Autonomic Regulation and Blood Pressure in Children

Laura K. Fitzgibbon, HBKin

Submitted in partial fulfillment of the
requirements for the degree of
Master of Science
(Kinesiology)

Supervisors: Dr. Panagiota Klentrou, PhD
& Dr. Deborah O'Leary, PhD

Faculty of Applied Health Sciences, Brock University
St. Catharines, Ontario

Abstract

Vagal baroreflex sensitivity (BRS) is a measure of short term blood pressure (BP) regulation through alterations in heart rate. Low BRS reflects impaired autonomic system regulation and has been found to be a surrogate marker for cardiovascular health. In particular, it has found to be associated with the pathogenesis of adult hypertension. However, only limited information exists as to the negative consequences of childhood BP on baroreflex function. The objective of this study was to investigate BRS in children with 2 different BP profiles while controlling for the effects of age, maturation, sex, and body composition. A preliminary subsample of 11-14 year-old children from the HBEAT (Heart Behavioural Environmental Assessment Team) Study was selected. The children were divided into 2 BP groups; high BP (HBP; $\geq 95^{th}$ percentile, n=21) and normal BP (NBP; $<90^{th}$ percentile, n=85). Following an initial 15 minutes of supine rest, 5 minutes of continuous beat-to-beat BP (Finapres) and RR interval (RRI) were recorded (standard ECG). Spectral indices were computed using Fast Fourier Transform and transfer function analysis was used to compute BRS. High frequency (HF) and low frequency (LF) power spectral areas were set to 0.15-0.4 Hz and 0.04-0.15 Hz, respectively. Body composition was measured using body mass index. After adjusting for body composition, maturation, age and sex ANCOVA results were as follows; LF and HF BRS, LF and HF RRI, and RRI total power were lower in the HBP versus NBP participants ($p<0.05$). As well, LF/HF SBP ratio was significantly higher in the HBP compared to the NBP group ($p<0.05$). The regression coefficients (unstandardized B) indicated that in changing groups (NBP to HBP) LF and HF BRS decreases by 4.04 and 6.18 ms/mmHg, respectively. Thus, as BP increases, BRS decreases. These data suggest that changes in

autonomic activity occur in children who have HBP, regardless of age, sex, maturation, and body composition. Thus, despite their young age and relatively short amount of time having high BP compared with adults, these children are already demonstrating poor BP regulation and reduced cardiovagal activity. Given that childhood BP is associated with hypertension in adulthood, there is a growing concern in regards to the current cardiovascular health of our children and future adults.

Acknowledgements

Over the past two years I have had the privilege of calling Dr. Deborah O'Leary my mentor and supervisor. It is difficult not to overstate my sincere gratitude to Debbie, as she routinely went beyond her supervisory obligations to guide me through this process and provide exceptional advice, support and encouragement. I want to thank Debbie for exposing me to academically challenging opportunities, unique learning experiences, and instilling me with confidence. Of all the things I have learned from Debbie, the following will remain with me forever, 'ALWAYS back EVERYTHING up', 'never assume', 'double.... no triple check everything', and finally, 'work hard and party harder!'

Dr. Panagiota Klentrou always provided an open learning environment where I felt comfortable approaching her at any time with any problems or concerns. Nota is an exceptional supervisor who exuded professionalism and leadership qualities that I hope to aspire to. I want to thank Nota for always making my concerns feel appreciated and valued, and I want to thank her for teaching me that 'a clear working area, allows for a clear working mind'.

Thank you Dr. Deborah O'Leary and Dr. Panagiota Klentrou for inspiring me to set and reach new academic heights and goals, and for enriching my experiences at Brock University. You have provided me with valuable research skills, enabling me to move forward in academia.

I also want to thank Dr. Brian Roy for listening to three hours of baroreflex sensitivity while jet legged, and Dr. Maureen MacDonald for making the drive to St.

Catharines. I appreciate the input both of you have given me and I feel my thesis is more polished because of your contributions.

Jose, thank you for teaching me everything I know about the lab. I wouldn't have made it past three months without you. Emily, Eric, Aaron, Nicole, Dan and the rest of the HBEAT team thanks for your help and support in the lab, and thank you for always listening to me vent on those bad days.

Mom and Dad, I will forever be appreciative of your unconditional love, support and encouragement. I am proud to say you are my parents and I am grateful to be your daughter. As a little girl I remember you thought I might be colour blind because I simply could not distinguish between red and blue. However, you quickly discovered that a visual disorder was not the issue, in fact my eyes were perfectly fine, the diagnosis was….. a slow learner. But with your effortless patience and heartened words I ended up where I am today, a PhD hopeful. Thank you for everything…….especially the cottage!

I want to thank my brothers, Jordan and Bennett, for never letting me off easy and always giving me a hard time, I think I'm a better person because of it. Finally, I want to thank Michael and my friends for being there daily, through the good and the bad, I couldn't have done it without you guys!

This thesis wasn't done alone and I want to thank everyone for their contributions.

Table of Contents

List of Figures

List of Tables

Abbreviations

α	Alpha
β	Beta
BMI	Body Mass Index
BP	Blood Pressure
BRS	Baroreflex Sensitivity
Ca^{++}	Calcium with a positive charge
DBP	Diastolic Blood Pressure
FFT	Fast Fourier Transform
HBEAT	Heart Behavioural Environmental Assessment Team
HBP	High Blood Pressure
HNBP	High but Normal Blood Pressure
HR	Heart Rate
HRV	Heart Rate Variability
HF	High Frequency
Hz	Hertz
LF	Low Frequency
LF/HF	Low Frequency to High Frequency Ratio
ml	Milliliters
NBP	Normal Blood Pressure
NTS	Nucleus of the Tractus Solitariums
NW	Normal Weight
OB	Obese
OW	Overweight
PHV	Peak Height Velocity
RRI	RR Interval
SBP	Systolic Blood Pressure
TP	Total Power
%	Percent

Chapter 1: Introduction

1.1.0 Preamble

Chronically elevated blood pressure (BP), commonly referred to as arterial hypertension, has traditionally been a concern in the adult population as it is a well known risk factor for heart disease [1]. If high BP is left untreated the potential for developing atherosclerosis, coronary artery disease, kidney failure, left ventricular hypertrophy, a stroke or heart attack, substantially increases [2]. Researchers have extensively studied the benefits of anti-hypertensive drugs to aid in the management of high BP. However, future research should be aimed to go beyond traditional disease management to explore the relative aetiologies and preventative processes associated with high BP. Recent studies support the association of poor autonomic nervous system regulation with the development of hypertension in adults [3-8]. Heart rate variability (HRV) and arterial baroreflex sensitivity (BRS) are two such measures of autonomic nervous system function that have been found to be associated with high BP [3-8], as well as cardiovascular disease and mortality in adults[9, 10]. Nevertheless, in recent years childhood hypertension has become more prevalent[11]. Given that childhood hypertension predicts adult hypertension, there is a need for more research in this area[12, 13]. By identifying underlying mechanisms associated with high BP before the condition progresses to damaging consequences, such as atherosclerosis, researchers and health care professionals alike can intervene while there is little to no damage done to the arteries. By measuring autonomic function through HRV and BRS, we can assess the early effects of elevate BP in childhood.

Both HRV and BRS measures evolve from the variability in heart rate (HR) and BP [8, 14-16]. Spectral analysis of HRV is a time series computation of beat-to-beat alterations in HR from an electrocardiogram. This non-invasive tool is used to evaluate cardiac autonomic activity and has been found to be highly correlated with adult hypertension[4], as well as demonstrating promising findings in the area of childhood hypertension [1, 3-8, 17]. Diminished arterial BRS suggests a deregulated autonomic system and is often found to be depressed in cardiovascular disease [18]. Genovesi and colleagues (2008) and Krontoradova et al. (2007) are the only investigators to date to have looked at BRS and high BP in children. Both Genovesi et al. (2008) and Krontoradova et al. (2007) report lower BRS in hypertensive vs. normotensive children, even after accounting for body composition [17, 19]. Although these findings are promising, both studies have their limitations. First, both Genovesi et al. and Krontoradova et al. failed to account for the effects of sex and maturation[17, 19]. As well, the age of the subject group in the study by Krontoradova et al. (2007) was quite broad , defining children as being between the ages of 11-21 years[19]. Age and sex have been shown to affect BRS in both adults[18]and children[20, 21], while maturation has been shown to have an effect on arterial stiffness, an important determinant of BRS[22]. Therefore, although several studies to date highlight the negative consequences of childhood BP on arterial baroreflex function, more studies are required that control for the effects of age, sex, maturation and body composition.

1.2.0 Objective

The objective of this study was to provide a solid foundation for future autonomic regulation studies in children by investigating HRV and arterial BRS in 11-14 year olds

with varying BP profiles while controlling for the effects of age, maturation, sex and body composition.

1.3.0 Hypothesis

Based on previous literature, we anticipate lower HRV and BRS in children with higher BP when compared to controls. By investigating autonomic function and how it is affected by childhood BP, we can assess and identify the early consequences of elevated BP at a young age. As well, since childhood hypertension carries into adulthood, early diagnosis and treatment may help to reduce adult hypertension, in turn, lessening the burden placed on our already taxed health care system.

Chapter 2: Literature Review

2.1.0 Healthy Blood Pressure Regulation

Heart rate (HR) and BP are known to rise and fall to meet workload demands and maintain a homeostatic environment. BP homeostasis ensures adequate blood flow to the brain and organs while inhibiting an inordinately high BP, which can damage the vasculature [23]. BP is a measure of the pressure exerted on the arterial walls as the blood moves through the body[24]. This pressure is affected by both arterial blood volume and arterial compliance (vascular tone), which is in turn affected by both cardiac output (HR multiplied by stroke volume) and peripheral resistance[25]. Both HR and BP are impacted by the autonomic nervous system and humoral regulation, which are linked by various feedback mechanisms including the cardiopulmonary and arterial baroreflex, chemoreflex, cerebral ischemic responses, re-absorption of tissue fluids, release of endogenous vasoconstrictor substances and renal conservation of salt and water[26]. However, for the purpose of my thesis I will focus on the role that the arterial baroreflex has on regulating BP.

2.1.1 Autonomic Regulation of Heart Rate

The autonomic nervous system is divided into the sympathetic and parasympathetic (vagal) nervous systems. To maintain a homeostatic environment, the sympathetic and parasympathetic nervous systems reflexively balance one another in an antagonistic manner[24]. While sympathetic stimulation increases HR, parasympathetic/vagal outflow lowers HR. Thus, HR depends on the amount of vagal

outflow versus sympathetic drive. Parasympathetic pathways originate in the medulla oblongata and synapse on or within the myocardium, near the sinoatrial and atrioventricular nodes[26]. This innervation slows sinoatrial firing and impedes atrioventricular conduction resulting in a reduced HR[26]. In essence, acetylcholine binds to muscarinic cholinergic receptors quickly, activating potassium channels and allowing vagal stimulation of the heart to have a latency of only 50-100 ms. This results in a reduced HR within 1-2 seconds[26, 27]. As well, an abundance of cholinesterase found at the sinoatrial and atrioventricular nodes provides a rapid decay of this stimulus as cholinesterase acts to quickly hydrolyze acetylcholine[26]. Overall, this process allows for beat-to-beat regulation of parasympathetic outflow.

Sympathetic pathways originate in the lower cervical and upper thoracic divisions of the spinal cord and innervate the sinoatrial node, atria, ventricles, and permeate the myocardium, coronary vessels and the overall conduction system of the heart. Sympathetic stimulation results in release of the neurotransmitter norepinephrine (noradrenaline). Maximal secretion of norepinephrine can only facilitate minor adjustments in cardiac activity in comparison to the abundant production of acetylcholine during maximal parasympathetic stimulation. Sympathetic activity also relies on cyclic adenosine monophosphate, mediated by β_1 receptors and known as a second messenger, thus making sympathetic activation a slower process than parasympathetic stimulation, which is mediated through direct acetylcholine-regulated potassium channels. Thus, sympathetic activation is capable of mediating HR fluctuations at a slower rate (approximately 15-20 seconds)[27], compared to parasympathetic input (1-2 seconds) [26].

Due to the antagonistic relationship between the sympathetic and parasympathetic nervous systems, , cardiac activity produces spontaneous oscillatory frequencies referred to as HRV [14-16, 28, 29]. These variations in HR are the result of the relationship between the sympathetic and parasympathetic components of the autonomic nervous system [14, 15]. Measures used to analyse HRV segregate the contributions of sympathetic and parasympathetic influences in order to evaluate cardiac autonomic regulation of HR.

2.1.1.1 Heart Rate Variability

Researchers have been developing various methods to provide insight into the rhythmic variations of HR since the early 18th century [15]. The first record of HRV was documented in 1733 by Steven Hales who observed BP, respiratory cycles, and pulse patterns of a horse[16, 30]. Later, cardiac rhythms were measured using galvanometers, kymographs, and ink writing polygraphs[16]. With the development of HRV used in clinical research, investigators Hon and Wolf (1958 and 1967) associated HRV and activity of the nervous system when evaluating fetal distress and sudden cardiac death[16, 30]. These early methods derived a measure of HRV by collecting short term tachograms and processing numerical estimates from the longest to shortest cardiac cycle[16].

Since the works of Hon and Wolf, more contemporary measurements have been devised. Digital signal processing systems are now used to divide measurements of HRV into either time domain (heart beats plotted vs. time) and frequency domain variables (heart beats plotted vs. frequency) [14]. Chess et al. (1975) and Sayers (1973) were the first to analyse HRV using spectral analysis[16]. Power spectral analysis is a series of algorithms and computations used to quantify the frequency components of HRV [15]. In

1981, Akselrod et al. introduced spectral measurements for quantifying beat-to-beat cardiovascular control[30]. They identified the frequency-specific contributions of the sympathetic and parasympathetic nervous system to HR (respiration was related to vagal control, while slower frequencies were related to both vagal and sympathetic input)[16, 30].

Modern frequency domain analysis techniques employ either the discrete Fourier transform, known as the Fast Fourier Transform (FFT) (non-parametric), or the autoregressive model (parametric) [15]. The FFT is a technique that uses all data in the spectral distribution [16]. In comparison, the autoregressive model excludes 'noise' by using a best-fit model to concentrate on the more significant peaks [16]. The autoregressive model provides a better frequency resolution in small samples, whereas the FFT is often used in larger samples [1, 5, 16]. As well, the FFT method produces reproducible results, has a high processing speed, whereas disadvantages include requiring experience with overlapping and windowing to filter the power spectrum[31]. Nevertheless, both methods produce similar results and are significantly correlated[29]. For the purpose of this paper, HRV measures will be done using FFT analysis because of the selected sample size and experience of the investigators with overlapping and windowing.

In order to determine HRV, abnormal beats (ectopic origin, arrhythmias, preventricular contractions) need to be removed as they alter cardiac rhythms and result in difficult or unfeasible interpolations[16]. HRV analysis relies on the assumption that cardiac rhythms are generated at the sinoatrial node, thus offering insight into physiological mechanisms holding this relationship[16]. Abnormal beats can distort the RR interval (RRI) characteristics. This results in a compromised assumption of the

underlying analytical methods exercised in HRV analyses that reflect autonomic function[16].

The FFT method, used for assessing cardiac reflexes, uses computer processing to plot a frequency spectrum. This spectrum can be separated into two bands. High frequency (HF) ranges from 0.15-0.4 Hz, while the low frequency (LF) component ranges between 0.04-0.15 Hz [14]. HF bands are also referred to as respiratory peaks or respiratory sinus arrhythmias because of the mechanical influence respiration has on HRV [15]. HF reflects a predominance of parasympathetic activity, while LF reflects both sympathetic and vagal activity [15]. Therefore, the ratio of LF to HF (LF/HF) is also used to identify the predominance of sympathetic to parasympathetic activity. Total spectral power (TP), as a function of frequency, is measured by calculating the total area for both the LF and HF components [16]. Decreased total power suggests sympathetic overdrive, vagal withdraw, and/or depressed vagal activity [14, 32]. A reduced LF could indicate reduced sympathetic input and/or reduced vagal activity, while a low HF component represents diminished parasympathetic outflow.

2.1.2 Autonomic Regulation of Blood Pressure

The baroreflex is a reflex loop which continuously monitors BP[33]. Input from the pressure sensitive mechanoreceptors located in both the carotid sinus and aortic arch, also known as arterial baroreceptors, provides a beat-to-beat negative feedback mechanism that controls fluctuations in both mean arterial pressure (MAP determinants = cardiac output x total peripheral resistance) and pulse pressure [23, 34, 35]. Stimulation of this reflex provides a rapid adjustment of BP by 'mediating sympathetic and vagal effects under the

influence of neural impulses'[26]. The signal from the arterial baroreceptors is sent to the nucleus tractus soliarius (NTS) in the medulla oblongata via the glossopharyngeal and vagus nerves (cranial nerves IX and X)[26]. Stimulation of the NTS inhibits sympathetic activity, while repressing the NTS increases sympathetic activity inducing vasoconstriction[26]. Thus, an increase in BP sensed by the baroreceptors results in an increase in firing rate, in turn adjusting autonomic activity by inhibiting sympathetic outflow and augmenting parasympathetic stimulation[36]. This reflexively slows heart rate, reduces cardiac contractile force and vasodilates the peripheral vasculature, which ultimately results in a decrease in BP [23, 24, 34-36]. Conversely, a fall in arterial pressure reduces the impulse firing rate transmitted to the NTS, reflexively increasing BP[36].

2.1.2.1 Baroreflex Sensitivity

Baroreflex sensitivity (BRS) is a measure of the arterial baroreceptors ability to regulate beat-to-beat BP variability [37, 38]. With computer processing, dynamic estimates of BRS are now possible and elicit a quick measure of autonomic cardiovascular regulation [37]. Initial assessment of BRS began in1854 when Vierordt designed the first instrument used to measure human arterial pressure[39]. This led to the discovery that HR slows when BP increases (Marey 1859)[39]. Considerable progress was made over the next hundred years, leading to the development of four 'spot' estimates of BRS. These methods are not estimates of spontaneous behaviour, but do evaluate the reflex response of BP and HR to various forms of stimuli[37]. These stimuli include neck suction, pharmacological injections, and passive orthostatic hypotension through head-up tilt and/or lower-body negative pressure[37].

The neck suction technique was originally designed to 'counteract neck distension during positive pressure breathing' for pilots and was first published by Ernsting and Parry in 1957[39]. By applying a negative or positive neck pressure to the outside of the carotid sinus, baroreceptor function is stimulated and the result is a linear increase or decrease in arterial diameter[39]. Alterations in HR and BP by neck suction/pressure do not occur as the result of decreasing/increasing pressure within the carotid sinus, but rather through changes in vessel distension by decreasing/increasing the pressure within the adjoining tissue. By altering pressure in the adjoining tissue, the pressure gradient across the arterial wall is altered, initiating the baroreflex response [40]. This method requires no cannulation of arteries or physiological modifications related to drug use[39]. Rather, neck suction chambers are a non-invasive method of measuring BRS by means of mechanical stimuli [39]. When compared to the pharmacological method, neck suction allows for a wider rage of pressures to be used when studying baroreflex responses[39]. This was seen when Sprenkle et al. (1986) used a range of neck pressures between 40 to -65 mmHg to measure baroreflex function [39]. However, neck suction does have its disadvantages; 1) different neck chambers are designed differently (around the entire neck, anteriorly and laterally), inducing varying responses, 2) the investigators are limited by their equipment, some chambers have finer control of stimulus parameters than others, 3) there are no accurate measures of pressure transmission through neck tissue, thus real stress applied to the baroreceptors cannot be measured and therefore this influence cannot be accurately accounted for [40], 4) rate of neck pressure change and duration of stimuli applied varies among studies, 5) responses found with neck suction compared to neck pressure differ,

lastly, 6) influence of tracheal receptors may contribute to the responses seen with neck pressure changes[39].

In contrast to neck suction techniques, pharmacological methods of examining BRS (often referred to as the oxford method) are invasive and require intravenous injection of a pressure agent (either phenylephrine or sodium nitroprusside) [33, 41] to increase or decrease BP[42]. The resultant BP changes stimulate the baroreflex to decrease or increase HR [43] and peripheral resistance in an attempt to regulate BP [33, 44, 45]. By plotting systolic blood pressure (SBP) on the x-axis against RRI on the y-axis, the slope of the plotted values provides a measure of BRS or 'gain' in ms/mmHg [46]. Smyth et al. (1969) were the first researchers to use linear regression analysis to relate RRI to SBP following injection of the pressor drug angiotensin-II[39]. Pressure changes, by injection of phenylephrine, often induce BP elevations in humans greater than 20-30 mmHg and as great as 142 mmHg in dogs (Rea & Eckberg 1987; Pawelcxyk & Raven 1989)[39]. The primary advantage to the oxford method is that the stimulus for baroreflex measurement is arterial pressure[39]. As well, this technique does not require additional forms of equipment (i.e. neck suction) and non-invasive finger photoplethysmography can be used to accurately track BP changes [39, 47]. However, disadvantages include; 1) the injected drugs alter arterial pressure and thus this method cannot independently evaluate baroreflex control of arterial pressure, 2) some vasoactive drugs alter BRS by means other than pressure elevation/reduction, such as that reported by Peveler et al. (1983) where phenylephrine independently reduced carotid sinus diameter when BP was rising[48], 3) cardiopulmonary afferent activity may also be altered by vasoactive drugs[49], 4) altered responses may be seen due to the drug effects on central or efferent limbs of the reflex

arc, for example, Eckberg et al. (1971) observed cardioacceleration rather than cardiodeceleration in patients with severe heart disease following phenlyeprine administration[50], 5) excessive use of these agents, seen during serial measurements, may exceed metabolic and excretory capacities, thus accumulating and altering baseline autonomic activity[39].

