carbon monoxide, carbon dioxide, argon, neon, and methane to name a few. For this illustration of Dalton's law, these other gases making up the 1% will be combined with the nitrogen for a total of 79%. At sea-level we consider the atmospheric pressure to be 1 ATA. This pressure is a result of the weight of air in the atmosphere pressing down on the earth. As we ascend, the weight is less and atmospheric pressure is reduced; for example at 5,455 meters above sea level the pressure is half or 0.5 ATA. Water is denser than air and causes a more rapid change in pressure. An increase in atmospheric pressure of 0.5 ATA will occur in only 5 meters of sea water. At ten meters of sea water the total pressure is 2 ATA. The composition of air remains the same at 21% oxygen and 79% nitrogen, making the partial pressure of the gasses comprising air at 2 ATA to be PpO_2 .42 ATA and the PpN_2 1.58 ATA which when added together equal the total pressure of 2 ATA. Due to Dalton's law, gas partial pressures may reach values under pressure that are not possible terrestrially.

2.3.3. Henry's Law

The amount of gas dissolved in a liquid is directly proportional to the partial pressure of that gas above that liquid. As pressure increases, the body will dissolve N_2 into the tissues and organs until if given adequate time, equilibrium is achieved. Ascent reduces pressure and the dissolved N_2 will come out of solution by way of gas bubbles and microparticles in the venous system returning to the right side of the heart and then through the lungs; the gas is expelled until, given enough time, equilibrium is reached. Due to Henry's law a diver who is surfacing from a dive has a release of gas bubbles and microparticles into the venous system that returns to the lungs for elimination via the right side of the heart. This gas load increases preload and activates nitric oxide release from the endothelium. Echo imaging and ECG recordings have shown that divers demonstrate a trend towards right ventricular enlargement (58) perhaps as a result of distention due to the release of bubbles and microparticles on ascent (59).

2.4. Environmental Factors

The diving environment has many factors acting upon the diver that will all contribute to the physiological response (Table 2.1)

2.4.1. Hyperbaria

With increased pressure comes increased gas density according to Boyle's law and increased PiO_2 according to Dalton's law. Very few studies have looked at the effect of pressure separate from these effects. In cellular models, increased hydrostatic pressure at a constant heart rate decreased membrane excitability, slowed condition, and increased refractoriness. Associated changes are generalized membrane depolarization, decrease of the maximal upstroke velocity of the action potential, and increased action potential duration (60).

Studies that have compared hyperbaric hyperoxia to normobaric hyperoxia cannot separate the effect of total pressure from the effect of increased gas density. Below I will discuss hyperoxia in both normobaric conditions and hyperbaric conditions followed by the effect of increased density of a gas.

2.4.2. Increased PpO_2

Increased oxygen is known to cause toxicity in a dose and time-dependent manner. It is believed to be a result of the production of reactive oxygen species, a by-product of the metabolism of oxygen. Oxidative stress, DNA damage and acute toxicity to the lungs or central nervous system can result. Increased oxygen has been observed to reduce heart rate, decrease CO, produce hypertension and increase peripheral vasoconstriction leading to a redistribution of regional blood flow to the central circulation (61–65).

The lungs are exposed to the highest pressure of oxygen and are the first organ to be affected. Lower doses, greater than a PiO_2 of 0.50 ATA over time can cause pulmonary toxicity. It is often referred to as the Lorrain Smith effect after the pathologist who first described it. This higher dose of oxygen causes inflammation that starts in the airways and spreads to the lungs. Typically, recreational divers are not exposed to the high pressure of oxygen long enough to cause symptoms or long-term effects of pulmonary toxicity, and exposure limits have been created to avoid this phenomenon. The first signs are a mild irritation of the upper airway and cough, later leading to oedema in the lungs. Occupational divers perform spirometry testing of lung function as part of their medical screening for fitness-to-dive and track lung function over time for occupational exposure.

Short exposures to very high pressures of oxygen, above a PiO_2 of 1.0 ATA but more typically above 1.4 ATA in divers and above 2.0 ATA in a dry chamber can cause central nervous system toxicity, manifested by symptoms such as tunnel vision, tinnitus, nausea, twitching of the facial muscles, irritability, and confusion. However, many of these symptoms do not occur prior to convulsions. The decrease in allowable exposure of an open water diver versus a dry chamber dive is due to the elevated $PiCO_2$ that arises with a SCUBA regulator or diver's helmet, due to the increased dead air space increasing the $PiCO_2$. This is known to lower the threshold for oxygen toxicity seizures to occur.

Hyperoxia is a known vasoconstrictor. Although it does not appear to be associated with increased sympathetic activity, possibly it is influenced through arterial baroreflexes which evoke a suppression of efferent sympathetic activity and augment

parasympathetic outflow (61). The dominance of the parasympathetic system produces bradycardia. The vasoconstriction observed is thought to be a result of hyperoxia creating the formation of peroxynitrite from superoxide which accelerates the oxidative degradation of endothelium-derived nitric oxide (NO) which reduces the bioavailability of NO which is one of the endothelium derived factors responsible for maintaining vascular tone by dilating blood vessels. (66). Therefore, the increase in oxygen creates an influence on vascular function with a powerful vasoconstriction. In a study of patients with ischemic heart disease breathing 100% oxygen at normobaric pressure, a reduction of coronary blood flow velocity by 20% and an increased in coronary resistance by 23% was observed without significantly changing the diameter of capacitance arteries. This effect was promptly reversed upon administration of vitamin C, further suggesting that reactive oxygen species play a crucial role (67). Another study showed an increase in endothelin-1 concentration, and this may also be the cause or contribute to vasoconstriction during hyperbaric hyperoxia.

Normobaric hyperoxia at a PiO_2 of 1.0 ATA has been shown to induce bradycardia and increase vascular resistance (68) with a decline in CO proportional to the level of inspired oxygen (69). During a 50 m chamber dive, air produced bradycardia but did not impair contractility measured with seismocardiography (70). However, when examining the pre-post measures, compared to at 50m, diastolic function was reduced in healthy subjects (71). Hyperoxia incudes impairment of cardiac relaxation and increase left ventricular filling pressure by an increased left ventricular end diastolic pressure of 29% (±14%), and prolongation of the isovolumic left ventricular relaxation by 8% (±2%) (72). The result was increased left ventricular strain. Stroke volume and ejection fraction both decreased in a study using Doppler and echocardiogram after 15 minutes of hyperbaric hyperoxia with a PiO_2 of between 1.0 and 1.6 ATA. As mentioned earlier, reduced ejection fraction is a contributing factor to pulmonary oedema. Measurements showed decreases in left atrial and left ventricular end-diastolic diameter. After a 5-hour exposure, stroke volume and cardiac output were significantly further reduced (73). This study did not show any significant changes in heart rate or blood pressure despite previous studies mentioned earlier which observed this decrease in heart rate and an increase in blood pressure. A study by Whalen et al. similarly did not show a reduction in heart rate with either normobaric oxygen, PiO_2 of 1.0 ATA or hyperbaric air at 3.04 ATA with a PiO_2 of 0.63 ATA but did show a decrease in heart rate with hyperbaric hyperoxia

at 3.04 ATA/PiO_2. (64). Although they also did not see a change in blood pressure for any of the exposures, they did see a reduction in CO with an increase in stroke volume and peripheral resistance in the hyperbaric oxygen exposure. The results were contrary to the previous study that observed a decrease after 15 minutes in left ventricular preload as evident by a reduction in left atrium diameter, left ventricular end-diastolic pressure and stroke volume. However, there was no accompanying tachycardia, a reflex commonly observed with these changes.

When looking at HRV during hyperbaric air and hyperbaric oxygen exposure, an increase in vagal activity is directly associated with increases in PiO_2 and ambient pressure with hyperbaric oxygen having a more significant effect (74). An increase in HF power was observed indicating an increase in parasympathetic activity occurs with hyperbaric hyperoxia (63). This is likely due to the peripheral vasoconstriction activating the arterial baroreceptor reflex (65) which activates the vagal response and depresses sympathetic activity resulting in bradycardia.

In long-term observations of saturation divers in a hyperbaric hyperoxic environment, the decrease in HR recovered over time with an average time of eight days (75). In the same study, exercising in a hyperbaric hyperoxic environment PAC's were observed, and in air saturation divers, 10% of the divers had PAC's (76). During decompression there was also an elongation of the QTc accompanied by an increase in HR perhaps in response to a removal of PNS dominance (75,76).

With inhalation of 100% oxygen at 3.4-3.8 ATA, complete saturation of hemoglobin in the venous circulation is observed, along with less buffering of acid as reflected by a significant increase in venous pCO_2 as well as a small decrease in venous pH (64). However, results of sampling arterial blood gasses during hyperbaric oxygen showed an increase in pH with a reduction in $PaCO_2$ during hyperbaric hypoxia at PpO_2 of 2-3 ATA (69). in one study yet no change in another (64) suggesting a dose and time relationship. A change in pH reflecting a shift towards acidosis can induce long QT in those with LQT-3 and those with Brugada syndrome. There has been no increase in lactate with hyperoxia reported(77).

Hyperbaric hyperoxia has not been shown to increase plasma renin activity or anti-diuretic hormone (78). One small study of hyperbaric oxygen therapy (HBOT)

patients with a history of congestive heart failure (n=5) showed 4/5 had a decrease in BNP following 20-30 treatments (79). Another showed an increase in Pro-BNP with HBOT in people with diabetes with no change in HR or blood pressure (N=25); however, in this study there was no indication of the number of treatments before observing a difference (80) yet several studies showed no change in BNP in a single HBOT in healthy subjects both young and old (81,82). Similarly, the response of ANP to hyperbaric conditions is also controversial with studies suggesting an increase in ANP and diuresis and yet another study showing no increase in ANP (78).

One study observed a prolongation of the duration of the action potential with an increase in cTnI in mice exposed to hyperoxia of 100% oxygen at ambient pressure (83). However, another study in humans observed no change in cTnI after dry HBOT in young and old (81). Hyperoxia is thought to exacerbate CO_2 retention; however, some controversy remains (84). The effect of CO_2 retention will follow in the section on increased gas density.

2.4.3. Increased gas density

An increase in atmospheric pressure will increase gas density. One of the most noticeable effects of increased gas density is an increase in the work of breathing. This increase in the work of breathing acts to reduce ventilation and promote CO_2 retention. Retention of CO_2 will cause a drop in pH due to carbonic anhydrase which converts CO_2 and H_2O into bicarbonate (HCO3-) and free hydrogen ions (H+). A decrease in pH is observed in animal studies of hyperbaric air saturation dives to the same degree as breathing 5% CO_2 (85). In humans during dry hyperbaric hyperoxia, a small but not significant drop in pH was recorded in one study;(64) however, the extent to which pH is affected during a wet SCUBA dive has many logistical challenges. As mentioned earlier changes in pH may cause fatal arrhythmias in LQT and Brugada syndrome.

CO_2 retention will usually immediately trigger deep and fast breathing to blow off CO_2. However, the respiratory response to hypercapnia is directly related to the work of inspiration. The higher the gas density, the lower the ventilatory response to P_ACO_2 with respiration rate decreasing as depth increases. It is more pronounced in experienced divers (86,87) who are greater CO_2 retainers than the general population; a similar phenomenon is observed in athletes but to a greater extent in divers (88). This is notably

seen when exercising (89). The hyperoxic environment combined with the breathing apparatus will add external respiratory work reducing the hypoxic drive to ventilation (90–92). To date, there has only been one study in a wet environment during SCUBA due to logistical challenges, that study had significant scatter and further work needs to be done (88).

Increased air density in a dry chamber exposure is the suspected cause of impaired diastolic function. This is evidenced by a decrease in acceleration time-to-ejection time post exposure. This same group concluded that this decrease indicated an increase in pulmonary artery pressure,(71) enhanced negative inspiratory pressure (82) along with evidence that high density gas disturbs left cardiac chamber filling (93).

In wet dives and during immersion, inspiratory pressure is increased and there is an assisted expiration due to the hydrostatic compression on the chest wall. This reduces vital capacity due to the translocation of blood to the central region. There is an increased demand of blood flow to the lungs as a result of muscle fatigue (88).

An increase in P_aCO_2 will cause coronary vasodilation which increases O_2 delivery. It may even be cardioprotective (84). However, as the diver ascends in the later part of a dive, both PiO_2 and P_ACO_2 drop, and coronary O_2 delivery will be reduced while decompression stress produces venous gas emboli and increased preload.

Not only does SCUBA expose the diver to the impact of breathing increased gas density but their position in the water column will also affect static lung load. When upright, the diver's extrathoracic airways are exposed to less external pressure than in the prone position. Moderate positive pressure breathing has been shown to enhance tolerance to maximal exercise byway of preclusion of inspiratory muscle fatigue and larger expiratory reserve volume. In contrast the negative static lung loading in the prone position can lead to dyspnea. In addition to the increase in the work of breathing due to the increase in the density of the gas, a diver also has external respiratory loading due to hydrostatic pressure, which reduces ventilation through alterations in the work of breathing.

2.4.4. Immersion/Submersion

Both immersion (to the neck) and complete submersion cause a significant effect on the autonomic and cardiovascular systems. Water conducts heat from the body twenty times faster than air, and thermoneutral temperature in water (34-35^{o}C) is much higher than in air . Numerous studies have shown that immersion and submersion increase central venous pressure and produce a 700 ml shift of blood from the extremities to the intrathoracic central region (94). Hydrostatic compression of tissues will decrease cell volume with a shift from the intracellular to extracellular space. Along with the blood shift, it will increase venous blood volume causing an increase in venous return and an increase preload (93,95). As discussed earlier, the Frank-Starling Mechanism will cause an increase in atrial and ventricular distention due to the increase in left ventricular end-diastolic volume, left ventricular end-diastolic pressure, and stroke volume. The result is an increase in cardiac output and aortic pulse pressure. This increase in CO maintains arterial pressure in the face of decreased vascular resistance (96). The increase in stroke volume with immersion has been observed in many studies and varies from 9%-77% depending on the study design (34,71,97,98). Studies have shown an increase in CO of 28% to 162% depending on the study However, no increase in mean arterial pressure has been observed (88).

The blood redistribution to the thorax augments diastolic volume and stroke volume, promoting feedback caused by arterial pressure to the baroreceptors which in turn reduce heart rate via activation of the parasympathetic system through the vagus nerve(99–101). The effect on heart rate is not consistent. Some studies have shown a reduction with immersion (99,100) while others show no reduction in thermoneutral water (96,98,102). Bradycardia and increased wall stretch can contribute to an increase in arrhythmia incidence (34). The body tries to compensate for the increase in arterial pressure with peripheral vasodilation, but hydrostatic pressure counteracts this mechanism (102). So pronounced is the effect on the systemic and pulmonary systems that immersion in water has been said to be equivalent to a radical blood transfusion (103). Compensation for the hypervolemia sensed by the increase in CO and pulse pressure is counteracted with a rapid rise in ANP (100) and by the compensatory actions of diuresis and natriuresis (34,95).

HRV time domain measures during immersion have shown an increase in RMSSD, which strongly correlates to a rise in the parasympathetic system. There is also a rise in SDNN, indicating possible co-activation with the sympathetic system. Frequency domain analysis shows a significant increase in both the HF and LF range also indicating both a sympathetic and parasympathetic response to immersion (102). However, there has also been a decrease in the LF/HF suggesting that the sympathetic contribution is smaller than the parasympathetic (99).