Baroreceptor firing can also be altered by abrupt changes in body position or applying lower body negative pressure[39]. The proximity of the heart to the head identifies the capacity of cerebral perfusion pressure during standing, while the distance from the heart to the feet determines the hydrostatic force of venous pooling[51]. In an upright standing posture the body uses skeletal muscle as a second heart to pump enough blood back to the right ventricle in order to maintain a functioning level of cardiac output[51]. Passive head-up tilt exaggerates the reduction in venous return to the heart as seen during standing by preventing the skeletal muscles from acting as a secondary pump[52]. The diminished venous return triggers ventricular mechanoreceptors and provokes vasovagal syncope in predisposed individuals, thus providing a means to examine neuro-circulatory responses of this process[52]. Thus, passive head-up tilt is a non-invasive method of eliciting a baroreflex response. Similar to head-up tilt, lower body negative pressure is used to study cardiovascular responses, particularly the baroreflex response, by simulating orthostatic stress[52]. By applying a vacuum to the lower body, the suction serves to generate a negative pressure, in turn impeding venous return and reducing central blood volume[52]. Mechanistically, the negative pressure unloads cardiopulmonary and arterial baroreceptors, thus, reflexively inducing peripheral vasoconstriction and an increase in HR in an attempt to maintain BP[53]. The baroreflex is essential for regulating

orthostatic responses and therefore lower body negative pressure also provides a non-invasive method of arterial baroreflex stimulation[53]. However, pediatric researchers have found this method to be intimidating to children because of the unfamiliar feeling of lower body negative pressure and the loud vacuums used for suction.

Although the aforementioned traditional methods have limitations, they do hold some practical importance. These older methods allow investigators to evaluate the entire stimulus-response curve of the baroreflex over a short intermittent time period[37]. Furthermore, these techniques provide a much more robust measure of BRS compared to modern techniques, due to the fact that both environmental conditions and stimulus properties are controlled, where this is not always the case when using modern methods[37].

The modern methods used to quantify BRS they include both the sequence technique (time domain) and transfer function analysis (frequency domain). Both these methods provide a non-invasive measure of BRS by monitoring naturally occurring beat-by-beat fluctuations in HR and BP[33, 39], allowing investigators to evaluate BRS without the effects of mechanical devices, or physiological alterations due to pharmacological drugs[39].

The sequence technique employs computer processing to plot the beat-to-beat fluctuations of SBP against concordant RRI changes[35, 37, 39]. Using a regression calculation, spontaneously occurring sequences of three or more consecutive beats where SBP increases or decreases (ramps) are plotted against the corresponding RRI[37]. When SBP increases, RRI lengthens, and vice versa [35, 37]. These short progressive increases/decreases are interpreted as bursts of sympathetic and parasympathetic

modulation by the autonomic nervous system to control beat-to-beat BP and HR. The slope of the regression line is then used as a measure of BRS [35, 37]. In 1986 Fritsch et al. observed that BRS estimates using the sequence technique were similar to those measured by pharmacological injection (phenylephrine)[39].

Spectral analysis, as described above (section 2.1.1.1), is used to split the autonomic signals into LF and HF components. Once these components have been plotted, cross spectral analysis is used as a means to obtained either the alpha (α)-coefficient or the transfer function gain measure of BRS [33]. Digital processing used to associate RRI and arterial pressure were developed by Penaz (1978)[54], Sayers (1982)[55], deBoer (1987)[56], Robbe (1987)[42] and Baselli (1988)[57] and their colleagues[39]. The α-coefficient is defined as the square root of the ratio between RRI and SBP powers at both the LF and HF range[37]. As for transfer function gain, it is also the square root of the ratio between RRI and SBP powers while also adjusting for the input variable, that of SBP [20, 37]. When both methods are compared, transfer function gain yields a lower number compared to the α-coefficient. However, both methods are very similar and yield proportional results[20]. Both the α-coefficient and the transfer function gain represent fluctuations in RRI in response to SBP as a function of frequency, reflecting a measure of sympathetic and parasympathetic activity[39]. When comparing these spectral techniques to the sequence method, spectral indices reflect much smoother changes in SBP when estimating BRS, thus representing spontaneous behaviour that is more regularly sampled and an average measure of the entire data set[37]. In contrast, the sequence technique is more variable and obtains measures from various scattered fragments of the whole data window[37]. . Disadvantages of both the sequence and spectral techniques include; 1) the

requirement of long periods of data recording (1-6 min), and 2) only the linear portion of the sigmoidal baroreflex relation is delineated as the calculations are done under resting conditions [39]. However, the spectral technique has been highly correlated with the phenylephrine method in healthy adults ($r=0.94$; $n=8$) [58]. Studies using animals have also found that transfer function analysis has a significant linear relationship with the neck suction method ($r=0.63$, $p<0.001$, $n=26$) for comparisons between normotensive and hypertensive rabbits[33]. Watkins et al. (1996) also found a significant correlation between BRS estimates derived from phenylephrine-induced changes in SBP and RRI ($r=0.48$, $p<0.001$, $n=42$) to that of cross-spectral estimates in hypertensive adults[59]. As well, they found a strong relationship between cross-spectral and sequence-derived estimates ($r=0.076$, $p<0.001$, $n=42$) [59]. Thus, measures of spectral indices provide valid measures of BRS when compared to both pharmacological manipulation and the alternative sequence technique method[59]. As for reproducibility, cross spectral analysis measures of BRS in 18 animals on 5 separate occasions (each occasion separated by 1 week) yielded a maximum variance of 17% [33]. The above finding demonstrates that cross spectral analysis is a reliable and valid measure of BRS. For the purpose of this paper only transfer function analysis will be further discussed as it is used in the present study to measure BRS.

2.1.3 Prognostic Significance of Impaired Autonomic Regulation

Evidence for an association between cardiovascular disorders and HRV and BRS can be found throughout the literature [18, 60]. BRS becomes depressed in the presence of cardiovascular disease (hypertension, coronary artery disease and congestive heart failure) [18]. BRS is also impaired in several pathological conditions associated with

autonomic failure such as cardiac insufficiency, diabetes mellitus or uraemia [9, 21, 61-65]. A reduced BRS or HRV emulates diminished vagal control which affects cardiac control and is correlated with increased mortality by sudden cardiac death [38, 66-69]. BRS and HRV are also associated with obesity, myocardial infarction, ventricular fibrillation and hypertension [14, 60, 67, 68, 70]. The assessment of HRV and BRS reflects cardiovascular autonomic activity and provides markers and predictors of cardiac health.

2.1.4 Humoral Factors

HR and BP are not only regulated by autonomic regulation, but can also be influenced by hormonal factors. Humoral regulation is important for the prolonged (minutes to hours) control of orthostatic BP[51]. If vasoconstriction, activated by sympathetic vasomotor fibers, is prolonged, BP regulation is supported by circulating hormones [51]. Hormonal factors indirectly influence BP by affecting peripheral vasculature, cardiac contractility and plasma blood volume[26, 51].

Vascular resistance and cardiac performance can be altered by adrenomedullary catecholamines [26]. The adrenal gland releases the hormones epinephrine and norepinephrine into the circulatory system, which have an effect on peripheral vasculature[26]. Dependent on the amount of epinephrine released into skeletal muscle, low concentrations can have a β-adrenergic effect, while high concentrations can have an α-adrenergic effect causing dilation and constriction of the resistance vessels, respectively[26]. Vasoconstriction of skin vessels is obtained through epinephrine, and in all vascular beds by norepinephrine[26]. Infusion of norepinephrine in resting dogs has shown a rise in left ventricular pressure, where myocardial contractility was proportional

to norepinephrine concentrations in the blood[26]. Thus, vascular resistance and cardiac contractility, which is known to affect BP, is influenced by adrenomedullary catecholamines[26].

Cardiac performance can also be altered by thyroid hormones [26]. Secretion of thyroid hormones enhances Ca^{++} uptake and hydrolysis of adenosine troposphere by the sarcoplasmic reticulum, increasing cardiac contractility[26]. The opposite is seen with a reduction in thyroid hormone secretion[26]. Thyroid hormones also affect myosin isoenzyme composition in the myocardium and increase 'β-adrenergic receptors and/or their signals', thus altering myocardial contractility and sympathetic activity[26]. These alterations in cardiac performance affect cardiac output, thus affecting BP[26].

Hormonal reflexes act on the kidneys to regulate plasma volume and BP[51]. By controlling renal water and sodium loss through retention and excretion, hormonal reflexes exert an efferent role in maintaining long term BP[51]. The Renin-Angiotensin-Aldosterone system (primarily angiotensin II) and arginine vasopressin or antidiuretic hormones have a large and direct effect on plasma blood volume regulation[51]. A considerable fall in mean arterial BP, seen by a drop in blood volume >1000 ml, causes antidiuretic hormone or vasopressin release, which facilitates water reabsorption in the tubules of the kidney[51]. Vasopressin also has 'little or no effect on osmotic water clearance', thus also increasing sodium retention[51]. Therefore, the release of this hormone causes an increase in blood volume[51]. Similarly, angiotensin II is released by a fall in mean arterial BP (>1000 ml of blood loss), which stimulates the release of aldosterone[51]. The release of aldosterone increases both water and renal sodium retention, therefore increasing blood volume[51]. The release of angiotensin II also

stimulates vasoconstriction of the renal system, decreasing renal blood flow, causing a decrease in glomerular filtration rate and thus reducing urine volume to increasing blood volume[51]. These two mechanism increase blood volume and contributes to the resetting of the baroreflex therefore imparting a prolonged BP effect[71].

The humoral effects vary depending on the tissue exposed and the circulating concentrations, however it is clear that they do affect BP and HR regulation. Studies have shown that even after cardiac denervation in the dog, 'increased renal free-water clearance' is attributed to vasopressin regulation[51]. Therefore, hormonal factors contribute to BP regulation in spite of denervation. Although hormonal effects should be considered in long term BP regulation the present study only focuses on the short-term regulation of BP and therefore will not focus further on the humoral effects.

2.2.0 Hypertension

Hypertension is chronically elevated BP. In adults it is defined as having a diastolic blood pressure (DBP) $\geq$90 mmHg and or a SBP of $\geq$140 mmHg [36]. Pre-hypertension is identified as having a DBP between 80-89 mmHg and a SBP between 120-139 mmHg, while normotensive individuals are identified as having a BP <120 (systolic) mmHg over 80 (diastolic) mmHg [72]. Because children's BP are known to fluctuate as they grow, pediatric hypertension is classified as being $\geq$ the 95th percentile, while pre-hypertensive children are identified as being $\geq$ the 90th percentile and < the 95th percentile of BP adjusted for age, sex and height [13, 73]. In both adults and children, three measures from three or more separate occasions are required to make a conclusive diagnosis of hypertension[74].

2.2.1 HRV in Adult Hypertension

Hypertension is an established independent risk factor for cardiovascular diseases such as coronary atherosclerosis and congestive heart failure [1]. Research has shown that the management of BP is strongly influenced by autonomic regulation [3, 71, 75, 76]. Singh and colleagues (1998) found overall HRV to be lower in hypertensive men and women compared to their normotensive counterparts [3]. As well, Singh and colleagues (1998) found in those with new-onset hypertension (development of hypertension within 4 years), logistic regression analysis suggested that the presence of a reduced LF component was predictive of the development of hypertension in men, even more so than body mass index (BMI) [3]. The results of Singh and colleagues (1998) reflect a shift towards altered function of the sympathetic nervous system or vagal withdrawal and the deregulation of the autonomic nervous system. Abnormalities of the cardiovascular control system have also been investigated by Huikuri et al. (1996) for long standing hypertension treated by antihypertensive medications for a minimum of 4 years [4]. Huikuri and colleagues (1996) identified an overall decrease in TP, LF:HF, LF, and blunted autonomic responses (normalized LF and HF) with alterations in body posture (supine to sitting) for hypertensive patients when compared to normotensive matched controls [4]. Similarly, Takalo and colleagues (1994) found evidence indicating altered function of sympathetic tone in pre-hypertensive participants[5].

Altered measures of HRV in hypertensive populations can also been seen during periods of orthostatic stress. Guzzetti and colleagues (1988) observed measures of HRV during passive tilt [6]. They found that hypertensive subjects had a greater LF power and a smaller HF power at supine rest (vs. normotensive) [6]. While in response to passive tilt,

the normotensive subjects experienced larger increases in LF and decreases in HF compared to the hypertensive participants [6]. LF at rest and altered LF and HF responses during tilt correlated with the degree of hypertension [6]. Guzzetti and colleagues (1988) concluded that in the hypertensive subjects cardiac sympathetic tone was increased and vagal tone reduced, suggesting that sympathetic control could be impaired [6]. Other researchers using various methods of evaluating autonomic regulation in hypertensive vs. normotensive adult participants have also found the same trend of increased sympathetic activity [7, 8]. Lower HRV spectral power is associated with increased cardiac mortality and risk of cardiac events [3, 10, 67, 77]. Therefore, the identification of a diminished HRV for hypertensive individuals has prognostic significance for cardiovascular health.

2.2.2 BRS in Adult Hypertension

Assessment of BRS also has prognostic significance in terms of cardiovascular disease[78]. High intra-arterial pressures seen in hypertension increase the stiffness of the carotid sinus, causing it to be less deformable and consequently reducing BRS[26]. It can be argued that the reverse occurs, altered autonomic activity precedes hypertension, regardless of which comes first, hypertensive conditions raise the set point of the baroreceptor threshold, causing the receptors to be 'less sensitive to changes in transmural pressure'[26]. Therefore, an increase in BP for hypertensive populations results in a smaller diminution in BP when compared to normotensive individuals[26]. Parati and colleagues (1988 and 1995) monitored alterations of the HR baroreflex in normotensive and hypertensive participants over a 24-hr period [8, 79]. In the normotensive individuals, BRS increased during sleep compared to daytime values, however in the hypertensive

subjects this heightened nocturnal BRS was attenuated [8, 79]. In another study by Palmer and colleagues (1990), phenylephrine was administered to evaluate BRS in 64 hypertensive (>90 mmHg DBP) and 32 normotensive (<90 mmHg DBP) participants [80]. Similar to other studies, Palmer and colleagues (1990) found lower BRS in the hypertensive subjects [80]. Baroreflex control in pre-hypertensive and hypertensive (BP 130 to 159/85 to 99 mmHg) volunteers was assessed by Watkins and colleagues (1996) using spectral analysis, the sequence technique and phenylephrine [59]. When comparing the non-invasive vs. invasive methods of measuring BRS, all were significantly correlated and found to be accurate estimates of BRS [59]. However, as mentioned before, phenylephrine can influence HR unrelated to the baroreflex response, therefore these researchers suggested that non-invasive methods are optimal when measuring BRS [40]. Nevertheless, Watkins and colleagues (1996) found BRS to be significantly reduced in the pre-hypertensive and hypertensive group when compared to normotensive controls in all measures of BRS[59].

Adult hypertension has been found to be associated with reduced HRV and BRS [14, 18, 33, 81]. Attenuated HRV and BRS reflect an under-responsive cardiac autonomic system. Autonomic irregularities of the sympathetic and vagal systems have been shown to increase the risk of cardiac mortality [38, 66-68, 82]. Therefore, it is important to look at autonomic regulation in childhood since diminished HRV and BRS values are predictive of cardiovascular disease.

2.2.3 HRV and BRS in Childhood Hypertension

Childhood hypertension has been identified as an independent risk factor for adult hypertension and is associated with early identifiers of cardiovascular disease such as left ventricular hypertrophy, intima-media thickening, arterial compliance, atherosclerosis and diastolic dysfunction [13, 83]. Since hypertension begins years before organ damage is recognized, the importance of early identification is crucial for children and adolescents [1]. Adult hypertension is associated with increased sympathetic drive and diminished HRV and BRS [3-6, 8, 79, 80]. Findings support a deregulated autonomic system in hypertensive children, seen in studies by Urbina et al. (1998)[1], Krontoradova et al. (2008)[19], and Genovesi et al. (2008)[17]. Urbina and colleagues (1998) evaluated LF/HF ratios during cardiovascular reactivity testing (supine to standing, isometric handgrip, cold pressor and Valsalva maneuver) in 39 13-17 year olds. Urbina and colleagues (1998) controlled for BMI and used FFT to compare high to low BP groups and found LF/HF ratios of HRV to increase more in the low BP group compared to the high BP group during all reactivity testing [1]. Although these findings did not reach statistical significance, it implies a shift towards heightened sympathetic activity in the high BP group, similar to that reported in adult hypertensives [1, 5]. A study of BRS in children, adolescents and young adults was recently published by Krontoradova et al. (2008) who tested 34 hypertensive and 52 age-matched controls. They investigated whether BMI and BRS were independent factors associated with high BP in 11-21 year olds[19]. These researchers found that the hypertensive participants had a significantly lower BRS and higher BMI than controls. Although no correlations were found between BMI and BRS, regression analysis identified both BRS and BMI ($p<0.05$) to be independent variables associated with a

greater risk of hypertension. As for Genovesi and colleagues (2008), they continuously recorded HR and BP for 10 minutes of rest, followed by 10 minutes of standing in hypertensive (n=38), pre-hypertensive n=16) and normotensive (n=21) children (mean ± SE 9.75 ± 0.22 yrs). As anticipated, the pre-hypertensive and hypertensive children displayed a significant baroreflex impairment (α-coefficient) and a trend towards early vagal impairment when compared to the normotensive controls[17]. BRS progressively decreased in value from the normotensive to pre-hypertensive and the pre-hypertensive to hypertensive group during rest. This finding remained significant even after controlling for BMI. As for the effects of standing, significant increases in normalized LF and decreases in HF were observed in all three groups. However, standing-induced changes in BRS were significantly greater in the normotensive group when compared to the pre-hypertensive and hypertensive groups, even after controlling for BMI [17]. Therefore, there is strong evidence to suggest that impairment in spontaneous BRS indices for hypertensive and prehypertensive children exist as young as the age of 9 years.

2.3.0 Factors Affecting Autonomic Measures and BP Regulation

Several factors are known to influence autonomic activity. Measures of both HRV and BRS can be influenced by age, maturation, anthropometric variables, and sex. All these factors are discussed below.

2.3.1 Age, Maturation and Autonomic Function

2.3.1.1 Effects of Age and Maturation on Autonomic Function

Adult aging is associated with both functional and structural cardiovascular modifications [84]. As adults age, autonomic regulation declines, in part by a reduction in

BRS [18, 20, 85]. BRS has been shown to decrease in adulthood (20 years of age) and is significantly diminished by 70 years of age [20, 86-88]. Both Veerman and colleagues (1994) and Barnett and colleagues (1999) found diminished LF and HF values with age[89, 90]. Veerman and colleagues (1994) suggest that the decrease in overall HRV in the elderly might be related to reduced BRS and cardiac sympathetic modulation, thereby weakening the baroreflex feedback loop [89]. Monahan et al. (2001), along with Hunt and colleagues (2001) identified important underlying mechanisms of the age associated decrease in BRS [85]. These researchers found that both reduced carotid artery compliance and neural deficits contribute to the observed reduction in BRS in sedentary men (aged 20-75 years) [85]. Laitinen and colleagues (1998) also examined both HRV and BRS among 117 healthy men and women (aged 23-77 years) and found a reduction in both[18]. Furthermore, Laitinen and colleagues (1998) proposed that the decrease in BRS that occurs with age could be the cause for the associated increase in BP with age rather than vice versa [18].

There is almost universal agreement that autonomic activity becomes reduced as adults' age. There are significant decreases that occur with adult aging in all parameters of HRV and BRS[18]. However, the effect of age on autonomic function in pediatric populations is relatively unknown. Few studies have researched these changes in children and adolescents. Yeragani and colleagues (1994) found children (4-12 yrs) to have a significantly higher supine LF (0.02-0.07 Hz) and HF (0.2-0.5 Hz), along with a lower mid (0.07-0.15 Hz) to HF ratio when compared to adults (21-43 yrs), suggesting relatively lower sympathovagal balance in children vs. adults [91]. Another study by Finley and colleagues (1986) found LF power to be significantly lower in both supine and upright positions when comparing preadolescents (10-12 years) to children (5-7 years),

and young adults (20-24 years) to children[92]. As well, supine LF/HF ratio was also higher in the children compared to the preadolescents and young adults. Likewise, Tanaka and colleagues compared 6-12 to 13-16 year olds and found LF and HF components to be lower in the 13-16 year olds, while LF/HF was higher. These finding indicate that there may be developmental alterations in autonomic regulation up to the age of 16 years. There is speculation that these findings could indicate immature autonomic regulation in the younger group and/or be related to cardiac volume increases with age[92].

In conjunction with the above studies, Lenard and colleagues (2004) measured both HRV and BRS in 137 volunteers subdivided into four age groups; children (7-10 years old), pre-adolescents (11-14 years old), post-adolescents (15-18 years old) and young adults (19-22 years old) [20]. Contradictory to the aforementioned studies, HRV indices (LF and HF) presented significant increases from pre- to post-adolescents. As for BRS , Lenard et al. found it to be smaller in children and pre-adolescents compared to post- adolescents[20]. These observations suggest that changes in autonomic function do not occur until after the age of 14, attaining a peak level at adolescence [20]. However, in a recent study by Zavodna et al. (2006), a significant correlation between BRS (mHz/mmHg) and age was observed across ages 11-20 years[93]. Although uncertainty exists around the crucial age for autonomic development, the above studies suggest that age plays an important role in the development of autonomic regulation throughout childhood.

Nevertheless, age is not the only factor that must be considered when investigating BRS in children, the effects of maturation could also influence

cardiovascular autonomic regulation. Dietrich and colleagues (2006) did a study in pre-adolescents (Tanner 1) and adolescents (Tanner 2-5) between 10-13 years old [21]. As reported by Dietrich et al. (2006), both age and pubertal status did not negatively correlated with BRS in the supine position. Therefore, supporting the findings of Lenard and colleagues (2000), between the ages of 10-13 years there are negligible age and maturation related changes in BRS[20]. However, in looking at the above studies there is much controversy. In fact, other than Dietrich et al (2006), no study included maturation as an influencing factor. Rather, each study used age as a surrogate for maturation. Although Dietrich et al. (2006) did compare Tanner staging, they grouped their participants in either Tanner stage 1 or Tanner stage 2-5[21]. By combining Tanner stage 2-5, the authors fail to provide the reader with an even distribution of maturation or pubertal development. Maturation is the process of attaining full development, particularly mature germ cells. This process is accompanied by various hormonal influences. In adults (animal and human), sexual steroids are known to affect autonomic function[20, 94, 95], therefore when studying pre- to post-adolescents, the influence of these hormones becomes important. For example, El-Mas et al. (1997) investigated whether a reduction in endogenous estrogen levels resulted in a decrease of BRS in ovariectomized rats, with one group receiving 2 doses of 17β-Estradiol[94]. These authors found a significant increase in BRS in the rats receiving doses of estradiol compared to rats not receiving hormone therapy. This difference suggested that ovariectomy results in an significant attenuation of BRS, implying BRS is influenced by endogenous estrogen[94]. This finding is supported by Huikuri et al. (1996) who compared middle aged post-menopausal women who were receiving estrogen replacement therapy to those who were

not[96]. Women with estrogen replacement therapy had significantly higher BRS than age-matched controls[96]. Huikui et al. (1996) showed hormone replacement therapy to have a positive affect on cardiovascular autonomic regulation in postmenopausal women[94, 96]. In 2001, El-Mass et al. also investigated whether the male hormone, testosterone, influences baroreflex responsiveness comparable to that found with estrogen replacements[95]. Similar to their previous study in female rats, 3 groups of male rats were compared, shame-operated, castrated and treated with a vehicle, and castrated and treated with testosterone replacement[95]. All 3 groups had comparable baseline and peripherally mediated elevations in BP[95]. However, castrated rats had a significant reduction in BRS, measured by phenylephrine administration when compared to sham-operated rats, while the testosterone replacement rats had BRS similar to that found in the sham-operated rats[95]. However, these results were not found in tachycardiac responses, suggesting testosterone or endogenous androgens facilitate vagal modulation of BRS[95]. Therefore, it is important to evaluate maturational effects on autonomic activity in children and adolescents who have different hormone levels influencing their growth and development into adulthood[20].

2.3.1.2 Measurement of Maturation

Although growth is linear, the timing and magnitude of growth is variable for each individual[97]. Maturity assessment is particularly relevant during pre-, post- and adolescent years because of the variability between subjects of the same chronological age in somatic and biological development [98]. Estimates of maturation can be achieved by collecting and quantifying circulating hormonal levels, determining dental maturity,

identifying sex characteristics (Tanner staging) or by assessing skeletal development. There is no 'gold standard' measure for maturation, however, all of these methods evaluate various factors of maturation and have their limitations.

Skeletal development during pre-, post- and pubertal years has been studied for decades because of the marked acceleration in bone height and bone mineral accrual preceding sexual maturity[97, 99]. During maturational years, increases in sex hormone secretion increases bone growth and mass[100, 101]. Growth in stature has a definitive and measurable end point, providing an accurate landmark to associate other body dimension velocities between and within participants[98, 102]. This maximal growth in stature during adolescents is described as the age at peak height velocity (PHV) and is an indicator of somatic maturity[97]. Age at PHV is reached approximately 8 months before peak bone mineral accrual[103], where growth in bone mineral accrual is known to be more of a function of pubertal stage than chronological age (during adolescence)[97, 104]. Growth hormones are principal contributors to linear bone growth and also coincide with PHV[101]. Growth hormones and sex steroids act in concert to influence bone during and beyond puberty[101]. Oestrogen, a sex hormone found in both boys and girls, influences many aspects of bone growth and development, including linear bone growth[101]. Thus, body measurements, such as velocities of longitudinal growth, can be used as an indicator of maturity[105]. Age at PHV provides a benchmark of maximal growth, and if maximal growth dimensions are available, then the amount of height attained at various ages throughout growth can be used as an indication of maturity[105]. For instance, two youths of the same sex, age, and height may have acquired different percentages of their total adult height, therefore the youth who has attained a greater percentage of adult height is

closer to a mature state[105]. To predict the adolescent growth spurt in height, the timing of both leg length and sitting height velocities are used to predict age at PHV[102]. By subtracting chronological age at time of testing from predicted age at PHV, investigators can determine a continuous measure of biological maturity, years from PHV[102, 106]. Using the differential timings of growth (height, sitting height, leg length) for each sex, years form PHV provides an estimation of maturity offset[98].

The Saskatchewan Growth and Development Study (1964-1973) tested 207 boys annually for weight, height, and sitting height[107]. Assessment of the hand-wrist x-rays from when the participants were 11 years old were correlated to the years from PHV[98]. A maturational commonality was found between the two measures (r=0.83), identifying a relationship between skeletal age (x-ray) and maturity offset (years from PHV)[98]. Thus, years from PHV provides a prediction of somatic maturity in relation to growth by using a maturational benchmark, that of PHV[98].

2.3.2 Anthropometry and Autonomic Function

2.3.2.1 Anthropometric Measurement

Excess adiposity and body weight in childhood is associated with being overweight in adulthood and is linked to long term health consequences such as morbidity and mortality[108-112]. Adiposity, or the distribution of adiposity, can be measured by various technical and costly methods, including but not limited to, hydrostatic weighing, magnetic resonance imaging, dual x-ray absorbtiometry, computed tomography and bioelectrical impedance. However, anthropometrics can be measured by more simple techniques such as, BMI, skinfolds, waist to hip ratio and waist girth.

BMI (kg/m^2) is easy to obtain, relies on simple computations, and is less costly than the techniques mentioned earlier. BMI is a valid and reproducible method of measuring indirect values of body fat and levels of adiposity in children[113-115]. Sampei et al. (2001) found a strong correlation between BMI and bioelectrical impedance analysis in both 10-11 and 16-17 year old girls (r=0.91 and 0.75 respectively)[116]. Pietrobelli et al. (1998) validated BMI as a measure of adiposity in 188 5-19 year olds. Researchers compared total body fat and percent body fat by dual x-ray absorbtiometry to BMI. BMI was strongly associated with total body fat (R^2=0.85 and 0.89 for boys and girls), and percent body fat (R^2=0.63 and 0.69 for boys and girls). BMI has also been widely used in large epidemiological studies to characterize child fatness, although interpretation of measures should be done with caution[115, 117]. Daniels et al. (1997) observed sex, race, sexual maturation and distribution of fat (waist to hip ratio) to have significant independent effects on the relationship between BMI and body fatness, as measured by dual x-ray absorbtiometry (multiple R^2=0.77). Thus, consideration of body type (distribution of fat), sex, race and stage of maturation should be considered when interpreting results[115, 118].

2.3.2.2 Effects of Anthropometry on Autonomic Function

In recent years there has been a substantial increase in the prevalence of childhood obesity [119]. Findings from The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in children and adolescents report that approximately 30% of overweight children have hypertension and as BMI increases so does the prevalence of hypertension[74]. Childhood obesity is becoming increasingly

common in conjunction with childhood hypertension [11, 110, 120-126]. Most recently, Krontoradova et al. (2008) found hypertensive 11-20 year olds to have a significantly higher BMI compared to controls. Also, Genovesi et al. (2005) observed a significantly higher percentage of overweight children to have high BP compared to normal weight children[127]. Obesity-induced hypertension is suggested to be associated with sympathetic over activity [120]. This finding is in agreement with Riva et al. (2001) who found significantly lower TP, higher LF:HF and higher LF in obese versus non-obese children (13-15 yrs) [128]. Therefore, it is important to evaluate anthropometric variables that measure fatness or fat distribution, such as BMI, to identify any influence body fat may have on HRV and BRS values.

2.3.3 Autonomic Function and Sex

Adult females exhibit lower BRS and HRV measures when compared to males of the same age [18, 60]. Laitinen et al. (1998) found young and middle-aged men to have higher BRS compared to young and middle aged women [18]. Additionally, inter-individual variation of BRS was greater in women than in men [18]. Piccirillo and colleagues (2001) also identified higher LF and TP in adult males compared to females [60]. Although a sex difference has been established in adults, few studies have examined this effect in children. When comparing HRV in boys and girls (6-12 years old), Tanaka and colleagues (1994) found females to have less sympathetic activation compared to their male counterparts [129]. Also, Dietrich et al. found girls have a lower BRS than boys (10-13 years old, Tanner stage 2-5) in supine (14.3 +/- 8.7 vs 16.4 +/- 9.4 ms/mmHg) and standing positions (8.4 +/- 4.4 vs 9.5 +/- 5.4 ms/mmHg,) independent of age, pubertal

stage, BMI, and physical activity[21]. Based on these findings, consideration of sex differences is important in both adults and children when measuring autonomic function.

2.3.4 Additional Factors Affecting Autonomic Function: Exclusion Criteria

Autonomic regulation can be altered in individuals who have heart disease, diabetes mellitus, abnormal heart beats, and in those who are on medications that alter BP or autonomic activity (antihypertensive, vasovagal medications)[78, 130]. Some conditions of coronary heart disease have been regarded as responsible for altered BRS including atherosclerosis, acute myocardial ischemia, myocardial infarction, and heart failure[78]. However, there are lifestyle modifications and curative procedures (orthotopic heart transplantation) which have been shown to reverse BRS impairment[78, 131-134].

A significant reduction in BRS is evident in both type I and II adult diabetics when compared to age and sex-matched non-diabetics [62, 78]. It is speculated that these changes in BRS could be linked to glycemic control, microalburninuria, high sensitivity C-reactive protein, hyperinsulinemia, insulin resistance, structural defects of baroreflex pathways, and physical exercise. However, no one cause has been credited[78]. In children, Pozza et al. (2007) investigated whether this same reduction in BRS was found in 208 type I diabetics between 8-22 years of age[130]. With no significant group differences in age, weight, height or BMI, BRS and HF were significantly lower, and LF and LF/HF significantly higher in the diabetic children compared to the control group[130]. After adjusting for age and sex, multiple regression analysis revealed a negative correlation between BRS and duration of diabetes [130]. Furthermore, Faulkner and colleagues (2005) compared 13-18 year olds with type I and type II diabetes and found

type II diabetics to have significantly lower HRV values compared to type I[135]. Thus, an impaired autonomic system can be seen in both diabetic adults and children.

The above factors are reported to alter responses in autonomic activity. Comparative evaluation of subjects with heart disease, diabetes mellitus, abnormal heart beats, and those on BP medications to healthy matched controls reveals irregular autonomic activity in both children and adults. Thus, the above criteria are considered exclusion factors for the present study.

2.4.0 Objectives

Childhood BP is associated with hypertension in adulthood[13, 74], and given that autonomic activity becomes depressed in the presence of cardiovascular disease[18], it is important to investigate the relationship between autonomic regulation and elevated BP in pediatric populations. Although previous studies have looked at this relationship, none of them have accounted for all the factors known to influence autonomic activity. To date, there are no studies that have appropriately accounted for the influence of maturation when examining autonomic activity in pediatric and youth populations. Thus, based on preliminary studies and their limitations, the purpose of this study was to investigate HRV and BRS responses between children aged 11-14 years who have high and low BP while controlling for maturation, sex, age and body composition.

2.5.0 Hypothesis

Based on previous literature in adult hypertensive populations and preliminary pediatric studies, we anticipate to find a decrease in HRV and BRS in children with high BP when compared to low BP controls.

3.1.0 Study Population

After being approved by the Brock University Research Ethics Board and the Niagara Catholic District School Board, this cross-sectional study was conducted in 50 Niagara regional schools (school screen), as well as the Applied Health Sciences laboratories at Brock University (lab based data collection). The target population for the school screen was situated in the Niagara Region because of its population base in excess of 411,000 persons with 25% of them under the age of 18 years. This region provides a blend of urban and rural communities, and a spread of socioeconomic and ethnic diversity. To examine high BP in children entering both puberty (physiological adaptations) and adolescence (social effects) we focused on grades 6 to 8, comprising of about 5,800 students from 50 different regional schools. Schools were randomly selected for screening based on stratification across community-level socioeconomic status using ecological-level data which ranks and stratifies neighbourhoods and municipalities based on average household income and education. This information was collected from the 2001 census data and regional resource inventory (including child resource inventory).

To build the school screen sampling frame we tested 1,931 children for BP, body composition, demographic information, and parent questionnaires. Demographic data was collected in the class room, and included sex, grade, birth date, number of children in the household, household living arrangements, birth place, school absences due to illness or a doctor/dentist appointment within the last 2 weeks. Once the demographic questionnaires were completed, students went to the school library to have their BP and body composition recorded. Using the BPM-300 BP monitor (VSM MedTech Ltd.,

Coquitlam, BC, Canada) 6 resting BP measures were collected at 1 minute intervals[136]. Participants were asked to relax in a seated position with feet flat on the floor, their right arm was situated so that it rested at the midpoint of the sternum for 15 minutes. Cuff size was based on the circumference of the child's arm, with ≥80% of the cuff's bladder encircling the arm and ≥40% of the arm circumference was used to gage cuff width[137]. Following the European Youth Heart Study protocol[136] participants had the first 3 BP measures used to familiarize themselves with cuff pressurization, while the final three measurements were used to provide an average of both SBP and DBP. After adjusting for age, sex and height, students were classified as either normal BP (NBP) if systolic and/or diastolic BP was < the 90th percentile, normal but high BP (NHBP) if SBP or DBP was < 95th and ≥ 90thpercentile, and high BP (HBP) was classified as ≥ 95th percentile for either SBP and/or DBP[13, 138].

Anthropometric measures were taken without shoes, in loose clothing worn for physical education classes, while participants had relaxed breathing with arms at their side. Using a portable standiometer height was recorded (cm), and weight was recorded (kg) using a calibrated electronic medical scale. Waist circumference was taken around the narrowest point or around the belly button, and hip circumference was measured at the greatest protrusion of the gluteal muscles[139]. Waist and hip circumferences (cm) were averaged based on 3 separate measures.

Based on the 1,285 children that had completed data from the school screen and parent questionnaires, 226 children stratified across BP levels (NBP, NHBP and HBP) were recruited to laboratory testing where they were given a thorough assessment of their heart, blood, maturational offset, anthropometrics and autonomic regulation. Of these

participants, 2 children did not complete laboratory testing and 8 children were removed from further analysis because they fell into one of the exclusion criterions (outlined in section 2.3.4). Those participants who consistently remained in the same BP group (HBP, NHBP, and NBP) (after data cleaning seen in section 3.5.0) for both the school screen and lab based data collection were included for further analysis. However, due to the low number of HNBP subjects (n=4), only those subjects in the NBP and HBP groups were included in the analysis (n=106). Methodological procedures listed below are for the lab based data collection involving HRV and BRS measures.

3.2.0 Experimental Measurements

A large number of experimental measures were conducted. However, because this study is a smaller study within the overall protocol only measurements of anthropometry, maturation, BP, and HR are highlighted below for the laboratory testing component.

3.2.1 Anthropometry

Anthropometric classification and comparisons were made on all participants. Subjects were assessed without shoes and in athletic wear. Height (cm) was measured using a wall mounted standiometer. Body weight was assessed (kg) using a calibrated electronic medical scale. BMI was calculated from weight and height (kg/m^2). The same investigator completed all anthropometric testing in order to eliminate inter-observer variability.

3.2.2 Maturation

Somatic maturity was estimated by calculating years from PHV using the equation described by Mirwald et al (2002) (Appendix E). This method has been widely used as an indication of maturation status[103]. Subjects were seated with legs crossed (right over left) to have their sitting height (cm) taken upon expiration. Leg length was calculated by subtracting sitting height from standing height. True age was rounded to the nearest 0.01 years. The somatic maturity measurements were performed by the same investigator for all subjects to eliminate inter-observer variability.

3.2.3 Blood Pressure and Heart Rate

Automated BP values were collected with the same BpTRU Vital Signs Monitor (BMP-300, VSM MedTech Devices Inc., Canada) as in the field screen. The exact same procedure that was performed in the schools during the population screen was used in the laboratory. The BMP-300 is self calibrating and does a diastolic check before each use. The unit took 6 measures of resting BP and the last 3 were averaged to represent automated BP. Beat-by-beat BP values were collected noninvasively using photoplethysmography (Finapres, Omeda 2300, Arnhem, Netherlands). A photoplethysmograph cuff was attached to the left middle finger to collect beat-to-beat measures of SBP, DBP and mean arterial pressure (MAP). As well, manual BP was assessed on the right arm using a standard mercury sphygmomanometer. While resting in the supine position, participants had 3 manual BP readings taken before and after cardiovascular measures were collected. Averages of the last 2 BP measures were calculated to represent a resting brachial artery BP for both pre and post-cardiovascular

data collection. The pre BP average was used to adjust the beat-by-beat BP values obtained using the Finapres at the finger. The post BP average was taken to ensure the subject was still at rest and to insure Finapres accuracy.

RRI and/or HR was recorded using a standard single lead, 3-electrode electrocardiogram. Resting beat-to-beat BP and RRI were recorded for 5-7 minutes. Both BP and RRI were sampled at 1000 Hz providing a basic resolution of 1 ms, which is considered to be an optimal digitization rate[140].

3.3.0 Experimental Protocol

The experimental protocol highlighted below is a shorter version of the entire protocol, as other measures were collected but do not pertain to the overall purpose of my thesis.

The night before lab testing, participants were asked to refrain from eating or drinking after their dinner. Upon arrival to the laboratory, all participants and parents/guardians signed a letter of informed consent (Appendix C) and provided a list of existing medical conditions and/or medications (Appendix D). Following consent, whole blood was collected and lipid profiles were obtained. Participants were asked to void their bladder, as this is known to effect sympathetic nerve activity, consequently altering BP[141]. Then, height, sitting height, and weight were recorded. Afterwards, a 350 calorie breakfast was consumed.

Following 15 minutes of rest in an upright seated position with the right arm at the level of the heart, automated BP measures were taken. Following BP measurements, subjects then entered the cardiovascular and hemodynamics laboratory for beat-by-beat

recordings of RRI and BP. Participants laid in a motionless supine position, resting for a minimum of 15 minutes prior to any cardiovascular measurements. Manual BP was obtained and supine motionless beat-by-beat recordings of both RRI and BP were collected for 5-7 minutes. The entire protocol (including additional measures) took approximately 1½ hours.

3.4.0 Data Analysis

Calculations of BMI and years from PHV were performed after testing was completed. Average RRI was calculated using the average time (ms) from R peak to R peak within the last 1 minute of data collection. Average BP was calculated using the school screen average (last 3 of 6 measures) and automated lab based data averages (last 3 or 6 measures). Mean arterial pressure was calculated by adding 1/3 SBP and 2/3 DBP from the average automated cuff measures.