2.4.5. Cold

The effects of immersion and submersion are dependent on temperature of the water with colder temperatures having a more significant (104). The cold water will cause a greater translocation of blood to the thoracic region due to peripheral vasoconstriction. This redistribution will further increase preload causing an increase to stroke volume seen by a greater left ventricular end-diastolic (96). This results in a greater arterial diastolic pressure; however, no change in cardiac output was observed (100). An increase in vascular sympathetic activity is observed (100) likely as a response to the cold by vasoconstriction in an attempt to reduce heat loss.

When water temperature is reduced from thermoneutral to water as warm as 30^{o}C stroke volume and diastolic pressure is increased (96). The cold shock response includes tachycardia, peripheral vasoconstriction, hypertension and an inspiratory gasp reflex with hyperventilation which induces hypocapnia (105). Prolonged exposure will reduce minute ventilation (88). The initial increase in HR and ventilation is present even when torso and legs are protected from the cold water (100). Longer term responses to cold include elevated plasma norepinephrine levels, diuresis and an augmented increase in arterial blood pressure in older adults (26,75). An increase in blood pressure can induce MI or ischemic arrhythmias (106). When subjects immersed one hand in an ice bath, an increase in coronary artery resistance occurred only in those with coronary artery disease, and in some of these individuals arterial spasms were the observed cause. This response was not present in healthy individuals (107). Vasoconstriction from cold exposure will also increase afterload (93). Vasoconstriction increases blood pressure and may further increase diuresis (34). Cold stress and blood redistribution while diving may cause acute volume overload which can lead to acute decompensated heart failure in a compromised heart (106). The number of sudden cardiac deaths are

more significant in cold water and at occur in younger individuals than in temperate water (19). Prolonged cold water exposure leading to hypothermia can cause ST elevation that is not due to early repolarization, along with a reduced HR this may cause LQT (27,44)..

2.4.6. Age

During exposure to dry hyperbaric hyperoxia older subjects have a greater decrease in FMD. There is also a decrease in CO which is more pronounced in older subjects with a 10% greater decrease in ejection fraction (81).

Increased cardiovascular-related mortality has been credited to cold exposure, particularly in older adults. There is an increase in preload from cold skin exposure observed in older adults not seen in the young, along with an increase in myocardial oxygen demand (26). In head-out water immersion, the increase in CO is blunted in the older population, perhaps due to a less sensitive baroreflex resulting from less compliance of the carotid artery (100). Ectopic beats are more frequent in the older participants along with a rise in blood pressure (100). Cooling of the skin increased left ventricular preload without affecting left ventricular contraction in older but not younger adults. The increase in preload and afterload gives rise to the risk of cardiovascular events in cold water for older adults (26).

Overall HRV is reduced with age with an increase in sympathetic tone and a decrease in parasympathetic tone (108).

2.4.7. Exercise

During immersion and exercise, there is a persistent increase in preload. This cardovascular adjustment is more pronounced due to exercise rather than immersion alone, with mild exercise increasinng CO significantly more in water than air (96). When exercising on land, increased sympathetic activity occurs and there is vasoconstriction to the kidneys. However, in the aquatic setting there is a suppression of the renal SNS. Although no increase in renin or aldosterone has been observed, an increase in plasma vasopressen occurs (100). It has been observed in people with stable angina that exercise in a cold environment reduces the threshold for MI as evident by ST depression

(27). During exercise tachycardia ANP will rise; however, BNP does not (32). Both ANP and BNP rise with wall stress, but since BNP is unaffected by exercise intensity, it is a better marker of cardiac stress independent of workload (109,110).

Exercise without immersion will decrease PNS activity as evident by a decrease in HF in the frequency domain and an increase in LF/HF ratio (111). Sympathetic activity is increased resulting in increased heart rate, end-diastolic volume and blood pressure to enable oxygen delivery to muscles. LF decrease is often observed with exxercise along with a decrease in the time domain in both the SDNN and RMSSD (111). This is in contrast to the response to immersion and hyperbaria described above.

2.4.8. Mammalian Reflex

Activation of the sympathetic nervous system by cold exposure will increase heart rate. The exception to this is when the cold stimulus of the face combined with breath hold results in a response known as the mammalian reflex. This bradycardia response was first observed in frogs and lizards by Edmund Goodwyn in his doctoral thesis “The connection of life with respiration” in 1786 (112). Later cited by Paul Bert in his publication "Leçons Sur la Physiologie Conparée de la respiration" 1870, which despite referencing Goodwyn, is accredited with discovering this response. Later Charles Richet in 1890 described that bradycardia was an O_2 conserving reflex via stimulation of the trigeminal nerve with water immersion and would reduce the heart rate via the vagus nerve (112). Lawrence Irving and Per Scholander later published their findings that the diving reflex is present in all air-breathing vertebrate species and would, in addition to slowing of the heart rate, result in redirection of blood flow from the peripheral to the central organ and suppression of metabolism (113). However, in 1975 Gooden et al. showed that breath hold with face mask removal produced a 19% reduction in HR, where mask or breath hold alone did not provide a significant change (114) determining that the mammalian reflex requires not only cold stimulus on the face to stimulate the trigeminal nerve but also breath hold. The reflex is proportional to the temperature of the stimulus to the trigeminal nerve located on the face (115).

Exposure of the face alone will increase vagal activity but combining it with apnea activates both the SNS and PNS and results in vasoconstriction and vagaly mediated bradycardia. The increase in SNS activity can lead to ventricular

tachyarrhythmia and the vagal induced bradycardia which give rise to ventricular ectopic beats (116). In adolescence the bradycardia and associated arrhythmias are greater (100).

2.5. Diving Studies

When diving using an underwater breathing apparatus, the effects of hyperbaria, hyperoxia, increased gas density, submersion, exercise and water temperature simultaneously interact. The environment causes many logistical barriers to research, and thus relatively few studies have taken place. To date, two studies using 12-lead ECG Holter recordings have been published. The first such study, published in 2014 by Bosco et al. (117) determined the effectiveness of the device in a diving situation. The study was conducted in open water (temperature 16°C - 20.4°C). Neither time (34 min – 44 min) nor depth (7.2 m – 37.5 m) were controlled. The subjects ranged in experience and wore a combination of drysuit, wetsuit, or semi-dry suit. Many divers will wear a drysuit with a tight neck dam or a thick wetsuit with a hood that tucks into the collar that can be tight on the neck. Increased pressure sensed by the carotid baroreceptor will decrease heart rate; however, this was not a consideration in any of the diving studies to date. The aim of the study was not to examine the ECG trace, but rather to validate the ability to obtain a noise-free recording. They did report cardiac variables such as number of PAC's, PVC's or ST segment elevation and HR.

To date, studies of wet submerged SCUBA dives have lacked a consensus in terms of the effect on HR. Some have shown a decrease in heart rate (101,102,118) in dives with no or mild exercise (117,119); however, there was significant tachycardia pre-dive while immersed, perhaps due to anticipation (117). Post dive there was a significant decrease in HR from baseline, showing bradycardia in some subjects (117). An earlier study to a maximum depth of 15 m for an average of 30 min in 16°C water (N=12) with 3-lead, precordial, posterior and inferior leads showed persistent sinus tachycardia in all phases from pre-dive to immediately after, but workload was not specified (120). An early study of divers conducting scientific dives showed an increase in HR during open water dives (114). When comparing similar workload on a cycle ergometer on dry land vs. submerged on SCUBA as determined by oxygen uptake, SCUBA increases HR (22).

Parasympathetic activity decreases during a dive (101,102,118,119) which is reflected by a decrease in RMSSD. HF will increase with respiratory PNS activity and these studies observed some significant increases in HF (102,118,119). This increase was greater with depth (118); however, in shallow, resting dives there was no observation of an increase in HF (101). SDNN is highly correlated with VLF/LF and TP and is an overall indicator of autonomic activity with a decrease indicating vagal activity. Although all diving studies showed an increase in SDNN, only one of the three showed an increase in the LF and the consensus is that the PNS predominates (101,102,118,119). There was no change in the LF/HF with all but one study, which showed a decrease in the LF/HF (119) again showing inconsistencies in the results. However, all studies of HRV and the autonomic control during a dive agree that there is a parasympathetic increase most likely due to the hemodynamic change and this is further increased with depth due to the increase in oxygen pressure (102). This increase in parasympathetic activity was accompanied by a decrease in respiration rate An increase in parasympathetic activity is known to be related to cardiac supraventricular arrhythmia.

To date, no studies of SCUBA dives have examined the QTc or Tp-Te segment. Only the study by Bosco et al. (117) looked at ST changes and none were observed. This study was also the only one to look at PAC's and PVC's of which both were observed to increase during the dive. Overall, little research has been done on actual SCUBA dives, and the results vary with the experimental design; however, the consensus appears to be that there is an increase in parasympathetic activity with diving.

Three studies have looked at BNP production during SCUBA diving. Both Gemp et al. and Grassi et al. (82,93) looked at BNP production during open water one-hour 10m dives. They both saw a significant and persistent rise in BNP. Both dives were at minimal exertion. Grassi et al. compared the BNP production to the same dive profile in a dry chamber with a repeated-measures design. The wet dives produced significantly more BNP. Passino et al. (120) then reproduced these experiments at 15m without exertion. The wet exposure produced BNP independent of exercise. All of these dives took place in relatively cold water (~16^{o}C). Cold may also play a role in the amount of

BNP produced due to the increase in sympathetic activity increasing norepinephrine which is known to promote BNP in much the same manner as cold promotes ANP release (120).

Table 2.1. Autonomic influence of various environmental factors that affect HRV and ANS activity

Condition	HR	HRV Time	HRV Freq	SNS	PNS	references
Exercise	↑	↓ RMSSD & SDNN	↓ TP; ↑ LF/HF	↑	↓	Michaels
Immersion	No change	↑ RMSSD & SDNN	↑ HF; ↓ LF/HF	↑	↑	Schipke
Cold	Initial ↑ then ↓	↑ RMSSD	↑HF	↓ with time	↑ with time	Pendergast
Diving	↓	↑ RMSSD & SDNN	no change TP; LF/HF inconsistent	↓↑	↑	Schipke Noh Berry Chouchou
Age	No change/ % HR max decrease	↓ RMSSD & SDNN	↓HF	↑	↓	Jandackova
Hyperbaria	Decrease	↑ RMSSD & SDNN	↑HF	↓	↑	Lunnd, Wunderlich

Chapter 3. Methodology

3.1. Participants

Participants were volunteers from the occupational and scientific diving community in the Greater Vancouver area. All possessed current Canadian occupational diver medical certificate declaring fitness to dive, free from cardiovascular disease. Sample size was 23 (3 female), mean age 39.3 (se. 2.2) years, range 21-59 with a normal distribution (Shapiro-Wilk W Test p=0.81). Mean body mass index was 26.5 (se. 0.7) kg/m^2 range 21.9-35.6 normal distribution (Shapiro-Wilk W Test p=0.09)(Table 3.1). Informed consent was obtained from all participants, and the ethics committee of Simon Fraser University approved the study protocol.

3.2. Study design

All experiments were performed in the hyperbaric chamber located in the Environmental Medicine and Physiology Unit at Simon Fraser University. The chamber consists of 3 pressurized locks comprised of two dry sections and a wet section. The entire chamber is capable of pressurization to 30 ATA. Environmental control allows for control of water and air temperature (Fig.3.1)

Each subject was asked to perform both the control and the experimental dive with a minimum of 48 hours between exposures. Participants were blinded to the order of the dives. Prior to entering the chamber each participant was familiarized with the equipment, protocol, and monitoring equipment being used as well as being briefed on the chamber itself and safety measures. Each diver was assigned a unique subject number for all tests.

Dives were planned according to the Defence Canada Institute of Environmental Medicine (DCIEM) air diving tables no decompression limits adjusted for the altitude of SFU Burnaby campus of 367 m above sea level. Each dive began with a 30-minute swim in the wet pot, (water temperature 10^{o}C water +/-2^{o}C) on a swim ergometer with the resistance set to approximately 5 METs by weighting the swim ergometer with a 3.6 kg mass. Divers wore a rebreather (Lungfish LLC) with the PpO_2 set at 0.21 ATA

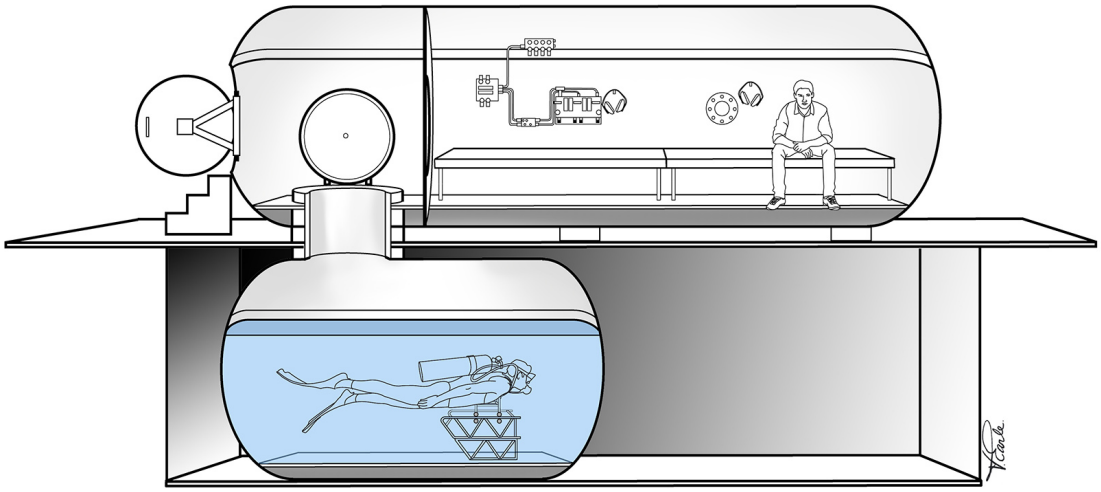

Figure 3.1. Hyperbaric chamber at the Environmental Medicine and Physiology Unit
Note: Depicts the wet pot below where the diver swims on an ergometer weighted for ~8 METs.