3.4.1 HRV and BRS

From the Chart 5 (ADInstudments, 2003) recorded beat-by-beat RRI and BP data were transferred into excel (Ms Windows, 2003). The cleanest or most stable 5 minutes worth of data was used for further analysis. The R-R sequences were visually inspected, and the data considered as artifactual were manually replaced by interpolated data. The amount of abnormal beats was, in principle, less than 2%. Then using Matlab 11.1, suitable series of both RRI and SBP were detrended to remove any linear trends, and re-sampled by using the mean cardiac frequency to obtain an equal interval between samples. A low-pass Butterworth filter was chosen and set at 0.95 Hz.

Variability was measured using FFT spectrum. The FFT used a Welch's periodogram method. In this method, the RRI and SBP data were first divided into overlapping segments. Using a Hanning window, each segment was then windowed to $\frac{1}{4}^{th}$ of the signal length and ½ of an overlap. FFT spectrums were calculated for each windowed segment and the segment spectra were averaged. Two frequency bands were considered, LF (0.04-0.15 Hz) and HF (0.15-0.4 Hz), while TP represented the sum of LF and HF. Both absolute and normalized (for TP) RRI and SBP power spectral areas were calculated.

BRS was calculated using mean transfer function gain of both the LF and HF regions. Gain relationships were only accepted when the coherence was ≥ 0.5, in line with current scientific practices[4, 142, 143]. This squared coherence identifies linearity between RRI and SBP signals (0=none and 1=perfect correlation)[39].

3.5.0 Data Cleaning

Subjects with diabetes (2), heart disease (1), on vasovagal medications (1), ectopic beats (1), preventricular contractions (1), too much movement of the photoplethysmograph (1), or loss of consistent pressure from the photoplethysmograph (1), did not have their spectral variability or BRS measures included in the data set. The same investigator analyzed all spectral variability and BRS variables to eliminate inter-observer variability.

3.6.0 Statistical Analysis

Analysis were completed using SPSS software version 15.0 Windows (SPSS Inc, Chicago, IL), and level of significance for all measures was set to $p \leq 0.05$. All analysis compared NBP ($<90^{th}$) and HBP ($\geq 95^{th}$) participants. Descriptive evaluation (using an independent t-test) of all variables were expressed as mean ± standard deviation, for both physical (anthropometrics, age, sex, maturational offset) and cardiovascular variables (BP and RRI).

A one-way analysis of covariance (ANCOVA) was used to compare all autonomic measures (spectral variability and BRS) controlling for the effects of age, sex, BMI (body composition) and years from PHV (maturation). As well, Pearson correlation was performed to determine factors associated with BP in children. A multivariate linear regression was performed to identify the association between BP and spectral variability and BRS variables, while controlling for the effects age, sex, BMI and years from PHV. Lastly, a statistical interaction was performed to identify any cumulative effects of BMI and SBP on BRS as suggested in other studies[19].

4.1.0 Sample Size

From the school screen both child BP and parental questionnaires were collected from at total of 1285 families. A sub-sample of 226 children stratified across three BP classifications ($\geq 95^{th}$; $<95^{th}$ and $\geq 90^{th}$; $<90^{th}$ percentile) were randomly selected from the school screen to come into the Brock University Cardiovascular and Hemodynamics Laboratory. Of the 226 participants only 2 children did not complete laboratory testing and are not included in the following analysis. There were 106 NBP, 46 HNBP and 72 HBP participants recruited for laboratory testing. However, the two-pronged sampling approach used to categorize the participants resulted in the sample size decreasing from 224 to 112 children (see Figure 1). Of the initial 46 HNBP children, only 4 participants (9%) remained in the same category following the laboratory BP screen. Approximately 74% (34 participants) moved from the HNBP to the NBP group. Similarly, the HBP group had 61% (44 participants) of its initial participants move to the NBP classification after the second BP screen. In total 24 subjects moved to a higher BP group, while 84 participants moved to a lower BP category after the second BP screen (see Figure 1). With each BP screen the prevalence of elevated BP diminished, this trend is consistent with other studies and is often reported as 'white-coat hypertension'[11]. Following the second BP screen it was determined that the HNBP group had a sample size (4 subjects) which was too small to include in any further analysis. Those participants with consistent BP measures $<90^{th}$ percentile (NBP) or $\geq 95^{th}$ percentile (HBP) from both the school screen and the lab based data collection are represented in the following analysis. After

excluding diabetics, those on medications, individuals with abnormal cardiac rhythms and irregular photoplethysmograph recordings, our sample size equaled 106 children.

Figure 1 Two-pronged Sample Approach for Categorizing Children with Normal Blood Pressure (NBP), High but Normal Blood Pressure (HNBP) and High Blood Pressure (HBP)

		Laboratory Screen			
	Category	**NBP**	**HNBP**	**HBP**	**Total**
School Screen	**NBP**	90	8	8	106
	HNBP	34	4	8	46
	HBP	44	6	22	72
	Total	168	18	38	224

Participants with consistent blood pressure measures from both the school screen and the lab based data collection

4.2.0 Physical, Maturational and Cardiovascular Characteristics

Average physical, maturational and cardiovascular characteristics for all subjects and are shown in Table 1. HBP subjects had significantly higher values for both weight and BMI compared to NBP participants (Table 1). Additionally, BP was significantly higher in the HBP group compared to the NBP group, while RRI was significantly lower (Table 1).

Table 1 Baseline Characteristics of Children with Normal Blood Pressure (NBP) and Children with High Blood Pressure (HBP)

	NBP (n=85)	HBP (n=21)
Demographic Variable		
Sex (n=Male, n=Female)	56, 29	11,10
Age (years)	12.8 ± 0.8	13.1 ± 0.9
Height (cm)	158.0 ± 9.3	160.6 ± 9.4
Weight (kg)	49.7 ± 11.9	68.6 ± 21.5†
BMI (kg/m^2)	19.8 ± 3.6	26.4 ± 7.1†
Somatic Maturity (years from PHV)	-1.71 ± 0.81	-1.68 ± 1.04
Cardiovascular Variable		
SBP (mmHg)	91 ± 5	110 ± 6†
DBP (mmHg)	55 ± 5	71 ± 5†
MAP (mmHg)	67 ± 4	84 ± 5†
RRI (ms)	808 ± 97	715 ± 93†
PP (mmHg)	35 ± 5	40 ± 8†

Mean ± SD, †Paired t-test $p \leq 0.001$ significantly different from group 1, BMI = body mass index, PHV = years from peak height velocity, SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure, RRI = RR interval, PP = pulse pressure.

4.3.0 RRI Variability

After running an ANCOVA (controlling for the effects of age, sex, somatic maturity, and BMI) for HF, LF and TP frequency components, HBP participants were significantly lower than NBP children (Table 2). In terms of normalized measures, LF/TP and HF/TP did not reach statistical significance. Likewise, no significant difference was found between groups regarding LF/HF ratio.

Table 2 RRI Variability of Children with Normal Blood Pressure (NBP) and Children with High Blood Pressure (HBP)

	NBP (n=85)	HBP (n=21)
LF (ms^2)	730 ± 520	449 ± 330†
HF (ms^2)	909 ± 959	445 ± 581†
TP (ms^2)	1612 ± 1343	904 ± 787†
LF/HF	1.1 ± 0.7	1.6 ± 1.0
LF/TP	0.5 ± 0.1	0.6 ± 0.2
HF/TP	0.5 ± 0.1	0.4 ± 0.2

Mean ± SD, †ANCOVA $p \leq 0.01$ significantly different from group 1; LF = low frequency, HF = high frequency, TP= total power, LF/HF = low frequency to high frequency ratio, LF/TP = low frequency divided by total power, HF/TP = high frequency divided by total power.

4.4.0 SBP Variability

Table 3 lists the SBP variability properties in both BP groups. There were no significant differences in LF, HF, TP, LF/TP, or HF/TP among groups after controlling for age, sex, BMI and years from PHV. However, LF/HF was significantly higher in the HBP group (6.5 ± 3.9) compared to the NBP group (4.0 ± 2.6).

Table 3 SBP Variability of Children with Normal Blood Pressure (NBP) and Children with High Blood Pressure (HBP)

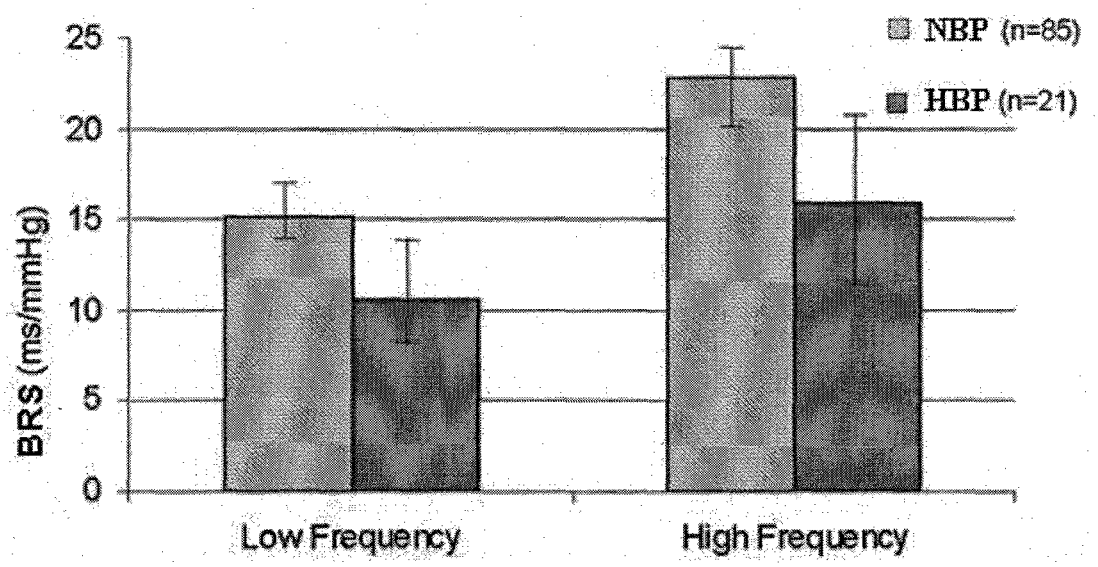
	NBP (n=85)	HBP (n=21)
LF ($mmHg^2$)	5.1 ± 4.3	7.6 ± 4.9
HF ($mmHg^2$)	1.5 ± 1.3	1.4 ± 0.9
TP ($mmHg^2$)	6.6 ± 5.1	8.9 ± 5.4
LF/HF	4.0 ± 2.6	6.5 ± 3.9†
LF/TP	0.7 ± 0.1	0.8 ± 0.1
HF/TP	0.3 ± 0.1	0.2 ± 0.1

Mean ± SD, †ANCOVA $p \leq 0.05$ significantly different from group 1; LF = low frequency, HF = high frequency, TP= total power, LF/HF = low frequency to high frequency ratio, LF/TP = low frequency divided by total power, HF/TP = high frequency divided by total power.

4.5.0 Baroreflex Sensitivity

Depicted in Figure 1, BRS is significantly lower in HBP subjects compared to NBP subjects for both LF (10.5 ± 6.8 vs. 15.1 ± 6.8 ms/mmHg) and HF (16.0 ± 9.4 vs. 22.8 ± 11.4 ms/mmHg) gain after controlling for age, sex, BMI and years from PHV.

Figure 2 BRS of Children with Normal Blood Pressure (NBP) and Children with High Blood Pressure (HBP)



4.6.0 Entire Cohort Determinants

Results regarding correlations in this section can be seen in Table 4. When analyzed as an entire cohort, BP group and autonomic measures (HR and SBP variability and BRS) significantly correlated ranging from r = -0.292 to 0.332, excluding HF SBP and TP SBP. When examining the relationship between average SBP and spectral indices and BRS measures, significant correlates ranged from r = -0.296 to 0.327, excluding HF RRI and HF SBP. RRI correlated with all RRI variability and BRS

measures, ranging from r = -0.286 to 0.551. Additionally, RRI also correlated with BP group (r = -0.361), SBP (r = -0.256), DBP (r = -0.317), and sex (r = 0.241).

As for the BMI, strong correlations existed for several of the spectral variability and BRS measures ranging from r = -0.301 to 0.359. As well, BMI positively correlated with BP group (r = 0.511), SBP (r = 0.651), DBP (r = 0.496), and PP (r = 0.404).

Table 4 Univariate Correlations

	BP group	SBP	DBP	RRI	PP	Age	Sex	BMI	PHV
SBP	0.830**	-							
DBP	0.791**	0.845**	-						
RRI	-0.361**	-0.256**	-0.317**	-					
PP	0.341**	0.528**	0.123	0.049	-				
Age	0.139	0.200*	0.081	0.180	0.139	-			
Sex	0.112	0.131	0.042	0.241*	0.098	0.238*	-		
BMI	0.511**	0.651**	0.496**	-0.091	0.404**	0.095	0.053	-	
PHV	0.013	0.112	0.026	0.147	0.094	0.744**	0.158	-0.060	-
LF RRI	-0.226*	-0.193*	-0.277**	0.361**	-0.057	0.235*	0.097	-0.036	0.165
HF RRI	-0.199*	-0.174	-0.201*	0.328**	-0.068	0.170	-0.008	0.009	0.088
TP RRI	-0.221*	-0.195*	-0.248*	0.361**	-0.066	0.199*	0.045	0.004	0.109
LF/HF RRI	0.276**	0.327**	0.254**	-0.286**	0.150	0.057	0.000	0.299**	0.035
LF/TP RRI	0.257**	0.296**	0.221*	-0.271**	0.160	0.055	0.039	0.219*	0.037
HF/TP RRI	-0.257**	-0.296**	-0.221*	0.271**	-0.160	-0.055	-0.039	-0.219*	-0.037
LF SBP	0.224*	0.273**	0.107	-0.104	0.180	0.048	0.013	0.392**	-0.016
HF SBP	-0.062	-0.002	-0.075	-0.023	0.052	-0.005	-0.090	0.096	0.022
TP SBP	0.177	0.234*	0.074	-0.094	0.167	0.040	-0.010	0.359**	-0.008
LF/HF SBP	0.332**	0.301**	0.203*	-0.128	0.156	0.056	0.063	0.293**	-0.018
LF/TP SBP	0.292**	0.278**	0.187	-0.097	0.120	0.030	0.024	0.301**	-0.037
HF/TP SBP	-0.292**	-0.278**	-0.187	0.097	-0.120	-0.030	-0.024	-0.301**	0.037
LF Gain	-0.263**	-0.231*	-0.201*	0.449**	-0.060	0.174	0.142	-0.235*	0.174
HF Gain	-0.240*	-0.245*	-0.234*	0.551**	-0.063	0.155	0.096	-0.204*	0.109

** Correlation is significant at the 0.01 level (2-tailed), * correlation is significant at the 0.05 level (2-tailed), SBP = systolic blood pressure, DBP = diastolic blood pressure, RRI = RR interval, PP = pulse pressure, Sex male = 0 & female = 1, BMI = body mass index, PHV = years from peak height velocity, LF = low frequency, HF = high frequency, TP= total power, LF/HF = low frequency to high frequency ratio, LF/TP = low frequency divided by total power, HF/TP = high frequency divided by total power, , LF Gain = low frequency gain of systolic and RR interval variability, HF Gain = high frequency gain of systolic and RR interval variability. Need to mention somewhere how sex was coded so the reader understands what a positive/negative relationship means.

As for the multivariate linear regression analyses between BP group and BRS, the p-values for each of the independent variables showed that BP group alone significantly predicted BRS (BP group for LF gain p=0.04 and HF gain p=0.05). The regression coefficients (unstandardized B) indicate that for an increase in BP group (NBP to HBP) LF and HF BRS decreased by 4.0 and 6.2 ms/mmHg respectively. None of the other dependent variables (BMI, sex, age or years from PHV) significantly predicted LF or HF BRS. Again using a multivariate linear regression to determine the relationship between absolute SBP and BRS, only the relationship between SBP and HF BRS had a significant R and adjusted R^2 value of 0.338 and 0.070 respectively. Although the entire model was significant (p=0.03), only SBP independently predicted HF BRS (p=0.05). The unstandardized B coefficient indicated that for every increase of 1 mmHg HF BRS decreased by 0.3 ms/mmHg.

4.7.0 Effects of Independent Variables

To ensure that BMI and BP group, as well as BMI and SBP did not have a cumulative effect on BRS, a statistical interaction was performed. It was found that BMI and BP group, along with BMI and SBP did not interact. Thus, the effect of BMI on BRS does not depend on BP and vice versa.

Chapter 5: Discussion

5.1.0 Introduction

The effects of elevated BP on autonomic activity, as measured by both BP and HR variability and BRS, were evaluated in a sample of 106 11-14 year olds. The principle finding of this study was that children with elevated BP had significantly reduced cardiovagal activity compared to children with normal BP levels, even after controlling for age, sex, body composition and maturation. Furthermore, as BP increased, BRS decreased.

5.2.0 Spectral Variability Parameters

5.2.1 RRI Variability

To our knowledge this is the first study to demonstrate significant reductions in HRV measures among children with elevated BP compared to those with normal BP levels while controlling for the confounding variables age, sex, body composition and maturation. The HRV values found in the present study in normal BP children (LF: 730 ± 520 ms^2, HF: 909 ± 959 ms^2, TP: 1612 ± 1343) coincide with previous reports[20]. Also similar to recent reports[17], the present study found HBP participants to have lower LF, HF, TP, and HF/TP RRI variability compared to NBP subjects, while LF/HF and LF/TP means were higher.

To date, Genovesi et al. (2008) and Urbina et al. (1998) are the only researchers who have looked at HRV measures in hypertensive and normotensive children/youth[1, 17]. Genovesi and colleagues (2008) found a significant reduction in resting HRV measures

when comparing normotensive (97.1±2.7/57.3±2.0 mmHg) to hypertensive (128.4±1.9/80.1±1.6 mmHg) children (9.7±0.22 years)[17]. However, after Genovesi and colleagues controlled for BMI, LF and HF RRI variability were no longer significant[17]. In the present study, LF, HF, and TP remained significantly different between groups after controlling for all covariates, including BMI.

The lower RRI HF variability observed in the HBP group compared to NBP children reflects a reduced parasympathetic (vagal) modulation in HBP participants [15]. Similarly, the lower LF RRI variability in the HBP versus NBP subjects reflects a reduction in autonomic regulation, that of both sympathetic and parasympathetic activity. However, due to the reduction in vagally mediated HF power, the observed reduction in LF power is predominantly indicative of reduced parasympathetic versus sympathetic activity[15]. Likewise, diminished TP in HBP compared to NBP participants suggests sympathetic overdrive, vagal withdraw, and/or depressed vagal and sympathetic activity[14, 32].

In accordance with earlier findings, this study did not find significant BP-related differences in LF/HF, LF/TP, and HF/TP RRI variability measures [17]. Urbina et al. (1998) found a trend towards reduced LF/HF ratios in youths (13-17 year olds) with high BP versus those with low BP, however these findings were not significant[1].

5.2.2 SBP Variability

In contrast to past studies, the present investigation reports both RRI and SBP variability in children with varying BP profiles, providing a complete picture of autonomic regulation and how it differs by BP. After controlling for age, sex, body

composition and somatic maturity, the present study found a significantly elevated LF/HF ratio in the HBP group (6.5 ± 3.9) compared to NBP group (4.0 ± 2.6) . This elevated LF/HF ratio in HBP subjects suggests sympathetic predominance in children with higher BP. Although not significant, HBP participants also had wider SBP variability for LF, HF, and LF/TP compared to NBP participants. Studies in adults have also reported a significantly wider SBP variability in isolated systolic hypertension[144] compared to normotensive subjects, suggesting poorer BP regulation for hypertensives.

5.3.0 BRS Parameters

Unique to this study is the finding that even after controlling for age, sex, body composition, and somatic maturity, children with elevated levels of BP have significantly reduced arterial BRS. Coinciding with previous studies, the LF BRS values for NBP children in the present study (15.1 ± 6.8 ms/mmHg) coincide with previously reported transfer function analysis estimates[21]. As well, the attenuated BRS found in HBP subjects is similar to the results of Genovesi et al. (2008) and Krontoradova et al. (2008), both of whom found significantly reduced resting measures of LF BRS in hypertensive children/ youth versus controls [17, 19]. Genovesi and colleagues' (2008) findings remained significant even after correcting for BMI[17]. Similarly, Krontoradova et al. (2008) found both BMI and BRS to be independent factors associated with elevated BP in 11-21 year olds[19]. However, they did not control for BMI, but rather used correlations and logistic regressions to conclude that both BMI and BRS are independent variables associated with an increased risk of hypertension[19].

The attenuated BRS observed in HBP children aligns quite nicely with the spectral results. BRS describes the relationship between reflex changes in RRI for a given change in BP[8]. As previously mentioned, LF represents both parasympathetic and sympathetic modulation, while HF is a measure of parasympathetic predominance. A lower LF, HF and TP RRI variability, coinciding with an elevated LF, HF and TP SBP variability displays altered autonomic regulation, suggesting that HBP children have greater BP fluctuations due to a lower BRS. Hence, an overall smaller change in RRI for a given change in BP. Therefore, by finding a diminished LF and HF BRS (ms/mmHg) in children with elevated BP (HBP), we can conclude that cardiovagal baroreceptor function is reduced in children with higher BP. The fact that the overall ability to regulate BP through changes in RRI in children with high BP is reduced is very important, as baroreceptors play a vital role in BP regulation, preventing excessive increases and/or decreases in BP throughout daily activities[26, 145]. As well, attenuated BRS has been linked to cardiovascular disease, morbidity and mortality in adults [9, 61, 65, 146]. Since childhood BP is associated with hypertension in adulthood, there is a growing concern in regards to the present and future cardiovascular health of these children[13, 74, 147].