Table 3.1. Participant demographics

Total N	Control Condition N=	Oxygen clamped on ascent N=	Mean Age (years)	Max/Min age (years)	Mean BMI (kg/m^2)	Max/Min BMI (kg/m^2)	Male/Female
19	19	16	39.3	59/21	26.5	35.6/21.9	16/3

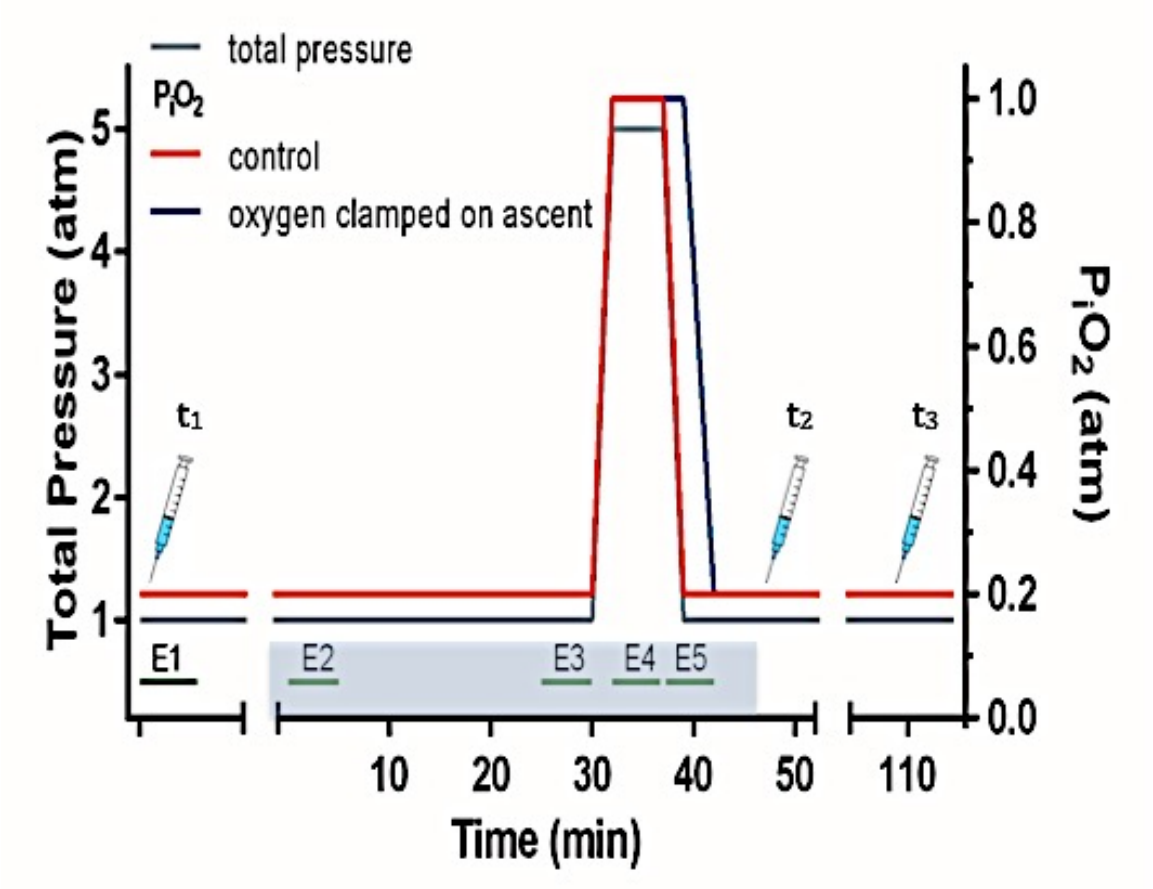

Figure 3.2. Experimental Design

Note: Depicts blood samples collected and analyzed with the iStat hand held analyzer. t_1 baseline measure for cTnI, BNP, lactate, pH; t_2 immediately following dive upon exiting the chamber measure for BNP, Lactate, pH; t_3 one hour post dive measure for cTnI; Shaded area represents time during constant swim. ECG 5-minute epochs E_1 baseline in lab; E_2 first 5 minutes of 30 minutes swimming at 1 ATA; E_3 last 5 minutes of 30 minutes swimming at 1 ATA; E_4 swimming at 5 ATA; E_5 swimming during ascent with either control with drop in PpO_2 or experimental condition with a constant PpO_2 from 5 ATA to surface of 1 ATA.

balance nitrogen. The head was connected to a computer at the chamber control panel by a communication cable with a thru-hull penetrator in order for the oxygen pressure to be clamped on the ascent by changing the set point from .21 ATA varying with depth to 1.0 ATA without varying with the decrease in pressure. The absorbent bed of soda lime removed CO2 from the inspirate. Divers wore a drysuit (Whites Hazmat Pro Series) and thermal undergarment protection including a hood and gloves. Immediately following the 30-minnute swim the chamber was compressed to 5 ATA (40 meters of seawater (MSW)) at a travel rate of 20msw/min. The ascent was at the same rate until the last atmosphere when the travel rate was at 10msw/min. The partial pressure of oxygen dropped with the total pressure reaching 0.21 ATA at the surface. The swim continued for 5 minutes at the surface for a total swim time of 45 minutes. For the experimental dive, the oxygen partial pressure was clamped at 1.0 ATA when leaving 5 ATA (40msw) for the ascent to the surface and the 5-minute swim post dive (Fig. 3.2). This was a no decompression dive and ascent was made directly to the surface in both conditions without a stop. Both dives were tended by an inside safety attendant. Prior to each dive, participants completed a daily medical form. Participants were asked to not complete a dive in the previous 24 hours and remained in the lab post dive for one hour to complete a decompression sickness watch.

3.3. Blood analysis

Prior to each dive venous blood was drawn (t_1). Blood samples were tested using the i-STAT® (Abbott Point-of-Care, Abbott Park, Illinois) handheld portable blood analyzer. Once a blood sample was drawn into a syringe, droplets were placed onto the test cartridges and inserted into the handheld analyzers. At t_1, three tests were performed, the cTnI, BNP, and the $^{CG}4^{+}$ cartridge which reports lactate and pH in vitro. Immediately following the dive at t_2, a second venipuncture was performed, and the BNP and $^{CG}4^{+}$ cartridges were tested. One-hour post-dive at t_3, the final blood sample was drawn and the cTnI cartridge was analyzed.

3.4. Analysis of the 12-lead ECG

Continuous 12-lead ECG recordings on a Holter monitor (H12+, Mortara instruments Ltd, Milwaukee, Wisconsin) were undertaken as follows. The diver's chest

was shaved, if necessary, and degreased with denatured alcohol and a cotton pad to remove dead skin cells to ensure good adhesion of the electrode patches to the skin (3M Red Dot 2255). The 10 electrodes were placed following standard procedures used for recording 12-lead Holter as follows: V1 fourth intercostal space at the right sternal border, V2 fourth intercostal space at the left sternal border, V3 midway between V2 and V4, V4 fifth intercostal space at the left midclavicular line, V5 anterior axillary line on the same horizontal level as V4, V6 mid-axillary line on the same horizontal level as V4 and V5, RA right clavicle, LA left clavicle, RL reference or ground lead, placed to maximize comfort mid-sternum above V1 and V2, LL lowest rib on the left side of chest in the modified Mason-Likar position.

The Holter recorder is capable of recording 12 channels in real time to be stored on a compact flash memory card. Its reliability in water compared to the surface was confirmed with a Bland-Altman test with an error of <2% of the recorded signals (117). The Holter recorder was placed in a water-resistant pouch worn under the drysuit. There were no flooding problems.

3.5. Measurements

Chamber master clock log recording times were synchronized with the Holter monitor to correlate the ECG tracings with diving events. The recordings were then divided into five epochs of five minutes each. E_1 was baseline while the participant was sitting in the lab prior to donning equipment. Participants were not restricted from talking or movement. E_2 the first five minutes swimming at ambient pressure, E_3 the last five minutes of the 30-minute swim at ambient pressure, E_4 the last 5 minutes swimming at 5 ATA, E_5 The ascent from 5 ATA to ambient pressure with a swim out to the five-minute mark. E_5 is the only epoch where there is the experimental condition of clamped oxygen pressure. Recordings were sent to AMPS LLC. for analysis. The generation of the extraction of the 5-minute epochs from the Mortara H-Scribe format was done using Antares v. 2.18.0 (AAMPS LLC, Brescia, Italy) in an embedded mode, within a Python script at 1000Hz in ISHNE format.

3.6. Heart rate and rhythm

ECG epochs were analyzed using a dedicated Python script, CalECG v. 4.0.0 (AMPS LLC. Brescia, Italy). Representative beats were computed and the following ECG annotations were measured; Global RR, PR, QRS, QT, JTp, Tp-Te, Tp-Tec and QTc with Bazett formula (QTcB=$\frac{QT}{\sqrt{RR}}$) and QTc with Fridericia formulae (QTcF=$\frac{QT}{\sqrt[3]{RR}}$), and the ST amplitudes. The ST segment was measured from the J-80 time point.

3.7. HRV

Analysis was completed using HeartScope v. 2.0.0 (AMPS LLC. Brescia, Italy) in manual mode; time series was obtained by QRS detection on lead II and the following HRV parameters; both time and frequency domain were obtained via AR modeling; Mean RR/Heart rate, RMSSD, LF/HF, HF and LF: Power in the band, normalized power (n.u.) LFn.u. is normalized by the total variance of the signal without the VLF (ie. LF/(TP-VLF) and same for the HFn.u. main frequency. Total power was equal to VLF + LF + HF + any component above 0.4Hz. Calculation of % HRmax performed (208-(0.7 x Age)). SDNN was calculated as the square root of the variance. Respiration rate was calculated from the HFHz: the main frequency of the HF band of the respiratory-autospectra in Hz is multiplied by 60 to obtain the value in cycle/minute and thus can be assumed the respiratory rate.

3.8. Statistical analysis

Statistical analyses were performed on JMP® (version 13.1; SAS Institute Inc., Cary, NC). Significance was set a priori at (alpha) 0.05. A two-way repeated measures analyses of variance (ANOVA) was used with an incomplete block design with epoch and condition as factors. Differences between factors were analyzed with a Tukey *post hoc* test. For comparison of ST elevation, PAC's, and PVC's between epochs, a Pearson Chi-square test was used for each. A 2-tailed t-test was performed to assess the differences in the change from E_4 to E_5 between the control and experimental conditions. Blood analysis was examined pre and post results using a t-test and an incomplete block repeated measure analysis of variance (ANOVA). In all analysis, statistical significance

was assumed at a p value of <0.05. Data are reported as least square means ± standard error (se).

Chapter 4.

Results

4.1. Heart Rate

Heart rate (HR) increased from a baseline (E_1) value of 85.5 ± 3.2 bpm during all epochs. The highest heart rate occurred immediately upon submersion during the first 5 minutes of swimming $p<0.0001$ (Fig 4.1). There was no difference in HR between the clamped O_2 and unclamped conditions of ascent (E_5). Age-adjusted percentage of HRmax only increased during the first 5 minutes of swimming (E_2) by 0.54 ± 0.02 bpm ($p=0.0054$). There was no difference between the clamed O_2 and control conditions of ascent.

The RR interval decreased from baseline (E_1) 727.15 ms ± 21.28 to all other epochs (E_2, E_3. E_4, E_5) with the main effect of epoch alone $p\leq0.0001$ (Fig 4.2). The first 5 minutes of swimming 1 ATA (E_2) had the greatest decrease 623.45 ± 21.28 ms. A two-factor ANOVA showed an effect of epoch and condition during the ascent (E_5) only in the control condition with a decrease from baseline ($p=0.0028$). In other words, RR interval remained shorter than baseline during ascent in the control but not clamped condition.

4.2. Rhythm and the ECG Trace

Two methods were used to assess the QT segment. The Bazett formula may overcorrect the QT segment when heart rates are fast or slow. It showed a main effect of epoch with significant prolongation from baseline (E_1) 423.64 ± 4.14 ms during swim at 1 ATA, (E_2) 430.84 ± 4.14 ms ($p=0.0124$) and (E_3) 431.20 ± 4.14 ms ($p=0.0073$) and the ascent (E_5) 432.24 ± 4.14 ms ($p=0.0015$). During the swim at 5 ATA (E_4), the prolongation approached but did not reach significance (429.70 ± 4.15 ms, ($p=0.0573$) (FIG 4.3). The effect of epoch and condition during ascent had a prolongation only in the control condition ($p=0.0005$) relative to baseline.

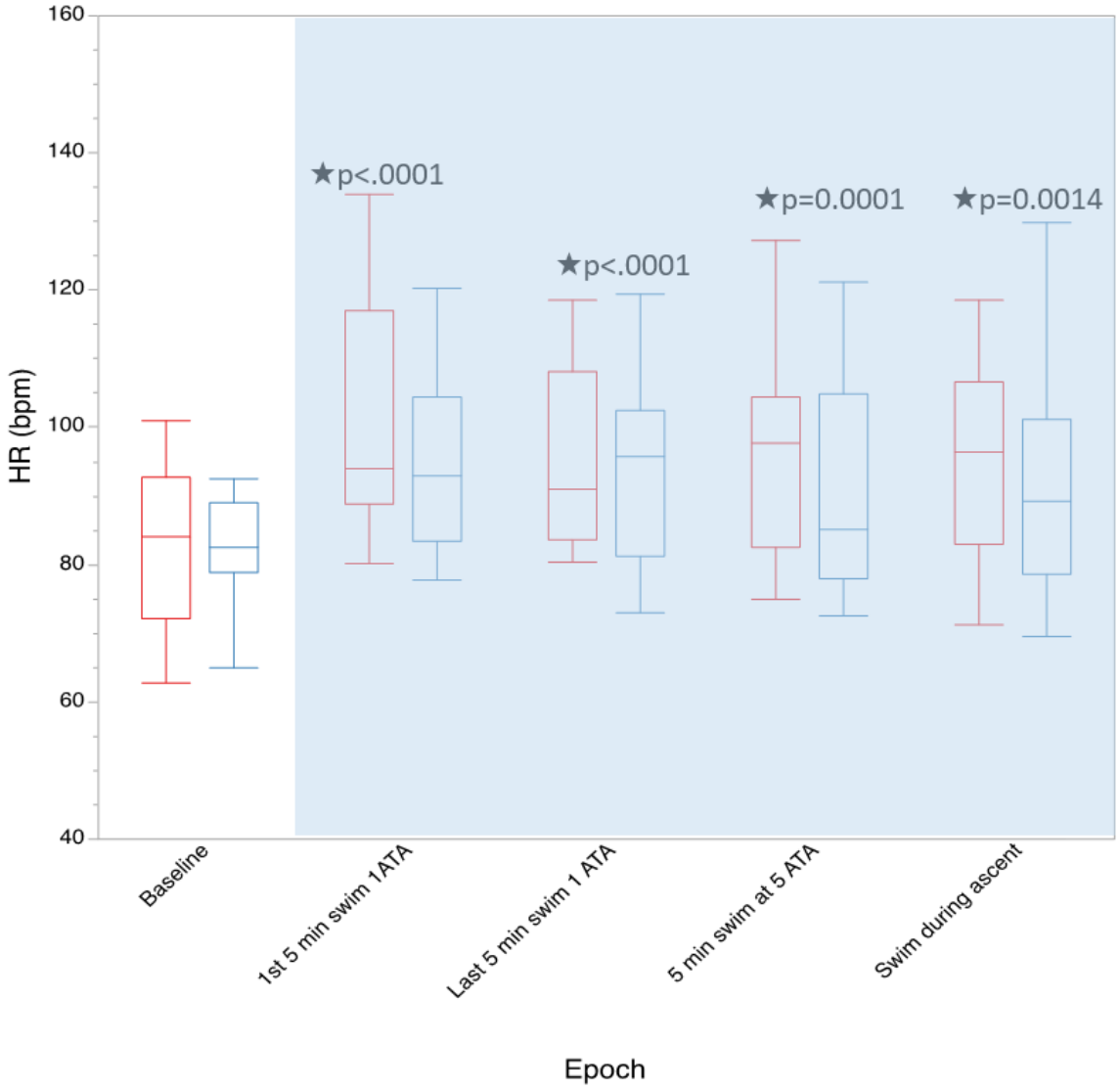

Figure 4.1. Impact of dive protocol in control and oxygen clamped conditions on heart rate

Note: Data show each of the 5 epochs of interest in the two experimental conditions. The grey shaded area denotes time spent swimming at ~5METs. Box plots reflect median and upper and lower quartile ranges, with confidence intervals. Red denotes control condition. Blue denotes oxygen clamped on ascent. ★ denotes main effect of epoch, independent of condition, relative to baseline. Abbreviations: bpm, beats per minute; ATA, atmospheres.