Furthermore, multiple linear regression analysis found that both average SBP and BP group are independent variables that significantly predict BRS. In moving from the NBP to HBP group classification, both LF and HF BRS was found to decrease by 4.1 and 6.2 ms/mmHg respectively. Thus, as BP increases, BRS decreases.

It is important to note that the absolute SBP and DBP values of our HBP participants (110 ± 6 and 71 ± 5 respectively) are not "truly" hypertensive, or even pre-hypertensive according to the National High Blood Pressure Education Program and

Working Group on High Blood Pressure in Children and Adolescents (2004) (see Appendix F for BP levels for boys and girls by age and height percentiles)[74]. However, the relationships found in this study between BP elevation, spectral variability (RRI and SBP) and arterial BRS are comparable to studies using much higher hypertensive cut-offs than those used in the current study (eg. Genovesi et al.[17] and Krontoradova et al.[19] had SBP/DBP values of 128.4±1.9/80.1±1.6 and 125±14/71±9 mmHg respectively), suggesting that impairment in autonomic function starts before a child is hypertensive and is seen as early as the onset of pre-hypertension. In fact, the findings of the current study coincide with those made by Honzíková et al. (2006). These authors found that in children, adolescents, and young adults with white-coat hypertension BRS was lower than in healthy controls, despite the fact that they had normal BP values over 24-hours and hence no reason for remodelling of the vessel's wall[148]. Thus, the conclusion set forth by the investigators was that lower BRS precedes BP increase[148].

5.4.0 Limitations

While this study presents important and novel findings, there are several limitations that need to be acknowledged and addressed. The first limitation concerns the relatively small number of children in the HBP group. A small number of participants in this group could account for the limited number of significant findings. An increase in the number of HBP subjects would provide more statistical power, in turn an increase in significance. However, we did find significance for BRS, our main variable of interest.

BP grouping or classifications were based on two separate BP readings. According to the National High Blood Pressure Education Program and Working Group

on High Blood Pressure in Children and Adolescents (2004), a diagnosis of hypertension should only be made after more than three BP measures on separate occasions[74]. The rationale behind this guideline stems from the finding that the incidence of hypertension decreases after each separate measure[11]. Studies have shown that following a single BP measure the prevalence of individuals with a reading above the hypertensive cut-off ($\geq 95^{th}$ percentile based on age, sex, and height) is approximately 19%[11]. However, after a second BP reading the prevalence drops to approximately 9.5%, while after a third measure the prevalence is only 4.5%[11]. Therefore, by using only 2 separate measures in the current study, we could be over diagnosing or improperly grouping some participants. However as stated previously, the absolute BP values for the HBP participants in the current study were significantly less than the hypertensive cut points reported in the National High Blood Pressure Education Program and Working Group on High Blood Pressure in Children and Adolescents (2004)[74]. As well, by only including subjects with consistent BP readings on 2 separate occasions in the analysis, we attempted to avoid the possibility of improperly grouping participants.

The present study used only the 2 extreme BP groups (SBP and/or DBP $<90^{th}$ percentile and $\geq 95^{th}$ percentile), eliminating the middle BP group (SBP and/or DBP $\geq 90^{th}$ but $<95^{th}$ percentile). By having a middle BP group, we could make clearer distinctions regarding the relationship between progressively increasing BP values and autonomic activity. However, after eliminating subjects with inconsistent BP on two separate occasions (described above), we were only left with 4 subjects in the middle BP group, not enough to be statistically relevant. Another limitation to address is the level of sexual maturation. Somatic maturity was determined by using an equation developed by

Mirwald et al. (2002) to determine how many years a child is from reaching their PHV. The literature describes alterations in autonomic activity with variations in sex steroids such as estrogen and testosterone[94-96]. Although years from PHV provides an estimate of maturational offset, measuring circulating hormonal levels would provide a direct measure of sexual maturation and could lend insight into the influences of estrogen and testosterone on autonomic regulation. However, years from PHV is non-invasive, provides a continuous measure of maturity and is simple to determine.

Lastly, another limitation is the lack of longitudinal tracking. Longitudinal tracking allows researchers to observe changes over time. This could particularly be useful when examining the associations between autonomic activity and maturation, growth and development, ageing and changes in body composition. As well, a longitudinal study would provide us with key insight into the timing of BRS function limitations and BP elevation. In essence, is it a reduction in BRS that precedes BP elevation or vice versa?

5.5.0 Future Considerations

High BP places a sheer force acting on the endothelium and causing micro tears in the vessel walls[71]. The torn areas are vulnerable to plaque and fatty deposits and soon develop a fibrous tissue cap (scar-forming fibroblasts) over the plaque deposits[34]. Eventually these fibrous caps calcify and cause the artery to become stiff and less distensible[34]. Reduced BRS in hypertensives is often ascribed to reduced distension from stiffening of the vessel walls[149]. Therefore, it is difficult to distinguish whether the

changes in BRS are caused from high BP or are a secondary outcome caused by arterial stiffening.

In 2004 Kornet and colleagues were the first to differentiate between mechanical stretch and neural involvement of the baroreflex in hypertensives[150]. By determining the distention rate of the carotid artery for a given response in BP changes, the researchers were able to examine the relationship between spontaneously occurring carotid diameter changes and the RRI relationship[150]. This carotid diameter change to RRI produced a 'stretch derived' BRS indices rather than the traditional 'blood pressure derived' (SBP changes for a given change in RRI) indices[150, 151]. The 'stretch derived' BRS measure allowed Kornet and colleagues to quantify the neural effects of BP related changes on the heart rate reflexes by 'excluded the influence of the arterial wall stiffness'[150]. When comparing hypertensives to normotensives less than 50 years of age, hypertensives demonstrated lower BRS values versus normotensive controls[150]. This diminished BRS in hypertensives was attributed to both decreased 'distension and reduced sensing and processing of neural signals'[150]. These findings indicate that neural activity of the baroreflex is altered in hypertensives 'irrespective of changes occurring in arterial wall structure'[150]. These findings are in line with Honzíková et al. (2006) (mentioned earlier in section 5.3.0) who found white-coat hypertensives to have lower BRS values than healthy controls, despite normal BP values over 24-hours and hence no reason for remodeling of the vessel's wall[148]. Both Kornet et al. and Honzíková et al. suggest neurological alteration of the baroreflex in hypertensives[148, 150]. Thus, a future direction for the present investigation would be to segregate the mechanical from neural influences of BRS in these children, to determine how much, if any, neural alterations might have

occurred in those with high BP. Another future direction would be to identify the 'white-coat hypertensives' or in the present study those children who were first grouped as HBP or HNBP after the school screen, and were then switched into the NBP classification after the lab screen. By identifying these 'white-coat hypertensives' it can be determined if these children have reduced BRS versus normotensive children despite remodeling of the vessel walls, as is expected in those with chronically elevated BP. Therefore, in support of the conclusions set forth by the aforementioned investigators, this study could consider these finding in future works to better understand the process of BRS and its relationship to elevated BP.

Chapter 6: Conclusions

Children with even slightly elevated BP levels have significantly reduced autonomic activity even after controlling for age, sex, body composition and somatic maturity. Despite their young age and relatively short amount of time having elevated BP, these children are already demonstrating poor BP regulation. Given that childhood BP is associated with hypertension in adulthood, and the fact that attenuated BRS has been linked to cardiovascular mortality in adults, there is a growing need for more research in regards to the present and future cardiovascular health of these children.

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Appendix A
Research Ethics Approval

Brock University Research Ethics Board (REB)

Application for Ethical Review of Research Involving Human Participants

Please refer to the documents "Brock University Research Ethics Guidelines", which can be found at http://www.brocku.ca/researchservices/, prior to completion and submission of this application.

If you have questions about or require assistance with the completion of this form, please contact the Research Ethics Office at (905) 688-5550 ext. 3035, or reb@brocku.ca.

Return your completed application and all accompanying material **in triplicate** to the **Research Ethics Office in MacKenzie Chown D250A.**
Please ensure all necessary items are attached prior to submission, otherwise your application will not be processed (see checklist below).

No research with human participants shall commence prior to receiving approval from the research ethics board.

DOCUMENT CHECKLIST **3 complete sets of the following documents (one original + 2 copies)** Please Note: Handwritten Applications will *not* be accepted.	✓ if applicable
Recruitment Materials	
• Letter of invitation	[✓]
• Verbal script	[ ]
• Telephone script	[ ]
• Advertisements (newspapers, posters, SONA)	[ ]
• Electronic correspondence guide	[ ]
Consent Materials	
• Consent form	[✓]
• Assent form for minors	[ ]
• Parental/3rd party consent	[ ]
• Transcriber confidentiality agreement	[ ]
Data Gathering Instruments	
• Questionnaires	[✓]
• Interview guides	[ ]
• Tests	[ ]
Feedback Letter	[ ]
Letter of Approval for research from cooperating organizations, school board(s), or other institutions	[ ]
Any previously approved protocol to which you refer	[✓]
Request for use of human tissue sample in research Please Note: this form is required for all research projects involving human tissue, bodily fluids, etc.	[ ]
Signed Application Form	[✓]

Office of Research Services
Brock University • 500 Glenridge Ave • St. Catharines, ON • L2S 3A1 • Fax: 905-688-0748

Revised: August 2006

SIGNATURES

Principal Investigator:
Please indicate that you have read and fully understand all ethics obligations by checking the box beside each statement.

[✓] I have read Section III:8 of Brock University's Faculty Handbook pertaining to Research Ethics and agree to comply with the policies and procedures outlined therein.
[✓] I will report any serious adverse events (SAE) to the Research Ethics Board (REB).
[✓] Any additions or changes in research procedures after approval has been granted will be submitted to the REB.
[✓] I agree to request a renewal of approval for any project continuing beyond the expected date of completion or for more than one year.
[✓] I will submit a final report to the Office of Research Services once the research has been completed.
[✓] I take full responsibility for ensuring that all other investigators involved in this research follow the protocol as outlined in this application.

Signature _____ Date: _____

Co-Investigators:

Signature _____ Date: _____

Signature _____ Date: _____

Signature _____ Date: _____

Faculty Supervisor:

Please indicate that you have read and fully understand the obligations as faculty supervisor listed below by checking the box beside each statement.

[ ] I agree to provide the proper supervision of this study to ensure that the rights and welfare of all human participants are protected.
[ ] I will ensure a request for renewal of a proposal is submitted if the study continues beyond the expected date of completion or for more than one year.
[ ] I will ensure that a final report is submitted to the Office of Research Services.
[ ] I have read and approved the application and proposal.

Signature _____ Date: _____

SECTION A – GENERAL INFORMATION

1. **Title of the Research Project:** Social Determinants of Child Hypertension

2. **Investigator Information:**

	Name	Position	Dept./Address	Phone No.	E-Mail
Principal Investigator	Terrance J Wade	Faculty	CHSC/CYS	4146	twade@brocku.ca
Co-Investigator(s)	Paul LeBlanc Deborah O'Leary	Faculty Faculty	CHSC CHSC	4216 4339	pleblanc@brocku.ca doleary@brocku.ca
Faculty Supervisor(s)					

3. **Proposed Date (dd/mm/yyyy)** (a) of commencement: 01/10/2007 (b) of completion: 30/06/2012

4. **Indicate the location**(s) where the research will be conducted:

Brock University	[✓]
Community Site	[ ] Specify
School Board	[ ] Specify
Hospital	[ ] Specify
Other	[ ] Specify

5. **Other Ethics Clearance/Permission:**

(a) Is this a multi-centered study? [ ] **Yes** [✓] **No**

(b) Has any other University Research Ethics Board approved this research? [ ] **Yes** [✓] **No**

If **YES**, there is no need to provide further details about the protocol **at this time,** provided that **all** of the following information is provided:

Title of the project approved elsewhere:
Name of the Other Institution:
Name of the Other Board:
Date of the Decision:
A contact name and phone number for the other Board:

Please provide a copy of the application to the other institution together with all accompanying materials, as well as a copy of the clearance certificate / approval.

If **NO**, will any other Research Ethics Board be asked for approval? [✓] **Yes** [ ] **No**
Specify University/College Niagara Catholic District School Board

(d) Has any other person(s) or institutions granted permission to conduct this research? [ ] **Yes** [✓] **No**
Specify (e.g.,. school boards, community organizations, proprietors)

6. **Level of the Research:**

[ ] Undergraduate	[ ] Masters Thesis/Project	[ ] Ph.D.
[ ] Post Doctorate	[✓] Faculty Research	[ ] Administration
[ ] Undergraduate Course Assignment (specify course)	[ ] Graduate Course Assignment (specify course)	[ ] Other (specify)

7. **Funding of the Project:**

(a) Is this project currently being funded [✓] **Yes** [ ] **No**

(b) If **No**, is funding being sought [ ] **Yes** [ ] **No**

If Applicable:

(c) Period of Funding (dd/mm/yyyy): From: 01/07/2007 To: 31/06/2012

(d) Agency or Sponsor (funded or applied for)

[ ] CIHR [ ] NSERC [ ] SSHRC [✓] Other (specify): HSFO

(e) Funding / Agency File # (not your personal PIN)

8. **Conflict of Interest:**

(a) Will the researcher(s), members of the research team, and/or their partners or immediate family members receive any personal benefits related to this study – Examples include financial remuneration, patent and ownership, employment, consultancies, board membership, share ownership, stock options. Do not include conference and travel expense coverage, possible academic promotion, or other benefits which are integral to the general conduct of research.

[ ] **Yes** [✓] **No**

If **Yes**, please describe the benefits below.

(b) Describe any restrictions regarding access to or disclosure of information (during or at the end of the study) that the sponsor has placed on the investigator(s).

none

SECTION B – SUMMARY OF THE PROPOSED RESEARCH

9. **Rationale:**
Briefly describe the purpose and background rationale for the proposed project, as well as the hypothesis(es)/research question(s) to be examined.

(A) Statement of the Health Problem:
Child hypertension (high blood pressure) is on the rise in Canada and the rest of North America. Since hypertension is a risk factor for the development of heart disease and stroke, our concern is that children who exhibit high blood pressure now will be at much greater risk for heart disease and stroke as they become adults. Although biological and genetic factors are important causes of hypertension, social and behavioural factors are also important. For example, some research has shown that children living in poverty are more likely to have high blood pressure than other children. Yet, we know very little about how social determinants affect hypertension in children and, more importantly, why these factors are linked to high blood pressure in childhood.

(B) Objective of the project:
Our study proposes to not only identify which social factors are related to hypertension, but also to explore why these factors are linked to high blood pressure in children. It is through this that we believe the clues for successful intervention will be found. For example, it is unlikely that much can be done to address poverty among families without considerable governmental intervention. But if we can show that children from disadvantaged families not only have higher blood pressure than other children, but also that they are less physically active, then we can intervene to change this lifestyle factor. However, it is only through identifying the social risk factors (e.g., family poverty) and the intervening factor that leads to child hypertension (e.g., inactivity), that we can truly begin to design programs to address this problem.
Once the most important social determinants have been identified, and the factors that explain why these social conditions lead to hypertension in children revealed, we will engage parents, teachers and community representatives to help design programs to improve the health and well-being of children. Next, we will actually implement the programs that result from our consultations and test to see if they did indeed work (if they lowered blood pressure among children at risk).

(C) How will this work be done?
There are two phases to our study. In the Phase 1 **lab component**, *for which this REB application applies*, a subsample of children and their parents across hypertensive, pre-hypertensive and normal blood pressure groups (~ 100 per group, from a 3,000 subject screen base which has already received approval REB # 06-315 to Terrance Wade) will complete detailed questionnaires and will undergo an extensive series of physiological tests including a full body and blood analysis, blood pressure, arterial distensibility, left ventricular mass and detailed nutrition analysis. *This protocol submission is based on a previously approved protocol (REB 04-419 to Deborah O'Leary).*

10. **Methods:**
Are any of the following procedures or methods involved in this study? Check **all** that apply.

[ ] Questionnaire (mail)
[ ] Questionnaire (email/web)
[✓] Questionnaire (in person)
[ ] Interview(s) (telephone)
[ ] Interview(s) (in person)
[ ] Secondary Data
[ ] Computer-administered tasks
[ ] Focus Groups
[ ] Journals
[ ] Audio/video taping (specify)
[ ] Observations
[ ] Invasive physiological measurements (e.g., venipuncture, muscle biopsies)
[✓] Non-invasive physical measurement (e.g., exercise, heart rate, blood pressure)
[✓] Analysis of human tissue, body fluids, etc. (Request for Use of Human Tissue Sample attached)
[ ] Other: (specify)

Describe sequentially, and in detail, all of the methods involved in this study and all procedures in which the research participants will be involved (e.g., paper and pencil tasks, interviews, questionnaires, physical assessments, physiological tests, time requirements, etc.)
Attach a copy of all questionnaire(s), interview guides, or other test instruments.

Sample Frame: The Niagara Catholic District School Board (NCDSB) will provide a subject base, facilitating access to their 50 elementary schools in the Niagara region (~16,700 students from kindergarten to grade 8). Our focus will be on children in grades 6 to 8 (age ~11 to ~13), a population of about 5,800 students.

Sampling Strategy: Using mapped community-level SES data based on average household income, education, and urbanicity, schools situated within neighbourhoods across different strata form the school sampling frame will be identified. Schools will be randomly selected across each community stratum. In September, 3,000 children in grades 6, 7 and 8 will be screened to assess blood pressure, body composition (waist and hip circumference, height, and weight), demographic information and activity level. A subsample of children and their parents across hypertensive, pre-hypertensive and normal blood pressure groups (100 per group) will complete detailed questionnaires (REB 06-315 to Terrance Wade) and undergo an extensive series of physiological tests including a full body and blood analysis, blood pressure, arterial distensibility, left ventricular mass (using Doppler echocardiography) and detailed nutrition analysis.

Lab Testing: After being recruited in the study, the child will participate in one, 1 ½ hour testing session. Before starting the testing session the child will be familiarized with the laboratory, in addition to the testing procedures being explained to them. The child and their parent will be asked to read an information sheet on the study and sign a consent form (Appendix A).

Some factors, such as food, exercise and temperature have been purported to affect performance. To account for this, subjects will be asked to fast for 12 hours prior to the testing session; avoid caffeine the day of testing; refrain from exercise on the testing day (prior to the procedure) and testing will be conducted in a temperature controlled room. The child will be asked to wear athletic attire for the testing session.

Upon arrival at the lab and after signing the informed consent, each subject will then immediately have their blood taken for analysis. Following this, each child will be given a preset meal (allergy sensitive) consisting of approximately 350 kcal. They will also be instructed to void their bladder, as this has been shown to have an effect on sympathetic nerve activity and hence blood pressure. Each subject's weight, height, skinfold thickness, waist circumference, hip circumference and Tanner stage (Appendix B) will then be recorded. Next, after 15-minutes of acclimatization, six resting blood pressure measures will be obtained using the automated BPM-300. Following blood pressure measurement, 5 minutes of beat-by-beat heart rate will be collected. As well, the left ventricle, along with the right common carotid artery will be imaged using Doppler ultrasound and the left common carotid artery pulse pressure will be recorded using hand-held tonometry.

Measurements:

Blood analysis
Body composition & Tanner stage
Blood Pressure
Baroreflex function
Arterial Stiffness
Left Ventricular Mass

Blood Analysis: After cleaning the middle finger of the non-dominant hand with an alcohol swab, two small drops of whole blood will be collected by finger pinprick utilizing disposable single use lancets. The site of the pinprick will once again be cleaned with a fresh alcohol swab and covered with an adhesive bandage. The subjects will feel a small prick but will not feel any pain or discomfort for the remainder of the sampling. The tip of that finger may feel sensitive and a little bit sore for about a day.

Blood analysis will test for total cholesterol, high density (HDL), low density (LDL) and very-low-density-lipoprotein cholesterol (VLDL), along with triglycerides (TG), glucose and glycosylated haemoglobin (HbA1C) to identify co-morbidities associated with hypertension (e.g., obesity, type 2 diabetes). The blood analysis will be done using the Cholestech GDX and LDX (Hayward, CA, USA),

small portable finger pinprick analyzer. This unit is a valid and reliable instrument capable of obtaining results in 5 minutes from one drop of whole blood. The analyzer is a U.S. National Glycohemoglobin Standardization Program (NGSP)-certified instrument for the quantification of blood HbA1C (% of total haemoglobin), which is directly proportional to the concentration of glucose in the blood over the past 2-3 months. The Cholestech LDX meets all U.S. National Cholesterol Education Program (NCEP) guidelines for precision and accuracy regarding measurements (in mg/dL) of total cholesterol (TC), HDL, TG, glucose, TC/HDL ratio, and estimates of LDL and VLDL.