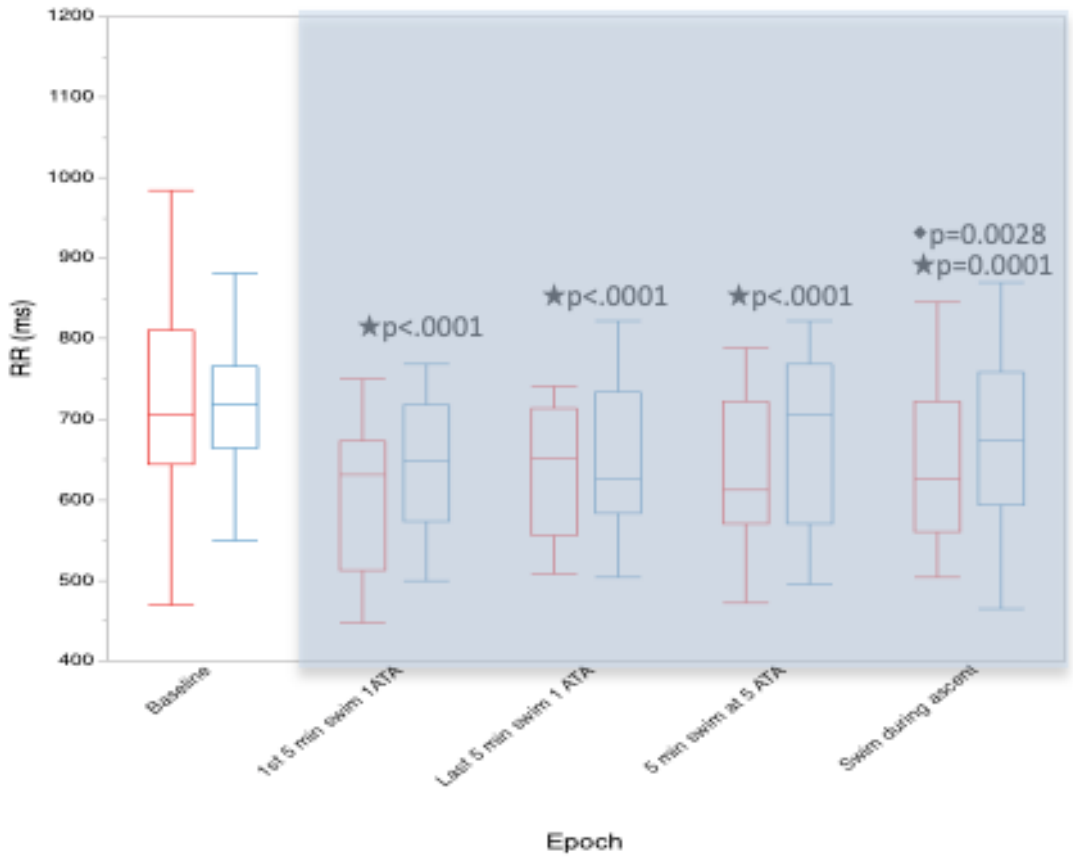

Figure 4.2. Impact of dive protocol in control and oxygen clamped conditions on RR interval

Note: Data show each of the 5 epochs of interest in the two experimental conditions. The grey shaded area denotes time spent swimming at ~5METs. Box plots reflect median and upper and lower quartile ranges, with confidence intervals. Red denotes control condition. Blue denotes oxygen clamped on ascent. ★★ denotes main effect of epoch, independent of condition, relative to baseline. ◆ denotes effect of epoch in the control condition, relative to baseline; Abbreviations: ms, milliseconds; ATA, atmospheres.

Using the Fridericia formula, there was no main effect of epoch in the QT interval from baseline. However, there was a prolongation during the ascent (E_5, 402.73 ± 3.76) compared to the first 5-minute swim at 1 ATA phase (E_2, 397.55 ± 3.76, p=0.0231) (Fig 4.4). The effect of condition and epoch showed prolongation during E_5 from baseline (E_1) in the control condition (p=0.0216) and not in the experimental condition (p=0.9956).

There was no change in PVC's between conditions or epochs (Table 4.1). The frequency of PAC's increased from 5% -19% at baseline (E_1) to 50-53% during E_4. Comparison of the frequency distribution across epochs and conditions by Pearson Chi-square analysis showed an increase in PAC's that was significant from baseline (p=0.0025). During the ascent (E_5), PAC frequency was significantly higher in the experimental than in the control condition (p=0.0016). One subject who had 10 PAC's during E_2 showed two left bundle branch blocks.

There was no depression of the ST segment in any lead during any of the epochs or conditions. There appeared to be greater percentage of participants with ST elevation >1mm in 2 contiguous leads at J-80 in the anterior leads (V3, V4) during all epochs and in both conditions compared to all other views, however it was not different than at baseline (Table 4.2).

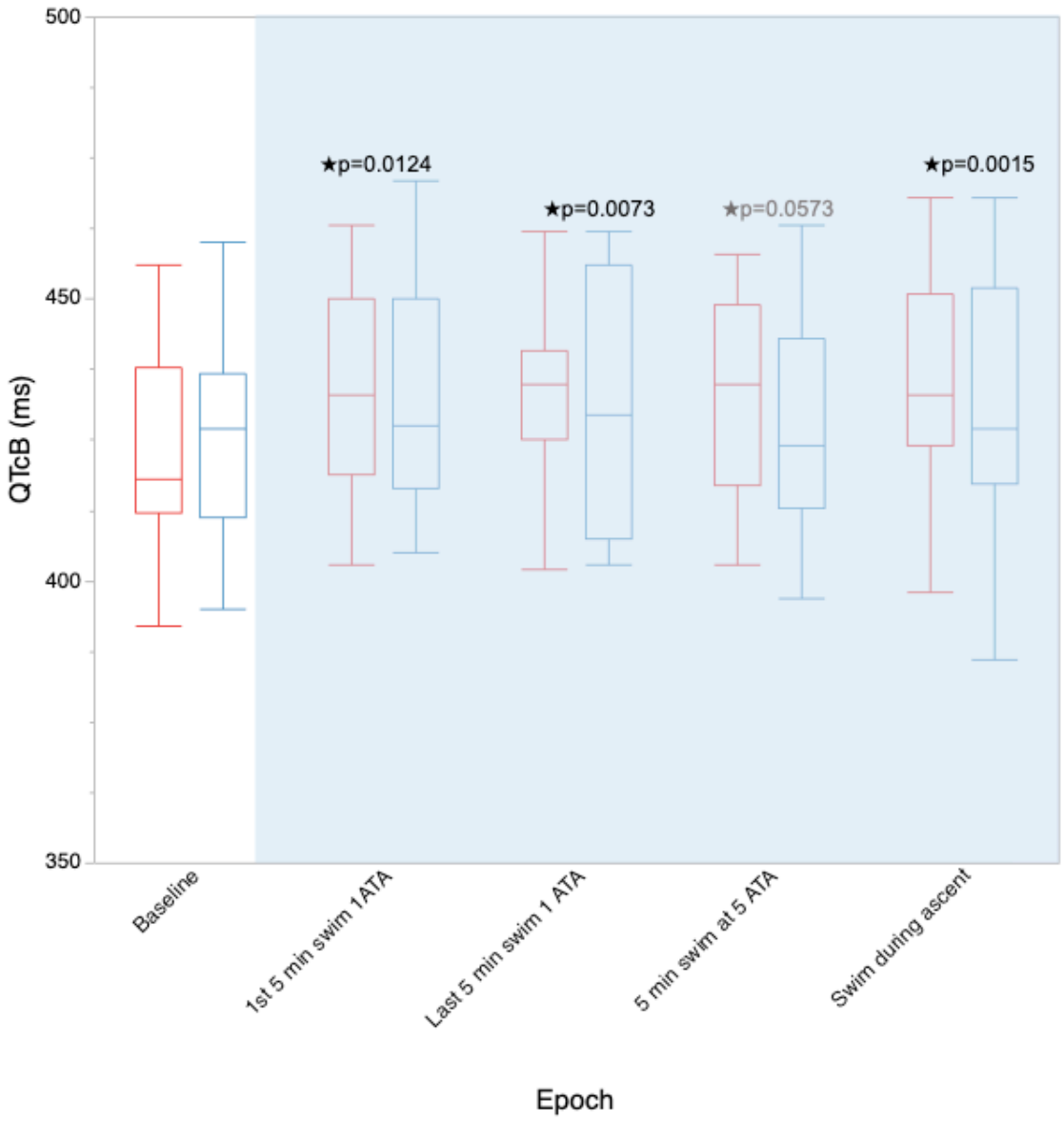

Figure 4.3. Impact of dive protocol in control and oxygen clamped conditions on the QTcB

Note: Data show each of the 5 epochs of interest in the two experimental conditions. The grey shaded area denotes time spent swimming at ~5METs. Box plots reflect median and upper and lower quartile ranges, with confidence intervals. Red denotes control condition. Blue denotes oxygen clamped on ascent. ★★ denotes main effect of epoch, independent of condition, relative to baseline. Abbreviations: QTcB, QT interval corrected for prevailing heart rate using theBazett formula; Abbreviations: ms, milliseconds; ATA, atmospheres.

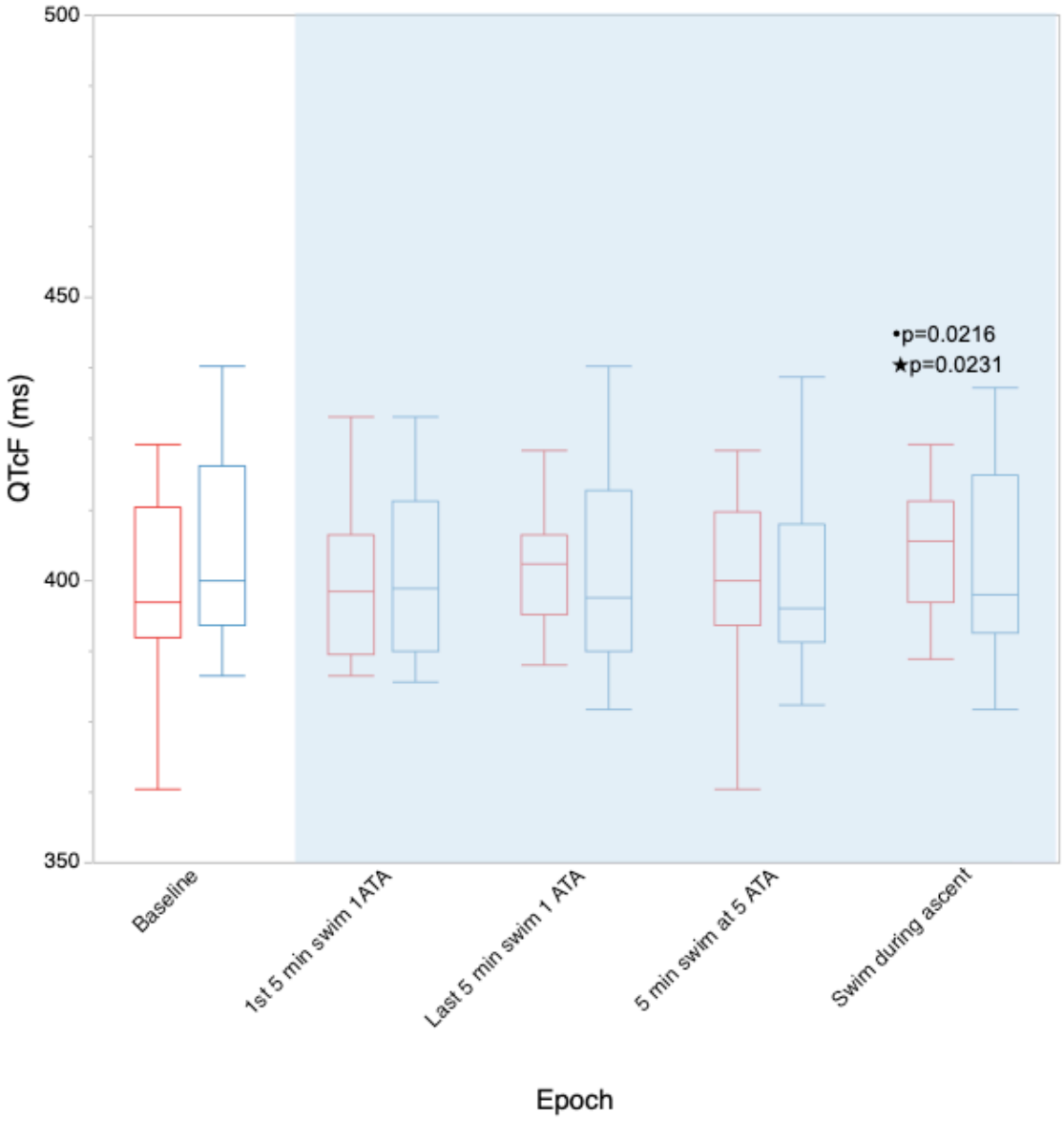

Figure 4.4.. Impact of dive protocol in control and oxygen clamped conditions on theQTcF

Note: Data show each of the 5 epochs of interest in the two experimental conditions. The grey shaded area denotes time spent swimming at ~5METs. Box plots reflect median and upper and lower quartile ranges, with confidence intervals. Red denotes control condition. Blue denotes oxygen clamped on ascent. ★★ denotes main effect of epoch, independent of condition, relative to baseline. ◆ denotes effect of epoch in the control condition, relative to baseline. Abbreviations: QTcF, QT interval corrected for prevailing heart rate using the Fridericia formula; Abbreviations: ms,milliseconds; ATA, atmospheres.

Table 4.1. Impact of dive protocol in control and oxygen clamped conditions on ST segment

Epoch	Condition	Inferior (II,II,aVF)		Lateral (aVL,V5,V6)		Anterior (V3,V4)		Septal (V1,V2)	
Baseline	Control	0/19	0%	0/19	0%	6/19	32%	0/19	0%
	O2 clamped on ascent	1/16	6%	2/16	13%	6/16	38%	0/16	0%
1st 5 min swim at 1 ATA	Control	0/19	0%	0/19	0%	4/19	21%	0/19	0%
	O2 clamped on ascent	0/16	0%	0/16	0%	2/16	13%	0/16	0%
Last 5 min swim at 1 ATA	Control	1/19	5%	1/19	5%	6/19	32%	0/19	0%
	O2 clamped on ascent	1/16	6%	1/16	6%	4/16	25%	0/16	0%
5 min swim at 5 ATA	Control	1/19	5%	0/19	0%	5/19	26%	0/19	0%
	O2 clamped on ascent	0/16	0%	1/16	6%	2/16	13%	0/16	0%
Swim during ascent	Control	1/19	5%	0/19	0%	5/19	26%	0/19	0%
	O2 clamped on ascent	0/16	0%	1/16	6%	3/16	19%	0/16	0%
Comparison of Epoch	Pearson Chi-Square	$X2(4,N=35)=2.00,p=0.7358$		$X2(4,N=35)=2.33,p=0.6747$		$X2(4,N=35)=2.70,p=0.6096$		$X2(4,N=35)=0.00,p=1.0$	

ST elevation J-80ms > 1mm in 2 contiguous leads

Table 4.2. Impact of dive protocol in control and oxygen clamped conditions on ectopic beats

Epoch	Condition	Subjects with PVC		Minimum/Maximum PVC	Subjects with PAC		Minimum/Maximum PAC
Baseline	*Control*	1/19	5%	1/1	1/19	5%	1/1
	Clamped PpO2	1/16	6%	1/1	3/16	19%	1/2
1st 5 min swim 1 ATA	*Control*	2/19	10%	1/4	4/19	21%	1/4
	Clamped PpO2	1/16	6%	2/2	5/16	31%	1/10
Last 5 min swim 1 ATA	*Control*	0/19	0%	0/0	1/19	5%	1/1
	Clamped PpO2	0/16	0%	0/0	2/16	13%	1/2
5 min swim 5 ATA	*Control*	3/19	15%	1/6	10/19	53%	1/7
	Clamped PpO2	2/16	13%	1/1	8/16	50%	1/18
Swim during ascent	*Control*	1/19	5%	1/1	3/19	15%	1/2
	Clamped PpO2	0/16	0%	0/0	6/16	38%	1/8
Comparison of Epoch	*Pearson Chi-Square*	*$X^2(4,N=35)=4.67,p=0.3232$*			*$X^2(4,N=35)=16.42,p=0.0025$*		** significant difference in the number of PACs across epochs*

4.3. Heart Rate Variability

4.3.1. Time Domain

RMSSD had a main effect of epoch with a decrease from baseline (E_1) 76.21 ± 6.11 ms during all subsequent epochs $p<0.0001$ (Fig 4.5). The effect of condition and epoch was a significant decrease in both the control condition $p=0.0017$ and the experimental condition $p=0.0118$ in E_5 from baseline. When examining the change in RMSSD from the swim at 5 ATA to the ascent (E_5-E_4) between the experimental condition and the control condition the increase was significantly greater in the experimental condition $p=0.0044$ (Table 4.3).

SDNN showed a main effect of epoch with a decrease from baseline in all epochs (E_2, E_3 $p<0.0001$ E_4 $p=0.0067$ and E_5 $p=0.0037$. Fig.6). The increase from the swim at 5 ATA to the ascent (E_5-E_4) in the experimental condition from the control condition was significantly greater in the experimental condition $p=0.0021$ (Table 4.3)

4.3.2. Frequency Domain

The frequency domain increased in the HFa from E_1 115.8 ± 321.0 ms^2/Hz in E_3 $p=0.0436$ E_4 $p=0.0455$ E_5 $p=0.0082$ without an increase in E_2 (Fig 4.7). When normalized the HF was increased over baseline during all epochs $p\leq0.003$ (Fig 4.8). The effect of epoch and condition showed an increase in the control condition over baseline only $p=0.0001$.

The LFa had a main effect of epoch with an increase E_3 to E_4 $p=0.0343$ (Fig. 4.9). When normalized the main effect of epoch showed a decrease from baseline (E_1) in E_2 $p=0.0060$, E_3 $p=0.0290$ and E_5 $p=0.0162$, but no decrease during the swim at 5 ATA (E_4) . The effect of epoch and condition was a significant increase from baseline during the ascent in the control condition only $p=0.0149$ (Fig 4.10). The LF/HF ratio showed a main effect of epoch with a decrease from baseline (E_1) 6.88 ± 1.18 ms in E_2 $p=0.0092$ and E_5 $p=0.021$ (Fig. 4.11.

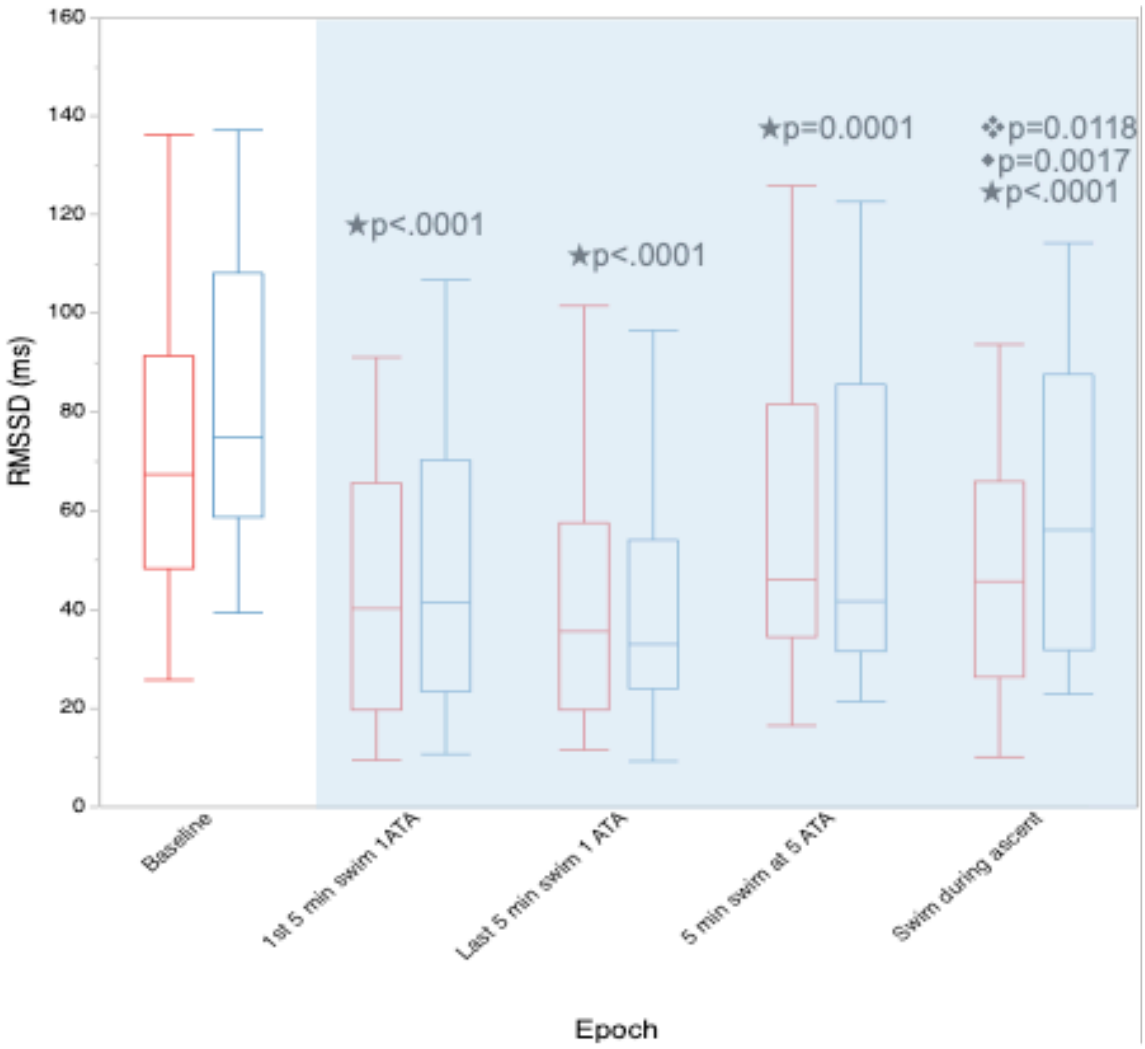

Figure 4.5. Impact of dive protocol in control and oxygen clamped conditions on RMSSD

Note: are denotes time spent swimming at ~5METs. Box plots reflect median and upper and lower quartile ranges, with confidence intervals. Red denotes control condition. Blue denotes oxygen clamped on ascent. ★★ denotes main effect of epoch, independent of condition, relative to baseline. ⬥ denotes effect of epoch in the control condition, relative to baseline. ✣ denotes effect of epoch in the oxygen clamped condition, relative to baseline. ms, milliseconds; Abbreviations: ATA, atmospheres.

Table 4.3. Impact of dive protocol in control and oxygen clamped conditions during ascent.

Variable	Oxygen Clamped (E5-E4) – Control (E5-E4)	SE	t-test 2 -tailed
RR	4.60	16.46	p=0.7840
HR	-1.01	2.50	p=0.6925
RMSSD	17.57	5.19	**p=0.0044**
SDNN	15.40	4.023	**p=0.0021**
HFa	22.47	354.16	p=0.9503
Hfnu	18.54	13.55	p=0.1928
LFa	982.25	564.45	p=0.1038
LFnu	20.01	15.01	p=0.2040
LF/HF	1.23	2.47	p=0.6266
VLF	878.63	493.61	p=0.0968
TP	1945.65	518.21	**p=0.0021**
QTcF	-2.47	2.68	p=0.3726
QTcB	-2.93	2.20	p=0.1694

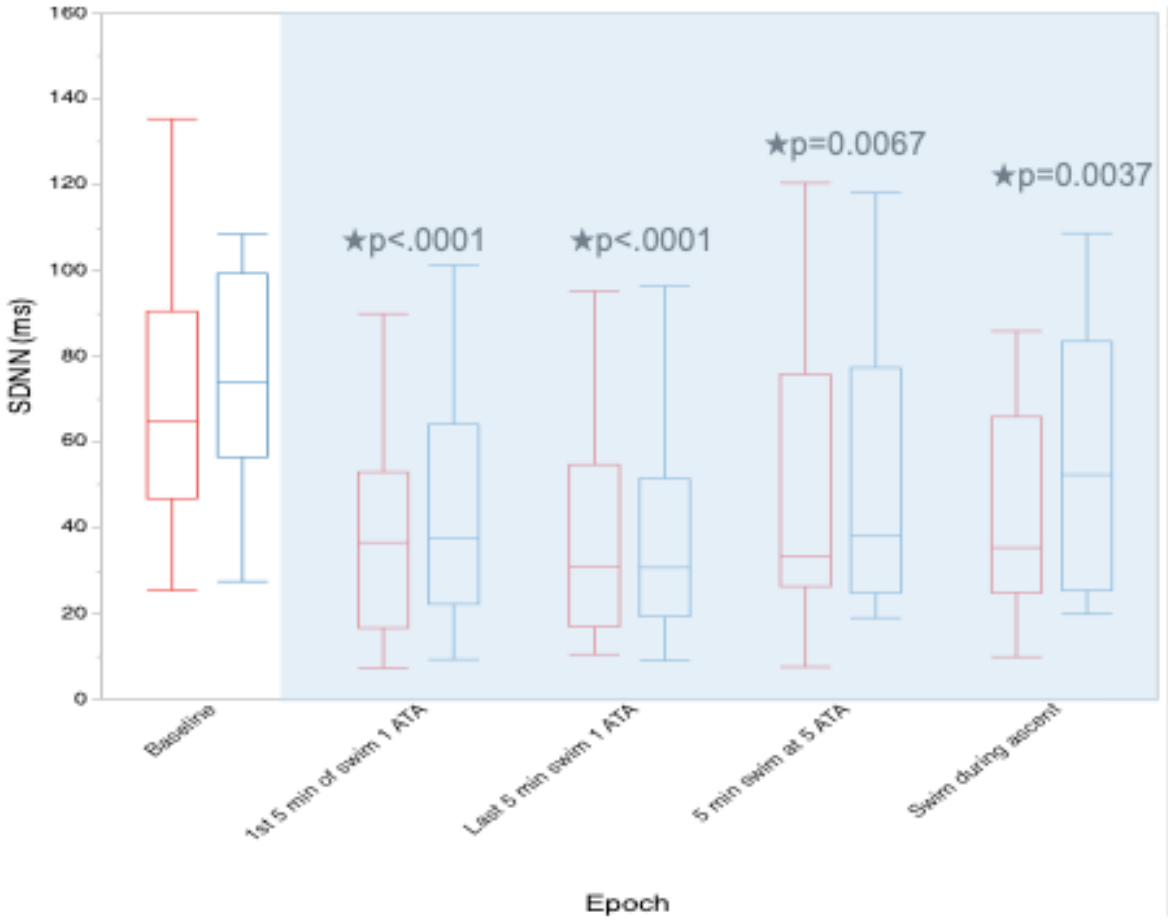

Figure 4.6. Impact of dive protocol in control and oxygen clamped conditions on SDNN

Data show each of the 5 epochs of interest in the two experimental conditions. The grey shaded area denotes time spent swimming at ~5METs. Box plots reflect median and upper and lower quartile ranges, with confidence intervals. Red denotes control condition. Blue denotes oxygen clamped on ascent. ★ denotes main effect of epoch, independent of condition, relative to baseline. ms, milliseconds; ATA, atmospheres.

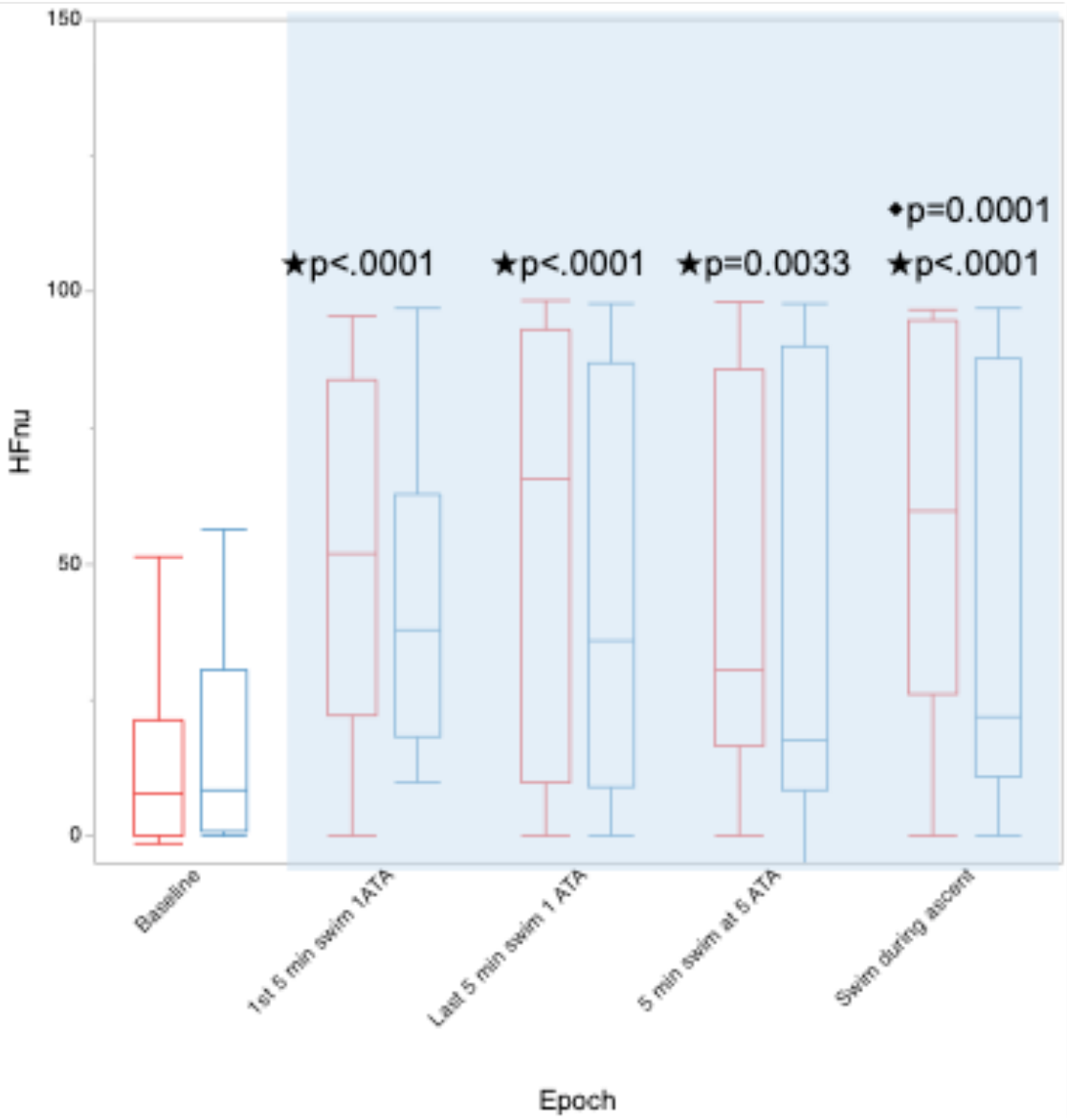

Figure 4.7. Impact of dive protocol in control and oxygen clamped conditions on HFnu

Note: Data show each of the 5 epochs of interest in the two experimental conditions. The grey shaded area denotes time spent swimming at ~5METs. Box plots reflect median and upper and lower quartile ranges, with confidence intervals. Red denotes control condition. Blue denotes oxygen clamped on ascent. ★★ denotes main effect of epoch, independent of condition, relative to baseline. ◆ denotes effect of epoch in the control condition, relative to baseline. Abbreviations: ATA, atmospheres.