Body Composition: *Height* will be measured without footwear and heels together. The subject will stand vertically erect with eyes forward, shoulders relaxed with arms downward. Height will be recorded to the nearest 0.2 cm from the highest point on the top of the head using a portable stadiometer. *Weight* will be measured and recorded to the nearest 0.1 kg using a calibrated electronic medical scale. The subject will be without footwear and wearing athletic attire. *Waist and hip circumference* will be measured with subjects standing upright, heels together, arms in resting position and breathing relaxed. Waist will be measured around the narrowest point (approx. belly button height); hip will be measured at the level of the greatest protrusion of the gluteal (buttock) muscles. Both waist and hip measurements will be taken 3 times each with a flexible-inelastic tape measure to the nearest 0.2 cm and averaged. *Skinfold thickness* (mm) will be assessed at two sites (triceps and subscapular) using a Harpenden calliper (British Indicators, Herts, England). *Percentage of body fat* (%BF) will be calculated using the two-site prediction equations developed for children (age and gender specific) $\leq$18 years of age. All body composition measures will take place behind a portable curtain for privacy. The parent can be present at all times during this testing.

Tanner Stage: Pubertal maturation will be determined by self-report using the pictures from the Sexual Maturation Scale by Tanner (Appendix B).

Blood Pressure: To verify the values collected in the field (REB 06-315 to Terrance Wade), as well as record current and precise readings, blood pressure will additionally be measured in the lab setting following the same protocol as the field testing (school data collection) using the BPM-300. Blood pressure levels that are $\geq$ 90th percentile but <95th percentile on an age/sex/height standardized normal curve will be categorized as pre-hypertensive, while those above the 95th percentile will be classified as hypertensive.

Baroreflex Function: Baroreflex sensitivity will be measured by determining the relationship between beat-by-beat heart rate (beats/minute) and blood pressure collected during supine rest. Blood pressure will be obtained non-invasively using the finger cuff photoplethysmograph system known as the Finometer (Finapres Medical Systems, Arnhem, Netherlands). This system calibrates finger blood pressure to brachial blood pressure by automated sphygmomanometer measures taken at preset times. As for heart rate, it will be recorded using 2 sets of 3-lead electrocardiogram (ECG). Baroreflex sensitivity is calculated as the change in heart rate (beats/minute) in response to a given change in blood pressure (mmHg).

Arterial Stiffness: Distensibility is an index of arterial stiffness and will be measured in the common carotid artery (CCA) using the Doppler ultrasound method. The right CCA will be visually assessed in the supine position with B-mode ultrasound video clips using a Doppler ultrasound (Vivid I, GE Medical Systems, Horten, Norway) and EchoPAC software (GE Medical Systems). Measurements will be taken 2-3 cm proximal from where the right CCA bifurcates into the external and internal carotid arteries. Diameters corresponding to systole and diastole will be measured, and pulsatile pressure of the left CCA will be measured simultaneously by hand-held tonometry (Millar SPT-301, Millar Instruments, Houston, TX, USA). Pulsatile cross sectional area and the corresponding pulsatile pressure will be used to determine vessel distensibility

Left Ventricular Mass (LVM): Numerous studies report that LVM is influenced by blood pressure. Therefore, LVM will be measured using non-invasive Doppler Echocardiography (Vivid I). Specifically, LV dimensions will be measured in the short-axis view with a 2-dimensional guided M-mode echocardiogram according to standard criteria. Three cycles will be obtained and averaged for LVM determination.

***NOTE*: The above procedures and measurements have been previously approved in REB #04-419 to Deborah O'Leary**

11. **Professional Expertise/Qualifications:**

Does this procedure require professional expertise/recognized qualifications (e.g., registration as a clinical psychologist, first aid certification)?
[✓] **Yes** [ ] **No**

specify: ECG and ultrasound techniques and methods

***Blood analysis via pinprick does not require any specific qualifications, other than attending a Health and Safety workshop in which all lab personnel will be introduced to proper procedures required when handling blood products (i.e. protective apparel, disposal of blood products etc.).

If **YES**, indicate whether you, your supervisor, or any members of your research team have the professional expertise/recognized qualifications required?
[✓] **Yes** [ ] **No**

12. **Participants:**
Describe the number of participants and any required demographic characteristics (e.g., age, gender).

300 students of hypertensive, pre-hypertensive and normotensive status in grades 6, 7, and 8 from the Niagara Catholic District School Board.

13. **Recruitment:**
Describe how and from what sources the participants will be recruited, including any relationship between the investigator(s), sponsor(s) and participant(s) (e.g., family member, instructor-student; manager-employee).
Attach a copy of any poster(s), advertisement(s) and/or letter(s) to be used for recruitment.

Students will be recruited from grade 6, 7 and 8 classes in randomly selected schools from the Niagara Catholic District School Board stratified across blood pressure group, aggregate community-level SES and urbanicity using aggregate socioeconomic census data.

14. **Compensation:**	**Yes**	**No**
(a) Will participants receive compensation for participation?	[✓]	[ ]
(b) If yes, please provide details.		

Twenty dollars will be given to each participant as a token of appreciation for participation.

SECTION C – DESCRIPTION OF THE RISKS AND BENEFITS OF THE PROPOSED RESEARCH

15. **Possible Risks:**
1. Indicate if the participants might experience any of the following risks:

a) Physical risks (including any bodily contact, physical stress, or administration of any substance)?	[✓] **Yes** [ ] **No**
b) Psychological risks (including feeling demeaned, embarrassed worried or upset, emotional stress)?	[ ] **Yes** [✓] **No**
c) Social risks (including possible loss of status, privacy, and / or reputation)?	[ ] **Yes** [✓] **No**
d) Are any possible risks to participants greater than those that the participants might encounter in their everyday life?	[ ] **Yes** [✓] **No**
e) Is there any deception involved?	[ ] **Yes** [✓] **No**
f) Is there potential for participants to feel coerced into contributing to this research (e.g., because of regular contact between them and the researcher)?	[ ] **Yes** [✓] **No**

2. If you answered **Yes** to any of 1a – 1f above, please explain the risk.

Physical Risks - Finger pinprick for blood analyses is associated with minor discomfort in the fingertip for up to 24 hours. When the surface of the skin is broken, there is always a risk of infection. However, with proper precautions taken in the laboratory during (proper cleaning before and after sampling, using sterile equipment) and after (adhesive bandage) testing, there is an extremely low risk of infection.

All Doppler Ultrasound procedures are non-invasive and offer minimal risk to participants. In rare instances, participants may experience numbness and/or tingling in the area and/or a minor rash from electrode adhesive and/or gel.

3. Describe how the risks will be managed and include the availability of appropriate medical or clinical expertise, qualified persons. Explain why less risky alternative approaches could not be used.

Participants will be informed prior to the study that they DO NOT have to take part in any procedure of the investigation that causes them discomfort. In accordance, participants know that they are able to withdraw from the study at any time, and all of their data collected to date will be destroyed. Additionally, participants will be instructed to contact the study coordinator if they feel any adverse effects from completing any portion of the investigation, and/or if they have any questions or concerns. In addition, all laboratory personnel will be sufficiently trained in the testing procedures, as well as being trained in the proper, tactful and professional manner of dealing with children of this age.

16. **Possible Benefits:**

Discuss any potential direct benefits to the participants from their involvement in the project. Comment on the (potential) benefits to the scientific community/society that would justify involvement of participants in this study.

A potential benefit to the participants includes the identification of any possible serious blood pressure/heart anomalies for the child that should be followed up by a general practitioner, as well as any underlying cardiovascular disease risk factors.
Potential benefits to the scientific community and society include the identification of social factors that are related to hypertension among children. This should assist in reducing the future incidence of heart disease, thus being a potential benefactor to the children themselves, parents, teachers, health care providers, along with health programming and policy experts. Heart disease is the number one cause of death in Canada and by early identification of the issue, the future health of our nation can hopefully be protected.

SECTION D – THE INFORMED CONSENT PROCESS

17. **The Consent Process:**

Describe the process that the investigator(s) will be using to obtain informed consent. Include a description of who will be obtaining the informed consent. If there will be no written consent form, explain why not.

For information about the required elements in the letter of invitation and the consent form, as well as samples, please refer to:
http://www.brocku.ca/researchservices/Certification&Polices/Certification&Polices_App_Guidelines.html

If applicable, attach a copy of the Letter of Invitation, the Consent Form, the content of any telephone script, and any other material that will be utilized in the informed consent process.

An initial letter of introduction and informed consent will be sent home with all children in grades 6, 7 and 8 at the beginning of the study, from all selected schools, to be signed by the parent or legal guardian and the child him/herself and returned to the school *(already approved – REB # 06-315 to Terrance Wade)*. For the lab component, randomly selected families stratified across blood pressure group, aggregate community-level SES and urbanicity will be mailed a package providing a letter of introduction inviting them to participate in the lab component of the study. We will follow up the letter with a telephone call to answer any questions, ask for their approval, and arrange a time to come to the lab. Upon coming to the lab, the child and their parent will be asked to read an information sheet on the study and sign a consent form (Appendix A).

18. **Consent by an authorized party:**

If the participants are minors or for other reasons are not competent to consent, describe the proposed alternative source of consent, including any permission form to be provided to the person(s) providing the alternative consent.

The parent and child will sign the consent form, and the student will be asked to give verbal assent at the time of the actual data collection.

19. **Alternatives to prior individual consent:**

If obtaining individual participant consent prior to commencement of the research project is not appropriate for this research, please explain and provide details for a proposed alternative consent process.

N/A

20. **Feedback to Participants:**

Explain what feedback/ information will be provided to the participants after participation in the project. Include, for example, a more complete description of the purpose of the research, and access to the results of the research. Also, describe the method and timing for delivering the feedback.

Participants and their parents will have access to their own data if they are interested by contacting the researchers. They will also have access to group data when it becomes available through a feedback report sent to participating schools describing the main findings of the research.

21. **Participant withdrawal:**

a) Describe how the participants will be informed of their right to withdraw from the project. Outline the procedures that will be followed to allow the participants to exercise this right.

The letter of introduction and informed consent will make it known to both the parent and child that they can opt not to participate at no risk, cost, or negative impact. As well, it will be made known at the time of measurement that each child can choose not to participate in any or all tests if they so choose.

b) Indicate what will be done with the participant's data and any consequences that withdrawal might have on the participant, including any effect that withdrawal may have on participant compensation.

If a parent or child refuses to participate in any specific test, the research assistant will proceed to the next test. If a parent or student chooses to withdraw completely from the study at any time, their complete data will be removed and deleted from the electronic database. We will keep their consent form on file. If they visit the lab at Brock and, after signing the consent form, begin the testing, they will receive the promised honorarium regardless of whether they choose to complete any or all testing protocols.

SECTION E – CONFIDENTIALITY & ANONYMITY

***Confidentiality*:** information revealed by participants that holds the expectation of privacy. This means that all data collected will not be shared with anyone except the researchers listed on this application.

***Anonymity of data*:** information revealed by participants will not have any distinctive character or recognition factor, such that information can be matched **(even by the researcher)** to individual participants. Any information collected using audio-taping, video recording, or interview cannot be considered anonymous. **Please note that this refers to the anonymity of the data itself and not the reporting of results.**

22. Given the definitions above, in the student project(s):

a) Will the data be treated as confidential? [ ] **Yes** [✓] **No**

b) Are the data anonymous? [ ] **Yes** [✓] **No**

c) Describe any **personal identifiers** that will be collected during the course of the research (e.g., participant names, initials, addresses, birth dates, student numbers, organizational names and titles etc.). Indicate how personal identifiers will be secured and if they will be **retained** once data collection is complete.

We will have parent/guardian name, address, and phone number and child name and school name on file. This information will be separated from the data file and linked by an identifying variable only. The identifying information and linking variable will be retained once data collection is complete to facilitate subsequent components of this study, but will be kept separated from the data file by the principal investigator and/or his representative(s).

d) If any personal identifiers will be **retained** once data collection is complete, provide a comprehensive rationale explaining why it is necessary to retain this information, **including the retention of master lists that link participant identifiers with unique study codes and de-identified data.**

This study will be conducted in a series of phases including a population screen, a detailed laboratory component, and the development, implementation, and evaluation of interventions. ***In this REB application, we are asking for approval for the laboratory component of the study only.*** At the time in which the protocol for each subsequent phase is finalized, we will seek REB consent at that time. As such, we will keep the personal identifying information that we collect from the lab component to facilitate direct contact with participants for future involvement in subsequent aspects of this study and for linking with subsequent data collection efforts.

e) State who will have access to the data.

The de-identified data will be available to all researchers named in the project and their representatives including employees hired for the project, along with graduate and undergraduate research assistants. All persons who access to identifiable data other than the named researchers will sign a confidentiality agreement with the Principal Investigator. Other students may be given access to the de-identified data for research and thesis projects as approved by the investigative team. Community service partners will have access to aggregate results of the de-identified data but not to the individual level data itself. Participants and their parents will have access to their own data if they are interested by contacting the researchers.

f) Describe the procedures to be used to ensure anonymity of participants and/or confidentiality of data **both during the conduct of the research and in the release of its findings.**

All results that are to be publicly released will be done so only in aggregate form and will not identify specific individuals or families.

g) If participant anonymity and/or confidentiality is not appropriate to this research project, explain, in detail, how all participants will be advised that data will not be anonymous or confidential.

N/A

h) Explain how written records, video/audio tapes, and questionnaires will be secured, and provide details of their final disposal or storage, including how long they will be secured and the disposal method to be used.

All paper data will be stored in a locked filing cabinet in a secure research lab that is alarmed. Access to the lab is monitored and restricted to approved personnel only. All data will be secured and stored for 7 years after the study. After this time, documents will be destroyed using a shredding machine/service.

SECTION F -- SECONDARY USE OF DATA

23. a) Is it your intention to reanalyze the data for purposes other than described in this application? [✓] **Yes** [ ] **No**

b) Is it your intention to allow the study and data to be reanalyzed by colleagues, students, or other researchers outside of the original research purposes? If this is the case, explain how you will allow your participants the opportunity to choose to participate in a study where their data would be distributed to others (state how you will contact participants to obtain their re-consent)

Participants will be informed on the consent form that their electronic data will be kept for further analysis beyond the original purposes of the study. They will be asked to provide informed signed consent of this to approve or deny the future use of their data beyond this study. They will also be informed that they have the option at any time to request that their individual data be removed from any and all subsequent analyses beyond the date in which they make this request.

If there are no plans to reanalyze the data for secondary purposes and, yet, you wish to keep the data indefinitely, please explain why.

N/A

SECTION G -- MONITORING ONGOING RESEARCH

24. **Annual Review and Serious Adverse Events (SAE):**

a) Minimum review requires the completion of a "Renewal/Project Completed" form at least annually. Indicate whether any additional monitoring or review would be appropriate for this project.

It is the investigator's responsibility to notify the REB using the "Renewal/Project Completed" form, when the project is completed or if it is cancelled.
http://www.brocku.ca/researchservices/Forms/Forms.html

Additional review of the overall project and the subsequent data collection phases will be submitted to the REB as appropriate as indicated above.

***Serious adverse events** (unanticipated negative consequences or results affecting participants) **must be reported** to the Research Ethics Officer and the REB Chair, **as soon as possible** and, in any event, no more than 3 days subsequent to their occurrence.

25. **COMMENTS**

If you experience any problems or have any questions about the Ethics Review Process at Brock University, please feel free to contact the Research Ethics Office at (905) 688-5550 ext 3035, or reb@brocku.ca

FROM: Linda Rose-Krasnor, Acting Chair
Research Ethics Board (REB)

TO: Terrance Wade, Community Health Sciences
Paul Leblanc, Deborah O'Leary

FILE: 07-060 - WADE

DATE: October 1, 2007

The Brock University Research Ethics Board has reviewed the research proposal:

Social Determinants of Child Hypertension

The Research Ethics Board finds that your proposal requires clarification: The researcher may proceed with the work as soon as the following issue(s) have been addressed and received clearance by the Board:

Section A – General Information
5 – Other Ethics Approval/Permission
· Please forward approval from the NCDSB once it has been obtained.
***This approval will be sought upon receiving Brock University Ethics approval*

Section D – The Informed Consent Process
Consent form
· Please explain the Tanner stage instrument and how it will be administered. Will parents be present?
***The Tanner Stage instrument has been removed. In its place, skeletal maturity assessment has been added. This is a non-invasive procedure using the Sunlight BonAge™ System (Sunlight Medical, Ltd, Tel Aviv, Israel) to determine skeletal age.*

This protocol has previously been approved in: REB 04-419 to Deborah O'Leary
***please see attachment entitled 'Overview of Lab Visit and Testing Procedures', body composition paragraph*

Parents will be invited to be present for all testing during the lab visit.

18 – Consent by an authorized party
· Please clarify the verbal assent process and provide a script or guideline for obtaining verbal assent.
***please see attachment entitled 'HBeat Verbal Assent Guidelines' for a detailed outline of the telephone script for obtaining verbal assent.*

***As well, please see attachment entitled 'HBeat Consent Form' for the consent form that parents and children will read and sign in the lab prior to testing that will again detail the lab tests and testing protocol.*

· Please add a statement to all participant materials that advises parents to keep a copy for their own records.

***please see attachment entitled 'Information Letter to Parents', paragraph three.*

***As well, we will provide them with a copy of the consent form at their lab visit.*

20 – Feedback to Participants

· In your application, you state that parents may access their individual child's results by contacting the researchers. This information should appear in the consent form. What explanation would accompany these results? Please make it clear to parents that results are not diagnostic.

***please see attachment entitled 'Information and Consent' for this information.*

For each point of clarification, please highlight the changes you have made on the corresponding documents.

If you would like further information or assistance in responding to these clarification requests, please contact Lori Walker (ext. 4876) in the Research Services Office.

No research with Human Participants will commence prior to receiving ethics clearance from this board.

Appendix B
Parental Information form

FACULTY OF APPLIED HEALTH SCIENCES • 905.688.5550 • www.brocku.ca/fahs/

Dr. Terrance Wade • ext 4146 • twade@brocku.ca
Dr. Deborah O'Leary • ext 4339 • doleary@brocku.ca
Dr. Paul LeBlanc • ext 4216 • pleblanc@brocku.ca

Dear Parents and Guardians:

Recently you were contacted by **HBeat** (Heart Behavioural Environmental Assessment Team) regarding your child being randomly chosen to participate in the second phase of the research study to examine high blood pressure (hypertension). Thank you for volunteering to participate in the second phase of the study! As we discussed, you and your child likely already completed some questionnaires that were sent home from school for the first phase of the study. At school, your child also had their blood pressure, height, weight, hip and waist circumference measured and completed some questionnaires about their physical activity.

For this phase of the study, the testing will take place at Brock University. The total testing should take about 1½ hours. We ask that the parent/ guardian is present for at least the first half-hour. Your child will receive $20 as a token of our appreciation for you and your child's participation in this phase of the study.

Although we already discussed some of this information over the phone, we ask that you read the attached information form detailing the visit and testing procedures that will be done (Overview of Lab Visit and Testing Procedures), and keep the information for your records.

Some factors such as food, exercise and temperature, may affect the lab tests. Therefore, we ask that your child does not eat or drink anything except water once they go to bed the night before testing. We will provide your child with an allergy-sensitive meal that morning. We also ask that your child avoids caffeine (for example, coffee, tea, cola) and refrains from exercise the morning of testing. Finally, your child should either be dressed in athletic attire (shorts, t-shirt, or tank top and running shoes) or bring these clothes to the testing session.

At the beginning of your visit to Brock University, we will go over the lab procedure and you will have an opportunity to ask any questions related to the tests. Once you are satisfied, we will have you and your child sign a consent form to allow your child to participate in this phase of the HBeat research study.

This study has been reviewed and approved by the Research Ethics Boards from both Brock University and the Niagara Catholic District School Board. If you have any questions about the study or lab testing procedures, please contact Dr. Deborah O'Leary at 905-688-5550 (x4339), Dr. Paul LeBlanc at 905-688-5550 (x4216), or Dr. Terrance Wade at 905-688-5550 (x4146). If you have any further questions regarding your rights as a research participant, contact the Research Ethics Officer in the Office of Research Services at (905) 688-5550 (x3035) or email at reb@brocku.ca.

We are very grateful that you and your child have agreed to take part in this important study. Thank you for your time.

Sincerely,

Terrance J. Wade, Ph.D. Deborah O'Leary, Ph.D. Paul LeBlanc, Ph.D.