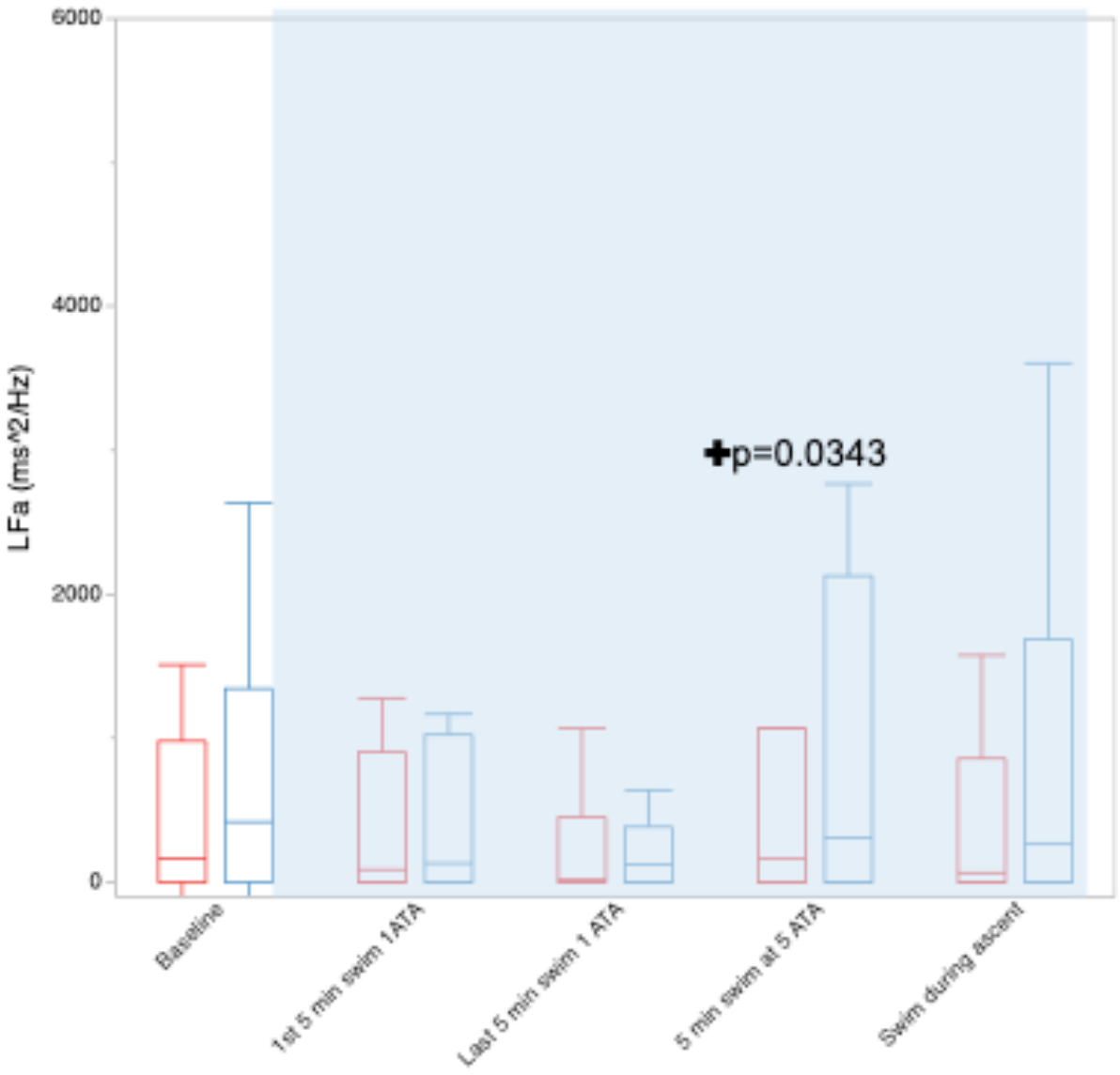

Figure 4.8. Impact of dive protocol in control and oxygen clamped conditions on LF

Note: Data show each of the 5 epochs of interest in the two experimental conditions. The grey shaded area denotes time spent swimming at ~5METs. Box plots reflect median and upper and lower quartile ranges, with confidence intervals. Red denotes control condition. Blue denotes oxygen clamped on ascent. ✚ denotes main effect of epoch, independent of condition, relative to last 5-minute swim at 1 ATA; Abbreviations: ms, milliseconds; Hz, hertz; ATA, atmospheres.

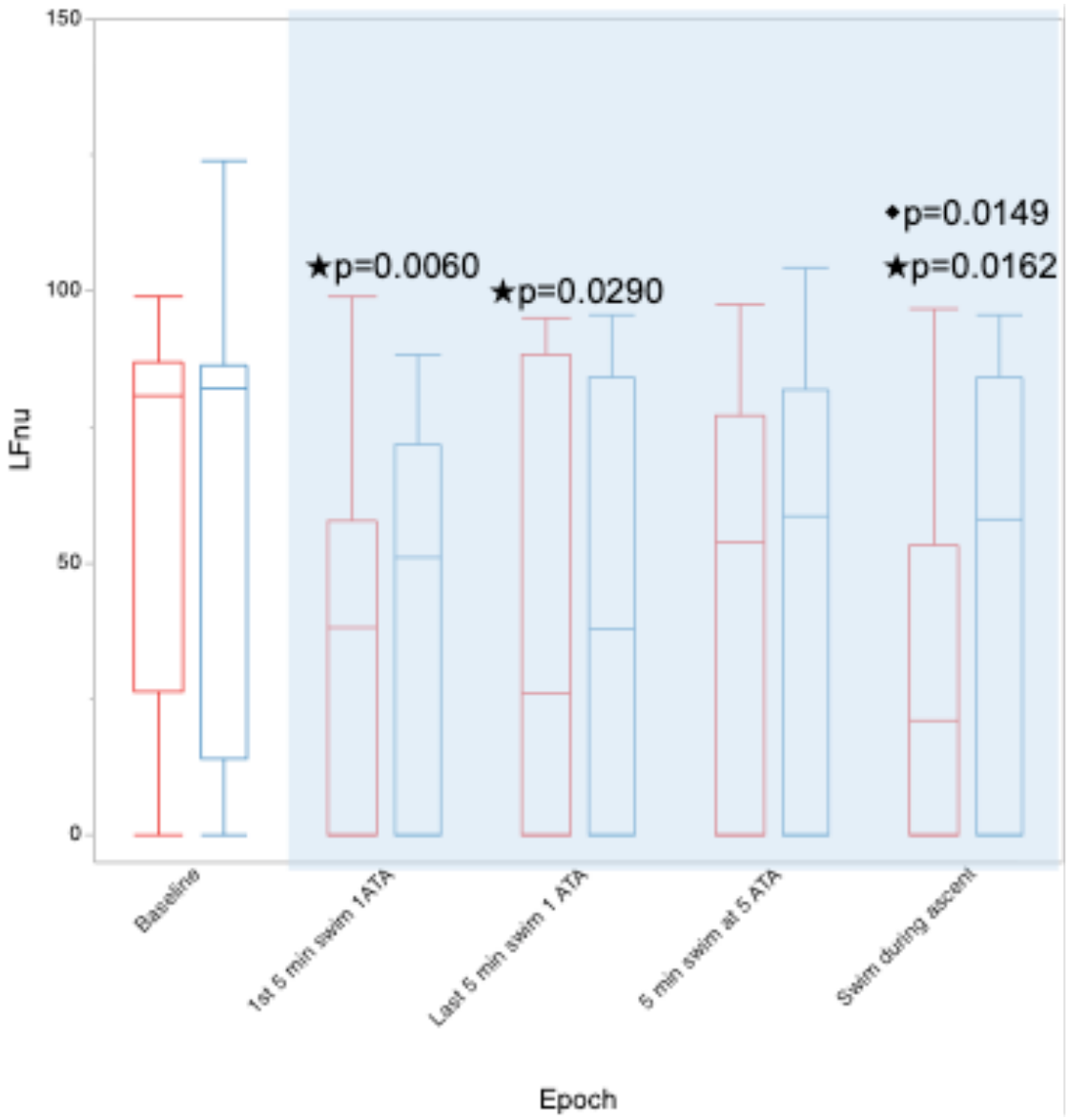

Figure 4.9. Impact of dive protocol in control and oxygen clamped conditions on LFnu

Note: Data show each of the 5 epochs of interest in the two experimental conditions. The grey shaded area denotes time spent swimming at ~5METs. Box plots reflect median and upper and lower quartile ranges, with confidence intervals. Red denotes control condition. Blue denotes oxygen clamped on ascent. ★ denotes main effect of epoch, independent of condition, relative to baseline. ◆ denotes effect of epoch in the control condition, relative to baseline; Abbreviations: ATA, atmospheres.

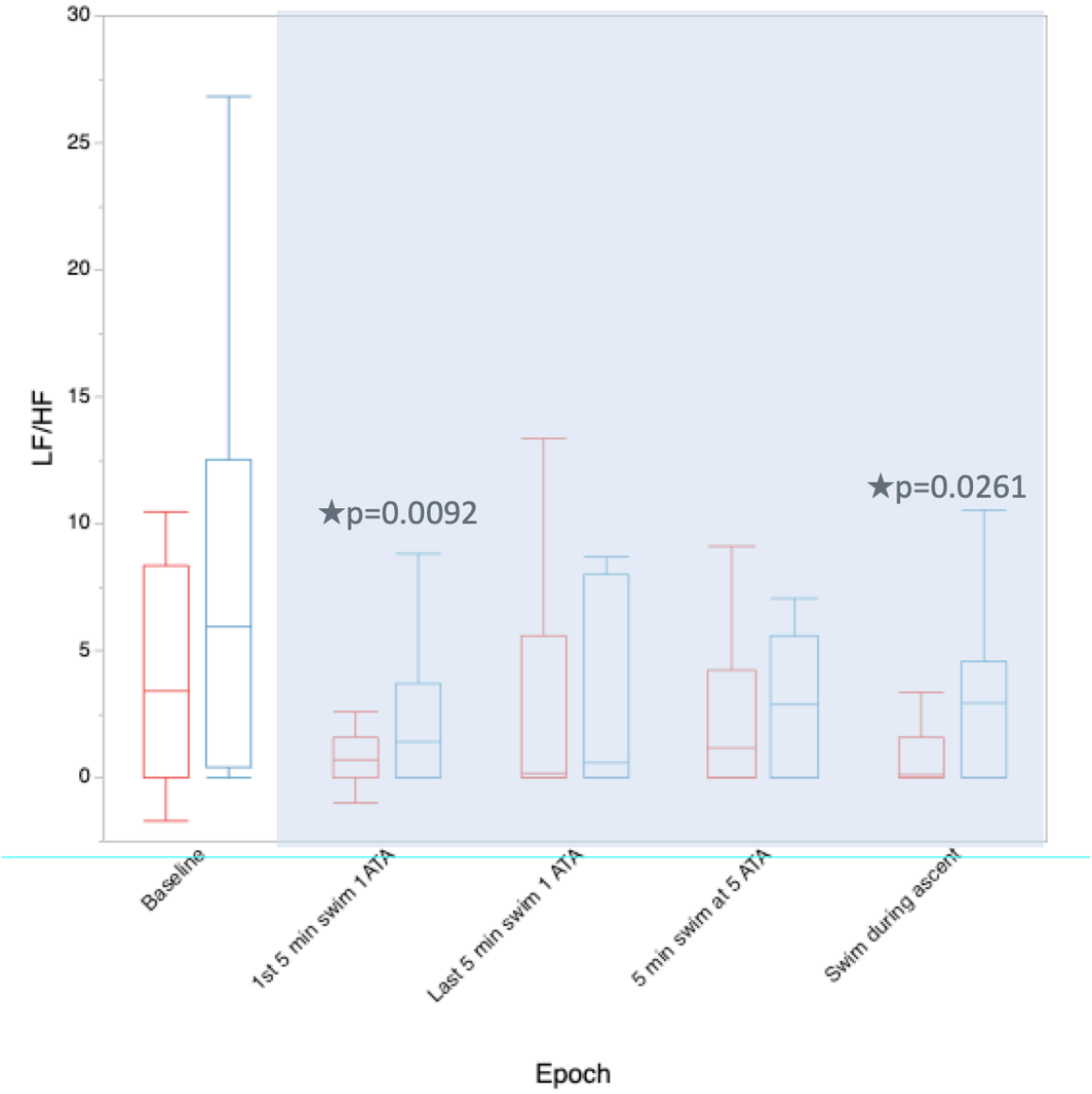

Figure 4.10.. Impact of dive protocol in control and oxygen clamped conditions on LF/HF

Note: Data show each of the 5 epochs of interest in the two experimental conditions. The grey shaded area denotes time spent swimming at ~5METs. Box plots reflect median and upper and lower quartile ranges, with confidence intervals. Red denotes control condition. Blue denotes oxygen clamped on ascent. ★ denotes main effect of epoch, independent of condition, relative to baseline; Abbreviations: ATA, atmospheres.

There was a main effect of epoch with a decrease in VLF from baseline in all epochs (E_2-E_5) $p<0.0001$ (Fig 4.12) and a decrease in epoch with condition from baseline to E_5 in both conditions $p<0.0001$. Total power is heavily influence by VLF and was decreased from baseline in all epochs (E_2-E_5) $p\leq0.0002$ and in epoch with condition in the control condition in E_5 from baseline $p=0.0008$ (Fig 4.13) The total power also showed a significant difference between conditions the increase from the swim at 5 ATA to the ascent (E_5-E_4) in the experimental condition from the control condition significantly greater increase in the experimental condition $p=0.0021$ (Tale 3)

4.4. Respiration

Breathing frequency derived from the main frequency in the HF-band of the respiratory-autospectra was unchanged from baseline (E_1) 15.38 ± 0.73 cycle/min in all epochs (E_2-E_5).

4.5. Blood Analysis

There was no change in cTnI levels taken prior to exposure (t_1) compared to samples taken a minimum of one hour after swim (t_3) in either condition. There was no difference in lactate or pH taken prior to exposure (t_1) compared to samples taken immediately following the dive (t_2) between conditions and no significant difference from baseline.

Pre-exposure (t_1) BNP measures were equal ($p=0.477$) across conditions. The BNP level increased post exposure (t_2) from the pre-exposure value (Fig 4.14). The increase was greater in the experimental condition using a Pearson Chi-square test ($p=0.0001$). With the two conditions having an unequal N a t-test with only the participants who had repeated measures (N=8) for BNP was performed, the BNP increase in the experimental condition being higher than the rise in control condition was approaching significance ($p=0.06$)

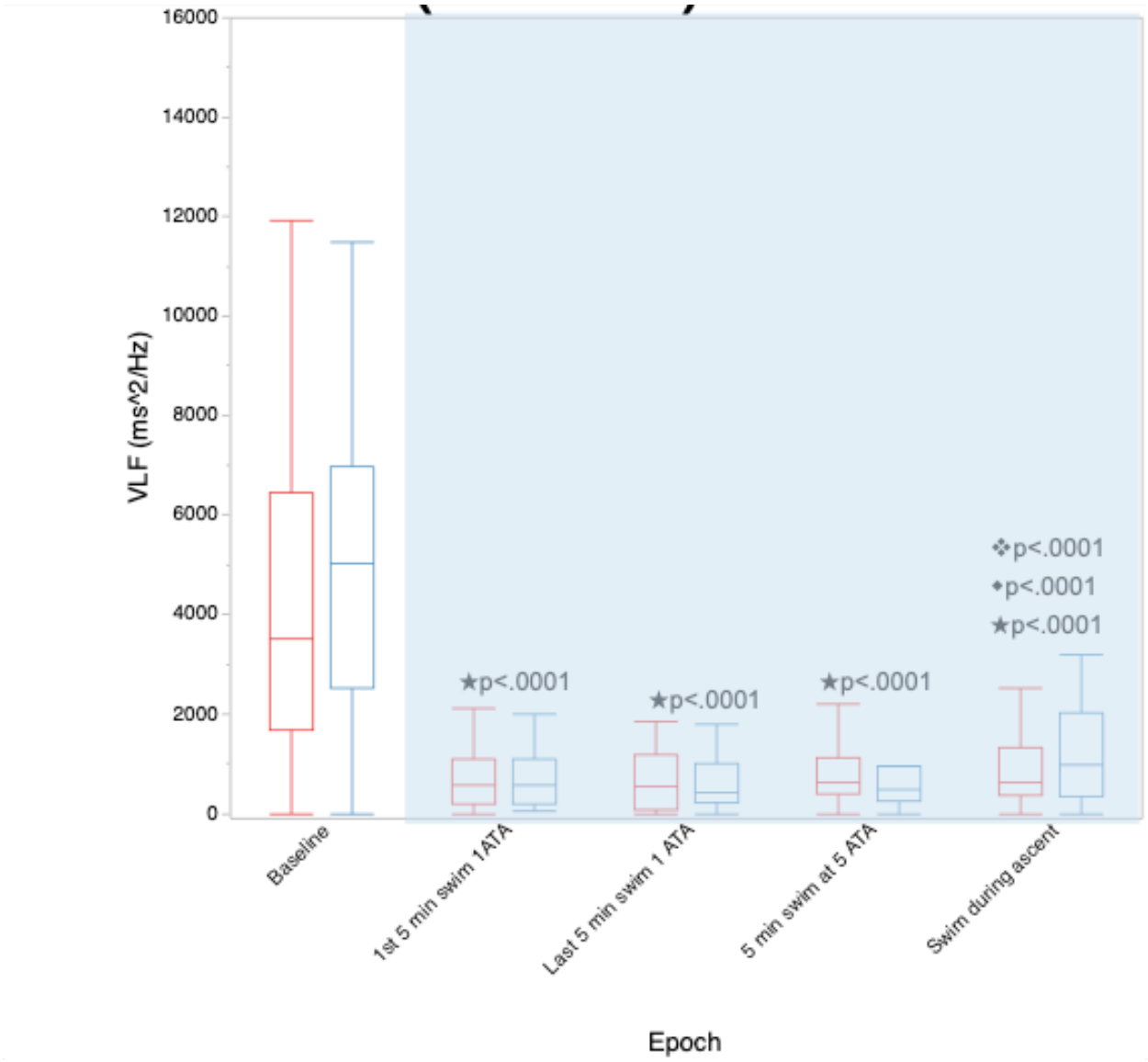

Figure 4.11. Impact of dive protocol in control and oxygen clamped conditions on VLF

Note: Data show each of the 5 epochs of interest in the two experimental conditions. The grey shaded area denotes time spent swimming at ~5METs. Box plots reflect median and upper and lower quartile ranges, with confidence intervals. Red denotes control condition. Blue denotes oxygen clamped on ascent. ★ denotes main effect of epoch, independent of condition, relative to baseline. ⬥ denotes effect of epoch in the control condition, relative to baseline. ❖ denotes effect of epoch in the oxygen clamped condition, relative to baseline; Abbreviations: ms, milliseconds; Hz, hertz; ATA, atmospheres.

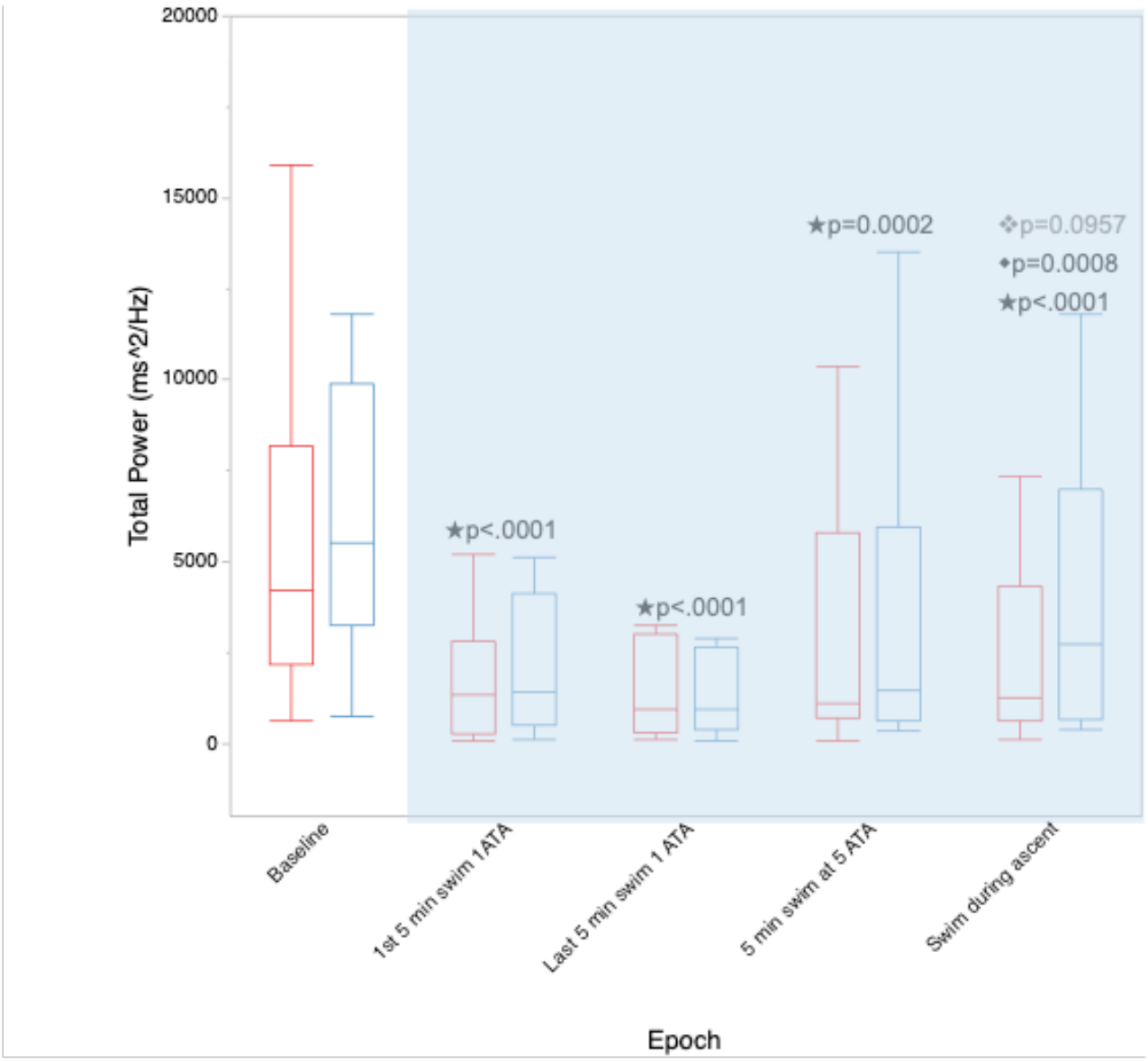

Figure 4.12. Impact of dive protocol in control and oxygen clamped conditions on total power

Note: Data show each of the 5 epochs of interest in the two experimental conditions. The grey shaded area denotes time spent swimming at ~5METs. Box plots reflect median and upper and lower quartile ranges, with confidence intervals. Red denotes control condition. Blue denotes oxygen clamped on ascent. ★ denotes main effect of epoch, independent of condition, relative to baseline. ⬩ denotes effect of epoch in the control condition, relative to baseline. ❖ denotes effect of epoch in the oxygen clamped condition, relative to baseline. Abbreviations: ms, milliseconds; ATA, atmosphere.

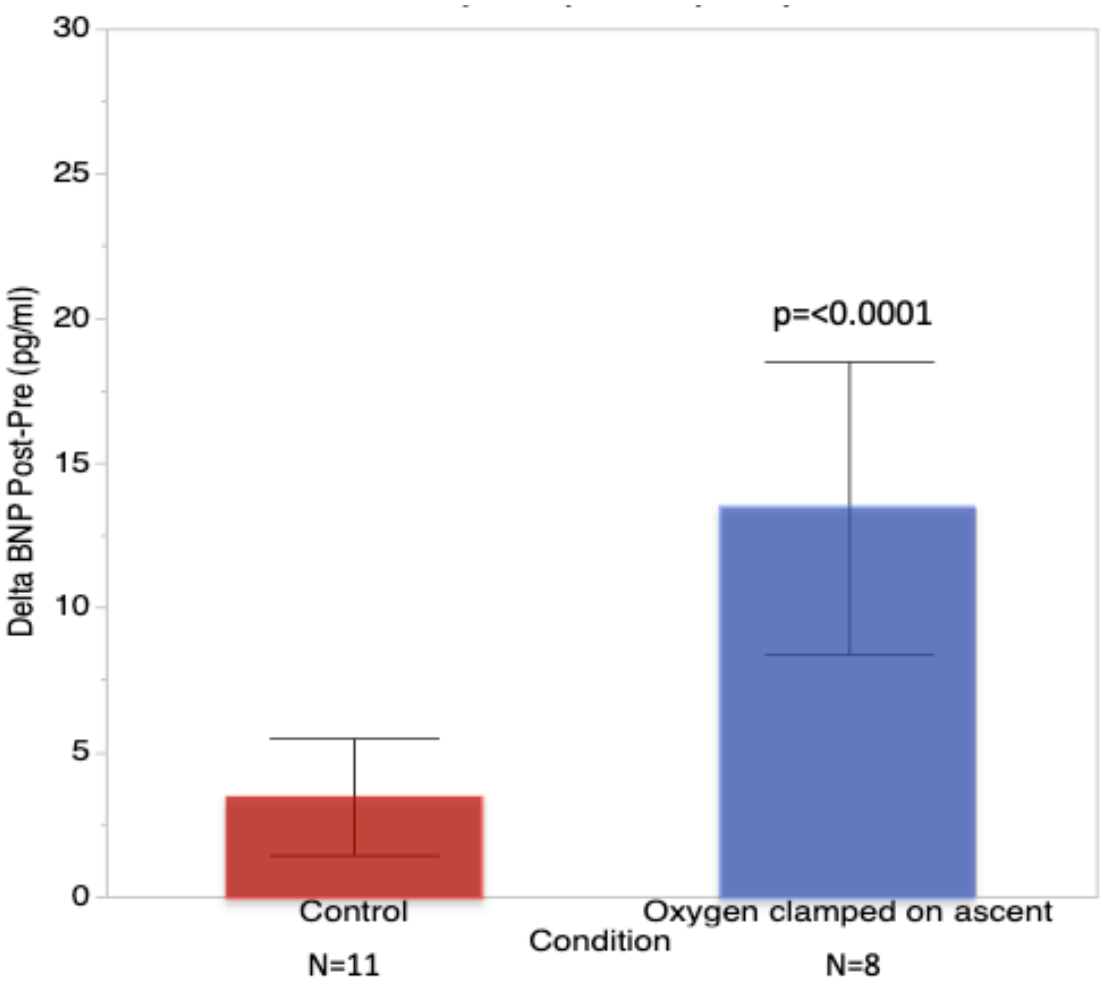

Figure 4.13. Impact of dive protocol in control and oxygen clamped conditions on BNP

Note: Mean difference post exposure - pre-exposure all results

Chapter 5. Discussion

This is the first study to examine the effect of the drop in PpO_2 during ascent compared to clamping the PpO_2 during ascent. In addition it is the first to describe the effect of submersion, diving and ascent during moderate exercise in a controlled study using HRV and rhythm using 12-lead ECG.

5.1. Drop in Inspired Oxygen Pressure During Ascent

It was hypothesized that the drop in inspired oxygen pressure during the ascent from a dive would result in a transient cardiac ischemic response manifested by ST depression and increased cardiac troponin levels. The results of this study suggest otherwise. There was neither depression of the ST segments nor increases in cTnI.

A surprise finding was that clamping oxygen on the ascent increased measures of HRV in the total power on ascent from the swim at 5 ATA significantly more than the control condition, which remained significantly lower than baseline. The result during ascent in the time domain for RMSSD and SDNN HRV measures similarly increased towards baseline values when oxygen was clamped compared to the results at 5 ATA. Why the clamped PiO_2 would improve HRV measures is unclear.

When oxygen is clamped on ascent, as pressure is reduced in order for the O_2 to remain at a constant 1.0 ATA, the PpN_2 in the breathing gas would be reduced. This would create a larger difference between the pressure of N_2 dissolved in the tissues and the pressure of N_2 in the alveoli promoting more N_2 release. With more N_2 release the volume of blood returning to the heart would also contain a potentially larger volume of bubbles increasing wall stretch and damaging the endothelium of the pulmonary artery (121). With a greater volume of gas returning to the heart, an increase in stretch of the right ventricle could occur and may be the explanation why BNP levels were higher in the experimental condition.. Further examination by Doppler or transthoracic echocardiogram would contribute to the understanding of the relationship of decompression and BNP production. However, this theory is counter to a retrospective study that showed increased levels of BNP in divers presenting with SDIPE and not DCS in the emergency room. Although SDIPE and the increase in wall stretch would

correlate, the study did not show an effect of DCS and BNP from wall stretch due to bubble load suggesting that bubble load may not cause increased stretch.