[1] **Principal Investigators:** Dr. Terrance J. Wade • Dr. Deborah O'Leary • Dr. John Cairney
Co-Investigators: Dr. Paul LeBlanc • Dr. Jian Liu • Dr. Colleen Hood • Dr. John Hay • Dr. Panagiota Klentrou • Dr. Brian Roy • Dr. Dawn Zinga • Dr. Kevin Shoemaker

[2] **File 06-315 WADE:** Research Services • Brock University • Room C315 • 905.688.5550 ext 4315

Appendix C
Informed Consent and Data Package

SOCIAL DETERMINANTS OF CHILD HYPERTENSION

Your child _____ is invited to participate in a research study being conducted by the investigators listed below. Prior to participating in this study you are asked to read and sign this form, which outlines the purpose and gives a detailed description of the testing procedures used in the study. The testing procedures will be conducted at Brock University.

Primary Investigators	Department	Phone	Email
Dr. Terrance J. Wade	Community Health Sciences	(905) 688-5550 x4146	twade@brocku.ca
Dr. Deborah O'Leary	Community Health Sciences	(905) 688-5550 x4339	doleary@brocku.ca
Dr. Paul LeBlanc	Community Health Sciences	(905) 688-5550 x4216	pleblanc@brocku.ca

PURPOSE

Adults in Canada and the United States have a 90% lifetime risk of developing high blood pressure, also known as hypertension. High blood pressure (HBP) is one of the strongest predictors of heart disease. Some scientists suggest that HBP may start in childhood, but we do not know what factors may be involved. This study will help us learn what factors may contribute to childhood hypertension. If we can learn what these factors are, we might be able to offer suggestions to families, schools, and communities to improve the heart health of children. This knowledge could help all children in Canada lead healthier lives and reduce their chance of having heart disease as adults.

OVERVIEW OF LAB VISIT

Upon arrival at Brock University, you and your child will be familiarized with the laboratory and the testing procedures will be explained. Once you are satisfied with the explanation of the testing procedures, you and your child will then be asked to read the information sheet about the study and sign the consent form. If your child is not already wearing athletic attire, she/he will be asked to change in the washroom.

The testing will begin with the child's blood test using a finger prick to obtain two or three drops of blood for analysis. Following this, your child will be given an allergy sensitive breakfast before any further testing.

After they have finished breakfast, they will also be asked to empty their bladder, as this has been shown to have an effect on blood pressure. Before testing blood pressure, your child will be in a sitting position for 15 minutes. Then their blood pressure will be taken using an automatic blood pressure monitor (the same unit that was previously used in school to measure your child's blood pressure).

Next, your child's weight, height, skinfold thickness, waist circumference, hip circumference, and skeletal maturity will be recorded. Finally, the child will lie down and have her/his heart rate monitored and have their heart and right carotid artery (artery in the neck) imaged using Doppler ultrasound (the same type of ultrasound seen in a hospital). At the end of testing, your child will receive $20 as a token of our appreciation for your involvement in the study.

Parents are more than welcome to be present for testing.

OVERVIEW OF TESTING PROCEDURES

The following procedures are described in further detail below:

Blood Analysis

Blood Pressure Measurement

Body Composition

Heart Rate

Carotid Artery and Heart Ultrasound

TESTING PROCEDURES

Blood Analysis
Finger pinprick blood sampling - The middle finger of the non-dominant hand (e.g. if right handed, the middle finger of the left hand will be used) will be pricked so two drops of blood can be sampled. They will feel the small prick but will not feel any pain or discomfort for the remainder of the sampling. The tip of that finger may feel sensitive and a little bit sore for about a day. It is important to keep the site clean and covered with an adhesive bandage until it is healed (up to 24 hours) to minimize any risk of infection.

Blood Pressure
Blood pressure is monitored using a non-invasive method. The method involves an automated arm cuff system that is similar to the method used in a doctor's office. A cuff is wrapped around the upper arm and is inflated then deflated. After sitting in a resting position for 15 minutes, the child will have their blood pressure taken automatically, 6 times in 1 minute intervals. No risk is involved.

Body Composition
All body composition measures will take place behind a portable curtain for privacy with the parent present if desired. Height, weight, hip and waist circumference will be measured. Skinfold thickness will be assessed using a non-invasive method that measures skin thickness. The tester pinches the skin at the appropriate site to raise a double layer of skin and the underlying adipose tissue, but not the muscle. The calipers are then applied at right angles to the pinch and a reading is taken. Skinfold measures will be taken at two sites including the subscapular (lower shoulder blade) and triceps (back of the upper arm). No risk is involved. Next, your child's forearm, lower leg and wrist will be measured using Doppler ultrasound to gauge skeletal maturity. The ultrasound technique used is completely non-invasive and similar to that used to visualize the development of a baby during pregnancy. Again, no risk is involved.

Heart Rate
Heart rate will be measured using sensors placed on the skin of your child's upper chest. These sensors are electrodes used to detect the electrical activity generated by the heart and do not transmit electrical signals into the body from the heart rate monitor. No risk is involved.

Carotid Artery and Heart Ultrasound
All carotid artery and heart ultrasound measures will be taken in a lying position in a private room. In addition to the ultrasound previously mentioned, two more ultrasound measures will be performed. First, the carotid artery ultrasound will be performed using a small transducer to visualize the carotid artery. As well, carotid artery blood pressure will be simultaneously obtained using a thin pen-like device that is lightly pressed against the neck. Both the probe and pen like-device will be pressed against the neck on opposite sides. It is a non-invasive procedure. Second, the ultrasound of the heart will be performed with a small probe placed between your child's ribs on the left side of their chest. This procedure is also non-invasive and no risk is involved.

POTENTIAL RISKS AND DISCOMFORTS

Please refer to the "Testing Procedures" previously mentioned for a complete description of the procedures to be performed during the study and the potential risks associated with these procedures. If an injury occurs at any time during the investigation, appropriate first aid/CPR will be administered and you will be advised to seek necessary medical help.

BENEFITS AND REMUNERATION

A potential benefit for your child's participation in this project is the knowledge of their blood pressure, heart and artery assessment, as well as any underlying cardiovascular disease risk factors. Your child will also be reimbursed $20 as a token of our appreciation for you/your child's involvement in the study.

CONFIDENTIALITY

All data collected during this study will remain confidential and stored in offices and on secured computers to which only the principal investigators, co-investigators, project coordinator, and research assistants will have access. The electronic file containing your answers and body measurements will only contain a unique identification number and no other identifying information to ensure your information is completely anonymous. You should be aware that the results of this study will be made available to the scientific community, through publication in scientific journals; however, we will only use the combined data from families so that no single child or family can be identified. You will have access to your child's data, as well as the group data when it becomes available and if you are interested. Please contact the researchers directly if you wish to obtain this information.

PARTICIPATION AND WITHDRAWAL

You can choose whether your child participates in this study or not. You may exercise the option of removing your child's data from the study if you wish. You may also refuse to answer any questions posed to you and/or your child during the study and still remain as a participant in the study. The investigators reserve the right to withdraw your child from the study if they believe that circumstances have arisen which warrant doing so.

RIGHTS OF RESEARCH PARTICIPANTS

You may withdraw your consent to participate in this study at any time, and you may also discontinue the participation of your child at any time without penalty. In signing this consent form or in participating in this study you are not waiving any legal claims or remedies. This study has been reviewed and received clearance from the Brock University Research Ethics Board (File 07-060 - WADE). If you have any further questions regarding your rights as a research participant contact the Research Ethics Officer in the Office of Research Services at (905) 688-5550 x3035 or email at reb@brocku.ca.

INFORMATION

Please contact Dr. Deborah O'Leary at 905-688-5550 (x4339), Dr. Paul LeBlanc at 905-688-5550 (x4216) or Dr. Terrance Wade at 905-688-5550 (x4146) if you have any questions about the study.

I have read and understand the above explanation of the purpose and procedures of the project and I am aware of the potential risks and my rights as a research participant. I understand that I can gain access to my child's individual results by contacting the researchers, and I understand that these results are not a clinical diagnosis. My questions have been answered to my satisfaction and I agree to allow my child to participate in this study.

CONSENT FORM	
☐ I do give permission for my child to participate in the Brock University HBeat lab component conducted by Dr. Terrance J. Wade, Dr. Deborah O'Leary and Dr. Paul LeBlanc.	
☐ I do not give permission for my child to participate in the Brock University HBeat lab component conducted by Dr. Terrance J. Wade, Dr. Deborah O'Leary and Dr. Paul LeBlanc.	
Signature of Parent/Guardian:	Date:
Printed Name of Parent/Guardian:	
Signature of Student:	Date:
Printed Name of Student:	

In addition to the current study, data collected may be used later to answer other research questions that may arise from this study. We would like your permission to keep the information that you and your child provided on file after this research study is over. All stored personal data will be kept strictly confidential and all information will be coded so that no one will be able to identify you or your child. At any time, you can ask to have your information removed and not included in any future projects by contacting Dr. Terrance J. Wade (905-688-5550 ext 4146) or Dr. Deborah O'Leary (905-688-5550 ext 4339).

☐ I do give permission to have my information and my child's information stored to use to answer future research questions after the HBeat study is over.	
☐ I do not give permission to have my information and my child's information stored to use to answer future research questions after the HBeat study is over.	
Signature of Parent/Guardian:	Date:
INVESTIGATOR	
In my judgment the participant is voluntarily and knowingly giving informed consent and possesses the legal capacity to give informed consent and participate in this research study.	
Signature of Investigator:	Date:

Appendix D
Participant Information

LABORATORY INFORMATION SHEET

Date: _____ Time (am/pm): _____

SECTION 1: STUDENT INFORMATION			
Student ID#:	**Name:**		
Gender:	**DOB**(mmddyyyy)**:**		**Age:**
Allergies:	**Medications:**		
Medical Concerns:			
Height: _____ **cm**	**Sitting Height:** _____ **(-74) =** _____ **cm**	**Weight:** _____ **kg**	**BMI:** _____ **(kg/m²)**

SECTION 2: QUESTIONNAIRES and CONSENTS	
STUDENT	**PARENT**
1. Consent (signed): Y N	1. Consent (signed): Y N
2. Current Med History: Y N	2. Missing Data (PQ & CQ), Sleep Questionnaire: Y N

SECTION 3: BLOOD ANALYZER	
Cholestech LDX StIcker	**Notes: (Please note any changes to protocol, problems during testing, other circumstances that would hinder test results)**

SECTION 4: BONE ULTRASOUND AND AUTOMATIC BLOOD PRESSURE

Bone age:_____ years	Note: Non-dominant arm only

Blood Pressure (SBP/DBP) **Right Arm Only (if errors occur, take an additional reading)**

2. 3. 4. 5. 6.

SECTION 5: BODY COMPOSITION MEASURES

Examiner:

Waist Circumference	**Hip Circumference**
Trial #1: _____ **cm**	Trial #1: _____ **cm**
Trial #2: _____ **cm**	Trial #2: _____ **cm**

Waist : Hip Ratio

_____ : _____ **cm**

Skinfold Measurements

Examiner:

SITE	**TRIAL 1 (mm)**	**TRIAL 2 (mm)**	**TRIAL 3 (>1mm)**	**MEDIAN (mm)**
SUBSCAPULAR				
TRICEPS				

SUM OF SKIN FOLDS: _____ **(mm)**	PERCENT BODY FAT: _____ **(%)**
1. Have you had your period?: Y N	2. How old were you when you first had your period?: _____ yrs
3. How often do you get periods?: _____ days	4. How long does your period last for?: _____ days

SECTION 6: ARTERIAL MEASUREMENTS

Doppler Settings

Examiner:

Frequency: 10.0 mHz	Power: 0 dB	Persistence: turn to minimum
Depth: _____ **cm**	FPS: change focus # (decrease to 2) to increase fps	

Blood Pressure (SBP/DBP)

Pre 1		**Post 1**	
2		**2**	
3		**3**	

Arterial Measurements	
Systolic Diameter: _____ **mm**	Compliance:
Diastolic Diameter: _____ **mm**	Distensibility:
Diameter Change: _____ **mm**	CaPP: _____ **mmHg**
Baroreflex Sensitivity: _____ **ms/mmHg**	Mean HR: _____ **bpm**
Distance Measurements	
Sternal notch to toe: _____ **cm**	Sternal notch to carotid: _____ **cm**
Notes for Cardiovascular Component	

SECTION 7: LEFT VENTRICULAR MASS MEASUREMENTS

Examiner:

Probe: _____	Depth: _____ **cm**
B-Mode Images:	M-Mode Images:
Interventricular Septum (end-distole): _____ **cm**	Ejection Fraction: _____ **%**
Left Ventricular Diameter (end-diastole): _____ **cm**	Circumferential Fiber Shortening: _____ **%**
Left Posterior Wall (end-diastole): _____ **cm**	Stroke Volume: _____ **ml**
End Diastole Volume: _____ **ml**	Left Ventricular Mass: _____ **g**
End Systole Volume: _____ **ml**	Left Ventricle Mass Indexed by BSA: _____ **g/m2**
	Left Ventricle Mass Indexed by HT: _____ **g/m2.7**
Notes: Please note any changes to protocol, problems during testing, medical conditions that would hinder test results	

Appendix E

Years from Peak Height Velocity Equations

Peak Height Velocity Equations

Boys predictive equation: (Eq. 3) Maturity Offset = -9.236 + 0.0002708·Leg Length and Sitting Height interaction -0.001663·Age and Leg Length interaction + 0.007216·Age and Sitting Height interaction + 0.02292·Weight by Height ratio
Where R = 0.94, R^2 = 0.891, and SEE = 0.592

Girls predictive equation: (Eq. 4) Maturity Offset = -9.376 + 0.0001882·Leg Length and Sitting Height interaction + 0.0022·Age and Leg Length interaction + 0.005841·Age and Sitting Height interaction -0.002658·Age and Weight interaction + 0.07693·Weight by Height ratio
Where R=0.94, R^2=0.890, and SEE = 0.569.

Mirwald RL, Baxter-Jones ADG, Bailey DA, Beunen GP. (2002). An assessment of maturity from anthropometric measurements. Medicine & Science in Sports & Exercise, 34(4), 689-694

Appendix F

BP Levels for Boys and Girls by Age and Height Percentile

BP Levels for Boys by Age and Height Percentile

Age (years)	BP Percentile	SBP (mmHg) Percentile of Height						
		5th	10th	25th	50th	75th	90th	95th
11	50th	99	100	102	104	105	107	107
	90th	113	114	115	117	119	120	121
	95th	117	118	119	121	123	124	125
	99th	124	125	127	129	130	132	132
12	50th	101	102	104	106	108	108	110
	90th	115	116	118	120	121	123	123
	95th	119	120	122	123	125	127	127
	99th	126	127	129	131	133	134	135
13	50th	104	105	106	108	110	111	112
	90th	117	118	120	122	124	125	126
	95th	121	122	124	126	128	129	130
	99th	128	130	131	133	135	136	137
14	50th	106	107	109	111	113	114	115
	90th	120	121	123	125	126	128	128
	95th	124	125	127	128	130	132	132
	99th	131	132	134	136	138	139	140

Age (years)	BP Percentile	DBP (mmHg) Percentile of Height						
		5th	10th	25th	50th	75th	90th	95th
11	50th	59	59	60	61	62	63	63
	90th	74	74	75	76	77	78	78
	95th	78	78	79	80	81	82	82
	99th	86	86	87	88	89	90	90
12	50th	59	60	61	62	63	63	64
	90th	74	75	75	76	77	78	79
	95th	78	79	80	81	82	82	83
	99th	86	87	88	89	90	90	91
13	50th	60	60	61	62	63	64	64
	90th	75	75	76	77	78	79	79
	95th	79	79	80	81	82	83	83
	99th	87	87	88	89	90	91	91
14	50th	60	61	62	63	64	65	65
	90th	75	76	77	78	79	79	80
	95th	80	80	81	82	83	84	84
	99th	87	88	89	90	91	92	92

* The 90th percentile is 1.28 SD, the 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

BP Levels for Girlss by Age and Height Percentile

Age (years)	BP Percentile	SBP (mmHg) Percentile of Height						
		5th	10th	25th	50th	75th	90th	95th
11	50th	100	101	102	103	105	106	107
	90th	114	114	116	117	118	119	120
	95th	118	118	119	121	122	123	124
	99th	125	125	126	128	129	130	131
12	50th	102	103	104	105	107	108	109
	90th	116	116	117	119	120	121	122
	95th	119	120	121	123	124	125	126
	99th	127	127	128	130	131	132	133
13	50th	104	105	106	107	109	110	110
	90th	117	118	119	121	122	123	124
	95th	121	122	123	124	126	127	128
	99th	128	129	130	132	133	134	135
14	50th	106	106	107	109	110	111	112
	90th	119	120	121	122	124	125	125
	95th	123	123	125	126	127	129	129
	99th	130	131	132	133	135	136	136

Age (years)	BP Percentile	DBP (mmHg) Percentile of Height						
		5th	10th	25th	50th	75th	90th	95th
11	50th	60	60	60	61	62	63	63
	90th	74	74	74	75	76	77	77
	95th	78	78	78	79	80	81	81
	99th	85	85	86	87	87	88	89
12	50th	61	61	61	62	63	64	64
	90th	75	75	75	76	77	78	78
	95th	79	79	79	80	81	82	82
	99th	86	86	87	88	88	89	90
13	50th	62	62	62	63	64	65	65
	90th	76	76	76	77	78	79	79
	95th	80	80	80	81	82	83	83
	99th	87	87	88	89	89	90	91
14	50th	63	63	63	64	65	66	66
	90th	77	77	77	78	79	80	80
	95th	81	81	81	82	83	84	84
	99th	88	88	89	90	90	91	92

* The 90th percentile is 1.28 SD, the 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics* 2004;114(2):555-76.

Appendix G
Statistical Output

Descriptives of Children Within Each BP Category

0 = high BP 1= normal BP		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
Sex (M/F)	0	85	.3412	.47692	.05173	.2383	.4440	.00	1.00
	1	21	.4762	.51177	.11168	.2432	.7091	.00	1.00
	Total	106	.3679	.48453	.04706	.2746	.4612	.00	1.00
Age (years)	0	85	12.7637	.81889	.08882	12.5871	12.9404	11.21	14.34
	1	21	13.0564	.91345	.19933	12.6406	13.4722	11.58	14.49
	Total	106	12.8217	.84210	.08179	12.6595	12.9839	11.21	14.49
Height (cm)	0	85	157.9812	9.28567	1.00717	155.9783	159.9840	134.00	174.50
	1	21	160.5524	9.42595	2.05691	156.2617	164.8430	142.30	177.10
	Total	106	158.4906	9.32538	.90576	156.6946	160.2865	134.00	177.10
Weight (kg)	0	85	49.7035	11.93021	1.29401	47.1302	52.2768	28.50	94.00
	1	21	68.6048	21.53250	4.69878	58.8033	78.4062	38.50	124.60
	Total	106	53.4481	16.10819	1.56457	50.3459	56.5504	28.50	124.60
BMI (kg/m^2)	0	85	19.7531	3.57676	.38795	18.9816	20.5245	14.01	32
	1	21	26.3871	7.1362	1.55725	23.1388	29.6355	17.11	41.92
	Total	106	21.0674	5.19548	.50463	20.0668	22.0679	14.01	41.92
PHV (years)	0	85	-1.7080	.80756	.08759	-1.8822	-1.5338	-4.19	-.01
	1	21	-1.6800	1.04358	.22773	-2.1551	-1.2050	-3.18	.65
	Total	106	-1.7025	.85399	.08295	-1.8669	-1.5380	-4.19	.65
SBP (mmHg)	0	85	90.7725	5.00845	.54324	89.6923	91.8528	81.67	106.00
	1	21	110.1429	6.11198	1.33374	107.3607	112.9250	98.83	125.33
	Total	106	94.6101	9.34656	.90782	92.8100	96.4101	81.67	125.33
DBP (mmHg)	0	85	55.1431	4.77857	.51831	54.1124	56.1739	46.00	64.50
	1	21	70.8810	5.38443	1.17498	68.4300	73.3319	58.17	81.67
	Total	106	58.2610	7.96945	.77406	56.7262	59.7958	46.00	81.67