5.2. The Effects Of SCUBA

Diving co-activated the PNS and SNS systems. The decrease in RMSSD and SDNN was consistent with a decrease in HRV likely due to exercise and the activation of the SNS. During the swim at 5 ATA the increase in LF is consistent with an increase in PNS activity. This co-activation has been suggested by a few previous studies, particularly with deeper depths. Reduced HRV is associated with ventricular dysfunction (122). It is currently not known if a decrease in HRV in healthy individuals increases the risk of sudden cardiac death. PACs and left bundle branch block are both associated with left ventricular systolic dysfunction. An abrupt increase in PNS tone will increase the risk of vagally mediated syncope and PACs. A prolongation in the Tp-Te is a risk for ventricular fibrillation and an increase in the QTc can lead to SCD. I saw no increase in the Tp-Te however there was an increase in the QTc upon reduction of pressure, which deserves further investigation.

5.3. Heart Rate

In contrast to previous studies where heart rate is decreased when diving (Noh, Schipke) heart rate increased during the immersion and the dive. However, this study is the only study where participants are continuously exercising at a set rate of approximately 5 METs. The increase could be in response to the workload. In the study by Schipke, head-out immersion and submersion did not change heart rate when not exercising. The HR reduction during the dive they observed may be due to the work of breathing, increased O_2 pressure, or cold (Lund). A reduction in HR has been observed with an increase in total pressure irrespective of the partial pressure of oxygen, suggesting that pressure itself or increased density of gas will decrease HR (123). When correcting heart rate for the percentage of maximal heart rate, it was only increased during the initial 5 minutes of swimming at 1 ATA . This may have been due to anticipation and an initial period of adjustment to the hydrostatic pressure, cold and exercise. Cold-water shock will initially increase HR then with time HR will decrease. The lack of HR reduction in this study was likely due to the effect of exercise.

5.4. Time Domain

Time domain is a more reliable measure than frequency domain for short-term recordings (102). Time domain is a global representation of HRV. There was a significant decrease in the RMSSD and SDNN observed. This was in contrast to the limited studies to date on HRV and diving conducted with divers at rest (101,102,118) or with limited exertion (119). The increase in RMSSD and SDNN concurs with the effect of exercise alone (111).. In the previous studies, only one went to a depth below 66 feet of seawater (FSW) where the effect of the dive took considerable time to become steady and at 150 FSW activated both the SNS and PNS without exercise (118). In this study, I limited bottom time due to the tables being used to plan the dive, the breathing gas, and altitude of the chamber. It is possible that given time there could have been a greater increase in PNS activity.

5.5. Frequency Domain

While it has been suggested that the time domain is a better measure for short recordings, (102) the frequency domain is more specific for determining specifically the contribution of the PNS and SNS by separating the contributions into wavelengths in Hz similar to how a prism separates light waves (30).

Submersion and diving both increased HF unlike the effect expected during exercise. This increase in HF was observed in other studies of immersion and diving (102,118,119); however, the increase in two of those studies took time (118,119). The effect was immediately seen in this study similar to (102) who had a period of immersion and submersion prior to the dive. The LF was decreased during the swim and the ascent at 1 ATA, but was unchanged during the dive (fig. 4.9). Similarly, like the recovery I saw in the LF during the dive, Schipke and Pelzer (102) saw an increase in LF during the dive only and not with immersion and submersion. However in his study the LF was significantly increased and in my study was a return to baseline. This shift during the dive phase in the study by Schipke and Pelzer (102) to an increase in LF was attributed to the reduction in breathing frequency shifting from the HF to the LF band. This study did not find a change in breathing frequency during submersion or the dive; however, the elimination of the reduction in LF during the bottom phase (E_4) is in the same direction suggesting an activation of both the SNS from exercise and PNS as observed in other

SCUBA studies, during the dive. Similarly, Noh et al. only saw an increase in the LF during the deep dives at and below 150 FSW and no change in the shallower dives between 33 – 99 FSW. Another possibility is the effect of narcosis at these depths on the ANS. To date no study has been done looking at this specifically. Narcosis can increase feelings of apprehension or well-being. How this would affect the experienced divers in the study is not known. During meditation an increase in PNS activity is observed (124). It is possible that the swim at 1 ATA was meditative for these experienced divers and the meditative mindset was interrupted by the travel to depth and narcosis resulting in a decrease in the PNS activity in the LF and HF normalized values.

The LF/HF ratio was decreased during the initial 5-minute swim at 1 ATA and during the ascent. This agrees with Schipke and Pelzer (102) who observed a decrease in the LF/HF ratio during immersion and submersion but not the dive. Noh et al. observed no change during the shallow dives but saw an increase in LF/HF with the deeper dives that they proposed was due to mental stress during the deep dive shifting the sympathovagal balance to the sympathetic system. However, Chouchou et al. (119) observed a decrease in LF/HF with their shallow dive to 66 FSW. With, The discrepancy in these studies is not unexpected due to the paucity of studies performed inconsistent depths and workloads.

The reduction in total power during submersion and the dive is expected with exercise. The calculation included the VLF which was reduced from baseline and is associated with a reduction due to exercise. Low VLF is also associated with arrhythmias. There is some controversy whether short 5-minute recordings of the VLF are a reliable measure since the oscillations are slow at approximately one per minute producing between 0 and 12 oscillations in a 5-minute recording (125). For this reason, the VLF was not reported in other diving studies. Short recordings in a previous study where the breathing rate was reduced to 7 breaths per minute (102) may not be as reliable as recordings where the breathing frequency remains between 11-20 breaths per minute (30)..

The results in the time domain are not consistent with the frequency domain, with the time domain reflecting a reduction in PNS and overall ANS likely due to exercise, where the frequency domain reflected an increase in PNS in the HF and LF when normalized, which removed the VLF which is where the effect of exercise is most

reflected. This suggests a co-activation of the SNS and PNS not observed when no exercise is present during the dive. Similar to the immersion in cold water, the diving reflex increases PNS activity while the cold shock response elicits SNS activity (105). While exercise will increase SNS activity, submersion, diving reflex, increased oxygen pressure and SCUBA will all activate the PNS. I saw a reduction in HRV in the time domain consistent with the decrease in total power. The frequency domain displayed contribution by the SNS and PNS in submersion and diving. Both Schipke and Pelzer and Noh et al. (102,118) suggest that diving will activate both SNS and PNS depending on depth; however, their studies did not include exercise that may be responsible for the co-activation observed in this study. Similar to other studies, my results support the PNS being dominant during submersion and the SNS increasing over the course of the dive.

5.6. QTc

Using the Fridericia formula, an increase in the QTc interval occurred during ascent, particularly when the partial pressure of oxygen dropped in the control condition. The Bazett's formula likely over-corrected with the increased heart rate. The prevalence of LQT syndrome is 1 in 2,500 births, and many carriers are unaware that they have the mutation. Although values did not exceed 440ms in male participants and 460 ms in female participants in this study using the Fridericia formula, this increase during the ascent potentially could contribute to the rate of SCD in the population with acquired LQT and deserves further investigation. The only other investigation into the QT segment during dives took place in a saturation environment with hyperbaric air at depths up to 132 FSW (76). Eckenhoff and Knight (76) observed an increase in the QT interval but explained the prolongation entirely by the bradycardia that was observed. During the ascent, I observed no bradycardia. Further investigation of the QT segment during diving is therefore warranted.

5.7. ST Segment

The ST segment elevation in the anterior leads was unchanged from baseline across all epochs. This elevation is typical of "early repolarization syndrome" of young, athletic, healthy, males with physically demanding jobs like the participant population (126). The elevation may be due to electrophysiological remodelling. Rates of LVH have

been reported to be higher in divers than the general population. This maybe due to the increased force of contraction required due to the hydrostatic pressure, and vasoconstriction produced by both the increase in O_2 pressure and cold creating increased afterload and preload and the Frank Starling response. Transthoracic echocardiogram imaging of the ventricles in conjunction with ECG recordings in future studies would be useful.

5.8. Rhythm

Exercise will reduce PVCs, and I observed no significant increase or prevalence of PVCs in my study. There was a significant increase in PACs during the swim at 5 ATA and when the oxygen was clamped on ascent. Increased oxygen pressure augments PNS activity and is associated with more frequent PACs. Only one study has looked at PVCs and PACs during SCUBA dives (117). The dives were to a shallower depth where PiO_2 was less than 1.0 ATA, and there was minimal exertion. There was one diver out of 16 who developed PACs and 8 divers who developed PVCs. Exercise can reduce the number of PVCs and may be the reason for the discrepancy between my study and the one by Bosco et al.(117). One subject in my study had 2 incidents of left bundle branch block and 10 PACs during the first 5 minutes of submersion and swimming at 1 ATA. Bosco et al. (117)also had one subject with a known diagnosis of rate-dependent left bundle branch block.

5.9. Blood analysis

BNP levels were the only blood marker to show a difference between conditions. BNP is a marker of MI, ventricular distension, and atrial fibrillation. Strenuous exercise has also been shown to increase BNP levels (120), likely due to increased wall distension. The relation of BNP to the observed PACs is unclear. Three diving studies show an increase in BNP after shallow dives (80,93,120,127). however in healthy participants BNP did not show an increase with dry hyperbaric hyperoxic dives (127). The quantity detected is related to the duration of exposure. BNP secretion is strongly regulated by the neurohormonal systems, including endothelin-1, angiotensin II and the adrenergic system i.e. epinephrine and norepinephrine receptors (120). The release of BNP was proportional to the amount of epinephrine circulating, suggesting adrenergic

activation promoting BNP release (120). BNP will protect the endothelium by decreasing shear stress and inhibiting platelet activation and inflammatory processes of the myocardium and smooth muscle cells (128). The relationship of release of BNP in response to decompression stress is unclear; however, one study has observed a higher concentration of BNP in divers presenting with SDIPE over divers presenting with DCS. Future studies looking at the relationship of BNP and decompression stress using transthoracic echocardiogram may lead to a better understanding of the mechanism for the production of BNP in divers.

Lactate and pH were not significantly affected by the dive protocols. Peacher et al. (129) did not observe a change in pH during diving. The study showed an increase in ventilation at the surface (1 ATA) submerged that did not occur at 3 ATA in both normoxic and hyperoxic conditions, despite workload remaining constant. This suggests that the decrease in pH from metabolic acidosis is balanced with the increase in respiratory alkalosis maintaining a constant pH (129). A decrease in pH is also observed with the diving reflex with breath hold due to an increase in anaerobic metabolism (106). Future studies would be useful to measure the pH at the time of increased total pressure and partial pressure of O_2 during a wet dive. This study only examined the levels immediately following the dive (t_2) which may have been lower than while at depth.

5.10. Limitations and Future Directions

The study did not control for the length of time between repeated measures. They were separated by a minimum of 48 hours; however, some were repeated months after the first exposure due to the nature of unpredictable schedules of occupational divers. The divers were blinded to the order of the dives; however, they did complete the control dive first. This could have influenced the response between dives. However, the anxiety of the dive would be reduced after the first few minutes of swimming at 1 ATA once the diver was familiar with the equipment and the chamber. All divers were familiarized with the equipment prior to the dive with written instructions, a thorough briefing of the gear and procedures, and they were all occupational divers with significant experience.

Baseline measures were taken while the diver was preparing for the dive, and not at rest. The diver was not restricted from talking or moving. The cleanest 5 minutes

of the pre-dive recording were used. A better design would be to perform the baseline measurement at rest while quiet. In future studies, a comparison to 5 METs on a cycle ergometer in a dry chamber both with and without increased pressure would better define the effect of exercise during a dive.

Collecting blood samples for cTnI and BNP at 8 hours post dive, would have been closer to peak expression and perhaps shown a different value. However, due to the limitation of using local occupational divers, having them remain in the lab or return to the lab at a later time would have been difficult for the divers.

During an open water dive, the ascent phase often involves a change from the prone position to the head-up vertical position. This study did not include such a shift in position, which could affect the work of breathing particularly if on closed circuit or unbalanced regulator. In addition, due to the constraints of the diving tables and avoiding decompression stop obligations, the dive time was quite short. Future studies in the field would allow for more provocative dive profiles of greater depth and duration. The addition of imaging with transthoracic echocardiogram could quantify the contribution of decompression stress from right side bubbles returning to the heart and subsequent impact on the pulmonary system.

Several variables were not measured that future studies may address. First, the contribution of CO_2 during the ascent should be considered. Oxygen is a powerful systemic vasoconstrictor. Increased PiO_2 reduces respiratory chemosensitivity (84) and increases physiologic dead air space which facilitates CO_2 retention. Higher CO_2 would promote vasodilation. Although it is not clear if this would have a significant effect at a PiO_2 as low as 1.0 ATA in healthy population, it has shown to promote vasoconstriction in patients with pulmonary hypertension at values from 0.50 ATA -0.70 ATA (130), In healthy participants oxygen has shown a vasoconstrictor effect at higher levels of 1.75 ATA (84). Resting $PaCO_2$ increases with ambient pressure by 0.5 mmHg/ATA, due to increased gas density (131). Increased gas density increases the work of breathing, and the effect is CO_2 retention by decreasing hypercapnic ventilatory response, increasing dead air space, and reducing respiration. The work of breathing was not different between conditions since the protocol and gas density and total pressure was the same. The Gauer-Henry hypothesis states that immersion promotes a cardiac response that is linked to a renal response. The cardiac response includes an increase in end-tidal CO_2,

decrease HR, stroke volume and increase preload leading to ANP release from atrial stretch (132). Furthermore, diving on a closed-circuit rebreather will deliver no CO_2 to the diver in the breathing mix unlike compressed air in open circuit diving due to the absorbent scrubber bed removing all CO_2. Potentially, had my study used open-circuit diving, the CO_2 influence may be greater. Divers are known CO_2 retainers (87), and a look at the contribution of end-tidal CO_2 pressure during the dive and ascent may shed more light on why there is a difference during the ascent.

5.11. Conclusion

In conclusion, my hypothesis that the drop in O_2 pressure that occurs during the ascent phase of the dive would promote cardiac ischemia was not supported by the ST measures or with production of cTnI. Diving, however, did produce both an increase in PACs and BNP production, particularly when O_2 was clamped high, which may indicate that there is distension and stress associated with diving and high O_2 pressure. The prolongation of the QT segment, although not clinically relevant in the healthy population studied here, deserves more investigation, as it may be fatal in persons with acquired or inherited LQT syndrome or Brugada syndrome.

My study supports the theory that, at deeper depths, there may be co-activation of the sympathetic and parasympathetic system. Further studies of longer duration at depth and investigating the relationship of narcosis to activation of the SNS, perhaps using helium-breathing mixes to mitigate narcosis would be useful. With my results, I can not recommend that increased oxygen during ascent would mitigate the cardiovascular stress of decreasing total pressure, as I do not yet know whether the drawbacks of high oxygen outweigh the risk during ascent.

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