MAP (mmHg)	0	85	67.0196	4.38267	.47537	66.0743	67.9649	59.22	77.67
	1	21	83.9683	4.84973	1.05830	81.7607	86.1758	74.33	94.17
	Total	106	70.3774	8.11885	.78857	68.8138	71.9410	59.22	94.17
RRI	0	85	807.6956	96.96434	10.51726	786.7809	828.6104	554.41	1059.45
	1	21	715.1654	93.42623	20.38727	672.6382	757.6925	583.12	978.40
	Total	106	789.3642	102.74900	9.97987	769.5759	809.1524	554.41	1059.45
Pulse Pressure	0	85	34.6705	5.04592	.54731	33.5821	35.7589	21.33	48.33
	1	21	39.8814	8.13981	1.77625	36.1762	43.5866	24.67	56.33
	Total	106	35.7028	6.11099	.59355	34.5259	36.8797	21.33	56.33
LF RRI	0	85	730.4086	520.07809	56.41039	618.2303	842.5868	1.78	2650.48
	1	21	448.9332	329.74437	71.95612	298.8353	599.0310	85.25	1220.19
	Total	106	674.6446	499.80211	48.54507	578.3887	770.9005	1.78	2650.48
HF RRI	0	85	908.7187	959.86239	104.11169	701.6812	1115.7562	7.48	7215.56
	1	21	455.2583	580.88155	126.75875	190.8442	719.6724	29.32	2495.86
	Total	106	818.8822	913.40987	88.71821	642.9704	994.7940	7.48	7215.56
Total Power RRI	0	85	1612.1574	1343.17525	145.68781	1322.4412	1901.8736	9.26	9008.47
	1	21	904.1915	787.30525	171.80409	545.8144	1262.5685	124.65	3101.76
	Total	106	1471.9000	1281.30638	124.45148	1225.1357	1718.6643	9.26	9008.47
LF/HF RRI	0	85	1.0736	.74294	.08058	.9134	1.2339	.21	3.94
	1	21	1.6431	.99718	.21760	1.1891	2.0970	.24	3.90
	Total	106	1.1865	.82642	.08027	1.0273	1.3456	.21	3.94
LF/TP RRI	0	85	.4712	.14358	.01557	.4402	.5021	.17	.80
	1	21	.5684	.16198	.03535	.4947	.6421	.20	.80
	Total	106	.4904	.15168	.01473	.4612	.5196	.17	.80
HF/TP RRI	0	85	.5288	.14358	.01557	.4979	.5598	.20	.83
	1	21	.4316	.16198	.03535	.3579	.5053	.20	.80
	Total	106	.5096	.15168	.01473	.4804	.5388	.20	.83
LF SBP	0	85	5.0979	4.25177	.46117	4.1808	6.0150	.69	22.83
	1	21	7.5945	4.85814	1.06013	5.3831	9.8059	.25	21.39
	Total	106	5.5925	4.46734	.43391	4.7322	6.4529	.25	22.83
HF SBP	0	85	1.5351	1.28327	.13919	1.2583	1.8119	.13	8.53

	1	21	1.3450	.91689	.20008	.9277	1.7624	.08	4.55
	Total	106	1.4974	1.21793	.11830	1.2629	1.7320	.08	8.53
Total Power SBP	0	85	6.6330	5.10344	.55355	5.5322	7.7338	1.00	28.25
	1	21	8.9395	5.34582	1.16655	6.5061	11.3729	.33	23.36
	Total	106	7.0900	5.20891	.50593	6.0868	8.0931	.33	28.25
LF/HF SBP	0	85	3.9613	2.60284	.28232	3.3999	4.5227	.65	13.47
	1	21	6.4974	3.90718	.85262	4.7189	8.2759	2.43	15.06
	Total	106	4.4637	3.05927	.29714	3.8746	5.0529	.65	15.06
LF/TP SBP	0	85	.7397	.13094	.01420	.7114	.7679	.39	.93
	1	21	.8322	.07466	.01629	.7982	.8662	.71	.94
	Total	106	.7580	.12709	.01234	.7335	.7825	.39	.94
HF/TP SBP	0	85	.2603	.13094	.01420	.2321	.2886	.07	.61
	1	21	.1678	.07466	.01629	.1338	.2018	.06	.29
	Total	106	.2420	.12709	.01234	.2175	.2665	.06	.61
LF Gain SBP	0	85	15.1245	6.78911	.73638	13.6601	16.5888	1.51	35.71
	1	21	10.5212	6.81796	1.48780	7.4177	13.6247	1.88	31.64
	Total	106	14.2125	7.00901	.68077	12.8626	15.5623	1.51	35.71
HF Gain SBP	0	85	22.7787	11.44342	1.24121	20.3104	25.2470	3.25	61.68
	1	21	15.9607	9.43837	2.05962	11.6644	20.2570	5.05	37.83
	Total	106	21.4280	11.36594	1.10396	19.2390	23.6169	3.25	61.68

ANOVA for Children Within BP Categories

		Sum of Squares	df	Mean Square	F	Sig.
Sex (M/F)	Between Groups	.307	1	.307	1.311	.255
	Within Groups	24.344	104	.234		
	Total	24.651	105			
Age (years)	Between Groups	1.442	1	1.442	2.054	.155
	Within Groups	73.017	104	.702		
	Total	74.459	105			

Height (cm)	Between Groups	111.328	1	111.328	1.284	.260
	Within Groups	9019.762	104	86.728		
	Total	9131.091	105			
Weight (kg)	Between Groups	6016.066	1	6016.066	29.473	.000
	Within Groups	21228.678	104	204.122		
	Total	27244.745	105			
BMI (kg/m^2)	Between Groups	741.130	1	741.130	36.824	.000
	Within Groups	2093.137	104	20.126		
	Total	2834.267	105			
PHV (years)	Between Groups	.013	1	.013	.018	.894
	Within Groups	76.563	104	.736		
	Total	76.576	105			
SBP (mmHg)	Between Groups	6318.375	1	6318.375	230.224	.000
	Within Groups	2854.230	104	27.445		
	Total	9172.605	105			
DBP (mmHg)	Between Groups	4170.818	1	4170.818	173.648	.000
	Within Groups	2497.961	104	24.019		
	Total	6668.779	105			
MAP (mmHg)	Between Groups	4837.293	1	4837.293	241.417	.000
	Within Groups	2083.854	104	20.037		
	Total	6921.146	105			
RRI	Between Groups	144178.357	1	144178.357	15.549	.000
	Within Groups	964344.222	104	9272.541		
	Total	1108522.579	105			
Pulse Pressure	Between Groups	457.265	1	457.265	13.729	0.000
	Within Groups	3463.881	104	33.307		
	Total	3921.145	105			
LF RRI	Between Groups	1334176.174	1	1334176.174	5.574	.020
	Within Groups	2.490E7	104	239375.475		
	Total	2.623E7	105			
HF RRI	Between Groups	3462670.179	1	3462670.179	4.280	.041

	Within Groups	8.414E7	104	809044.962		
	Total	8.760E7	105			
Total Power RRI	Between Groups	8440284.622	1	8440284.622	5.354	.023
	Within Groups	1.639E8	104	1576375.479		
	Total	1.724E8	105			
LF/HF RRI	Between Groups	5.460	1	5.460	8.571	.004
	Within Groups	66.252	104	.637		
	Total	71.712	105			
LF/TP RRI	Between Groups	.159	1	.159	7.339	.008
	Within Groups	2.257	104	.022		
	Total	2.416	105			
HF/TP RRI	Between Groups	.159	1	.159	7.339	.008
	Within Groups	2.257	104	.022		
	Total	2.416	105			
LF SBP	Between Groups	104.958	1	104.958	5.484	.021
	Within Groups	1990.543	104	19.140		
	Total	2095.502	105			
HF SBP	Between Groups	.608	1	.608	.408	.525
	Within Groups	155.144	104	1.492		
	Total	155.753	105			
Total Power SBP	Between Groups	89.587	1	89.587	3.377	.069
	Within Groups	2759.347	104	26.532		
	Total	2848.934	105			
LF/HF SBP	Between Groups	108.309	1	108.309	12.882	.001
	Within Groups	874.401	104	8.408		
	Total	982.710	105			
LF/TP SBP	Between Groups	.144	1	.144	9.663	.002
	Within Groups	1.552	104	.015		
	Total	1.696	105			
HF/TP SBP	Between Groups	.144	1	.144	9.663	.002
	Within Groups	1.552	104	.015		

	Total	1.696	105			
LF Gain SBP	Between Groups	356.831	1	356.831	7.729	.006
	Within Groups	4801.418	104	46.167		
	Total	5158.249	105			
HF Gain SBP	Between Groups	782.787	1	782.787	6.369	.013
	Within Groups	12781.607	104	122.900		
	Total	13564.394	105			

ANCOVA Tests of Between Subject Effects, Controlling for PHV, Age, BMI, & Sex

Between-Subjects Factors

		N
TwoCatDiag	0	85
	1	21

Tests of Between-Subjects Effects

Dependent Variable: LF RRI

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	3.573E6	5	714616.757	3.154	.011
Intercept	613513.260	1	613513.260	2.708	.103
phv	36982.586	1	36982.586	.163	.687
trueage	957180.652	1	957180.652	4.225	.042
bmi	163562.055	1	163562.055	.722	.398
gender	108408.358	1	108408.358	.478	.491
hype	1961325.043	1	1961325.043	8.657	.004
Error	2.266E7	100	226561.418		
Total	7.447E7	106			
Corrected Total	2.623E7	105			

a. R Squared = .136 (Adjusted R Squared = .093)

Tests of Between-Subjects Effects

Dependent Variable: HF RRI

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	8.809E6	5	1761856.523	2.236	.056
Intercept	2554054.790	1	2554054.790	3.241	.075
phv	442032.155	1	442032.155	.561	.456
trueage	2981573.438	1	2981573.438	3.784	.055
bmi	1081589.566	1	1081589.566	1.373	.244
gender	88971.691	1	88971.691	.113	.738
hype	5739561.400	1	5739561.400	7.284	.008
Error	7.879E7	100	787940.636		
Total	1.587E8	106			
Corrected Total	8.760E7	105			

a. R Squared = .101 (Adjusted R Squared = .056)

Tests of Between-Subjects Effects

Dependent Variable: TP RRI

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	2.166E7	5	4332735.466	2.875	.018
Intercept	5590143.394	1	5590143.394	3.709	.057
phv	963912.154	1	963912.154	.640	.426
trueage	6954761.806	1	6954761.806	4.614	.034
bmi	2362404.574	1	2362404.574	1.567	.214
gender	56655.673	1	56655.673	.038	.847
hype	1.410E7	1	1.410E7	9.356	.003
Error	1.507E8	100	1507196.571		
Total	4.020E8	106			
Corrected Total	1.724E8	105			

a. R Squared = .126 (Adjusted R Squared = .082)

Tests of Between-Subjects Effects

Dependent Variable: LF/HF RRI

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	8.176[a]	5	1.635	2.574	.031
Intercept	.225	1	.225	.354	.553
phv	.200	1	.200	.314	.576
trueage	.046	1	.046	.073	.788
bmi	2.549	1	2.549	4.013	.048
gender	.081	1	.081	.127	.722
hype	1.515	1	1.515	2.384	.126
Error	63.536	100	.635		
Total	220.926	106			
Corrected Total	71.712	105			

a. R Squared = .114 (Adjusted R Squared = .070)

Tests of Between-Subjects Effects

Dependent Variable: LF/TP RRI

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	.190[a]	5	.038	1.707	.140
Intercept	.045	1	.045	2.031	.157
phv	.005	1	.005	.211	.647
trueage	.001	1	.001	.060	.808
bmi	.028	1	.028	1.247	.267
gender	.000	1	.000	.008	.930
hype	.067	1	.067	3.003	.086
Error	2.226	100	.022		
Total	27.912	106			
Corrected Total	2.416	105			

a. R Squared = .079 (Adjusted R Squared = .033)

Tests of Between-Subjects Effects

Dependent Variable: HF/TP RRI

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	.190[a]	5	.038	1.707	.140
Intercept	.033	1	.033	1.488	.225
phv	.005	1	.005	.211	.647
trueage	.001	1	.001	.060	.808
bmi	.028	1	.028	1.247	.267
gender	.000	1	.000	.008	.930
hype	.067	1	.067	3.003	.086
Error	2.226	100	.022		
Total	29.939	106			
Corrected Total	2.416	105			

a. R Squared = .079 (Adjusted R Squared = .033)

Tests of Between-Subjects Effects

Dependent Variable: LF SBP

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	323.851[a]	5	64.770	3.656	.004
Intercept	.502	1	.502	.028	.867
phv	.000	1	.000	.000	.998
trueage	.103	1	.103	.006	.939
bmi	212.845	1	212.845	12.014	.001
gender	.314	1	.314	.018	.894
hype	1.533	1	1.533	.087	.769
Error	1771.651	100	17.717		
Total	5410.788	106			
Corrected Total	2095.502	105			

a. R Squared = .155 (Adjusted R Squared = .112)

Tests of Between-Subjects Effects

Dependent Variable: HF SBP

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	5.610[a]	5	1.122	.747	.590
Intercept	.357	1	.357	.238	.627
phv	.419	1	.419	.279	.598
trueage	.110	1	.110	.073	.787
bmi	3.699	1	3.699	2.464	.120
gender	1.093	1	1.093	.728	.396
hype	2.241	1	2.241	1.493	.225
Error	150.142	100	1.501		
Total	393.436	106			
Corrected Total	155.753	105			

a. R Squared = .036 (Adjusted R Squared = -.012)

Tests of Between-Subjects Effects

Dependent Variable: TP SBP

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	369.664[a]	5	73.933	2.982	.015
Intercept	.012	1	.012	.000	.982
phv	.436	1	.436	.018	.895
trueage	.000	1	.000	.000	.998
bmi	272.664	1	272.664	10.998	.001
gender	2.578	1	2.578	.104	.748
hype	.067	1	.067	.003	.959
Error	2479.270	100	24.793		
Total	8177.280	106			
Corrected Total	2848.934	105			

a. R Squared = .130 (Adjusted R Squared = .086)

Tests of Between-Subjects Effects

Dependent Variable: LF/HF SBP

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	129.653[a]	5	25.931	3.040	.013
Intercept	.338	1	.338	.040	.843
phv	.534	1	.534	.063	.803
trueage	.294	1	.294	.034	.853
bmi	18.690	1	18.690	2.191	.142
gender	.667	1	.667	.078	.780
hype	41.934	1	41.934	4.916	.029
Error	853.057	100	8.531		
Total	3094.749	106			
Corrected Total	982.710	105			

a. R Squared = .132 (Adjusted R Squared = .089)

Tests of Between-Subjects Effects

Dependent Variable: LF/TP SBP

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	.198[a]	5	.040	2.649	.027
Intercept	.063	1	.063	4.235	.042
phv	.001	1	.001	.063	.802
trueage	.000	1	.000	.008	.929
bmi	.050	1	.050	3.320	.071
gender	3.753E-5	1	3.753E-5	.003	.960
hype	.043	1	.043	2.891	.092
Error	1.498	100	.015		
Total	62.601	106			
Corrected Total	1.696	105			

a. R Squared = .117 (Adjusted R Squared = .073)

Tests of Between-Subjects Effects

Dependent Variable: HF/TP SBP

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	.198[a]	5	.040	2.649	.027
Intercept	.020	1	.020	1.362	.246
phv	.001	1	.001	.063	.802
trueage	.000	1	.000	.008	.929
bmi	.050	1	.050	3.320	.071
gender	3.753E-5	1	3.753E-5	.003	.960
hype	.043	1	.043	2.891	.092
Error	1.498	100	.015		
Total	7.903	106			
Corrected Total	1.696	105			

a. R Squared = .117 (Adjusted R Squared = .073)

Tests of Between-Subjects Effects

Dependent Variable: LF Gain

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	751.565[a]	5	150.313	3.411	.007
Intercept	.745	1	.745	.017	.897
phv	.667	1	.667	.015	.902
trueage	65.171	1	65.171	1.479	.227
bmi	73.019	1	73.019	1.657	.201
gender	82.542	1	82.542	1.873	.174
hype	198.760	1	198.760	4.510	.036
Error	4406.684	100	44.067		
Total	26569.706	106			
Corrected Total	5158.249	105			

a. R Squared = .146 (Adjusted R Squared = .103)

Tests of Between-Subjects Effects

Dependent Variable: HF Gain

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	1551.917[a]	5	310.383	2.584	.031
Intercept	61.921	1	61.921	.515	.474
phv	48.400	1	48.400	.403	.527
trueage	336.899	1	336.899	2.805	.097
bmi	156.354	1	156.354	1.302	.257
gender	87.971	1	87.971	.732	.394
hype	466.647	1	466.647	3.885	.051
Error	12012.477	100	120.125		
Total	62235.053	106			
Corrected Total	13564.394	105			

a. R Squared = .114 (Adjusted R Squared = .070)

Regression

BP Group: LF Gain

Variables Entered/Removed[b]

Model	Variables Entered	Variables Removed	Method
1	student gender (M/F), Body Mass Index, phv, hyper, trueage[a]	.	Enter

a. All requested variables entered.

b. Dependent Variable: gainlfsb

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.382[a]	.146	.103	6.63829

a. Predictors: (Constant), student gender (M/F), Body Mass Index, phv, hyper, trueage

ANOVA[b]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	751.565	5	150.313	3.411	.007[a]
	Residual	4406.684	100	44.067		
	Total	5158.249	105			

a. Predictors: (Constant), student gender (M/F), Body Mass Index, phv, hyper, trueage

b. Dependent Variable: gainlfsb

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-.170	16.646		-.010	.992
	hyper	-4.036	1.900	-.231	-2.124	.036
	Body Mass Index	-.189	.147	-.140	-1.287	.201
	Student gender (M/F)	1.891	1.382	.131	1.369	.174
	trueage	1.459	1.200	.175	1.216	.227
	phv	.143	1.159	.017	.123	.902

a. Dependent Variable: gainlfsb

BP Group: HF Gain

Variables Entered/Removed[b]

Model	Variables Entered	Variables Removed	Method
1	student gender (M/F), Body Mass Index, phv, hyper, trueage[a]	.	Enter

a. All requested variables entered.

b. Dependent Variable: gainhfsb

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.338[a]	.114	.070	10.96014

a. Predictors: (Constant), student gender (M/F), Body Mass Index, phv, hyper, trueage

ANOVA[b]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	1551.917	5	310.383	2.584	.031[a]
	Residual	12012.477	100	120.125		
	Total	13564.394	105			

a. Predictors: (Constant), student gender (M/F), Body Mass Index, phv, hyper, trueage

b. Dependent Variable: gainhfsb

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-16.848	27.483		-.613	.541
	hyper	-6.184	3.137	-.218	-1.971	.051
	Body Mass Index	-.277	.242	-.126	-1.141	.257
	student gender (M/F	1.952	2.281	.083	.856	.394
	trueage	3.318	1.981	.246	1.675	.097
	phv	-1.215	1.913	-.091	-.635	.527

a. Dependent Variable: gainhfsb

SBP: LF Gain

Variables Entered/Removed[b]

Model	Variables Entered	Variables Removed	Method

1	phv, bmi, student gender (M/F), LabFieldAveS, trueage[a]	.	Enter

a. All requested variables entered.

b. Dependent Variable: gainlfsb

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.362[a]	.131	.087	6.69587

a. Predictors: (Constant), phv, bmi, student gender (M/F), LabFieldAveS, trueage

ANOVA[b]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	674.785	5	134.957	3.010	.014[a]
	Residual	4483.464	100	44.835		
	Total	5158.249	105			

a. Predictors: (Constant), phv, bmi, student gender (M/F), LabFieldAveS, trueage

b. Dependent Variable: gainlfsb

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	15.698	17.718		.886	.378
	LabFieldAveS	-.156	.094	-.208	-1.649	.102
	bmi	-.160	.170	-.119	-.944	.348
	student gender (M/F)	1.879	1.395	.130	1.347	.181
	trueage	1.301	1.206	.156	1.079	.283

bmi	-.160	.170	-.119	-.944	.348
student gender (M/F)	1.879	1.395	.130	1.347	.181
trueage	1.301	1.206	.156	1.079	.283
phv	.437	1.174	.053	.372	.711

a. Dependent Variable: gainlfsb

SBP: HF Gain SBP

Variables Entered/Removed[b]

Model	Variables Entered	Variables Removed	Method
1	phv, bmi, student gender (M/F), LabFieldAveS, trueage[a]	.	Enter

a. All requested variables entered.

b. Dependent Variable: gainhfsb

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.338[a]	.114	.070	10.96241

a. Predictors: (Constant), phv, bmi, student gender (M/F), LabFieldAveS, trueage

ANOVA[b]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	1546.944	5	309.389	2.574	.031[a]
	Residual	12017.450	100	120.174		
	Total	13564.394	105			

a. Predictors: (Constant), trueage, bmi, student gender (M/F), LabFieldAveS, phv

b. Dependent Variable: gainhfsb

Coefficients[a]

Model	Unstandardized Coefficients	Standardized Coefficients	t	Sig.

		B	Std. Error	Beta		
1	(Constant)	11.723	29.009		.404	.687
	LabFieldAveS	-.303	.155	-.249	-1.960	.053
	bmi	-.157	.278	-.072	-.565	.573
	student gender (M/F)	2.021	2.284	.086	.885	.378
	trueage	3.103	1.975	.230	1.571	.119
	phv	-.685	1.922	-.051	-.357	.722

a. Dependent Variable: gainhfsb

Correlations

		hype	SBP	DBP	RRI	PP	Age	Sex	BMI	PHV	LF RRI	HF RRI
hype	PC	1.000	.830**	.791**	-.361**	.341**	.139	.112	.511**	.013	-.226*	-.199*
	Sig. 2T		.000	.000	.000	.000	.155	.255	.000	.894	.020	.041
	N	106.000	106	106	106	106	106	106	106	106	106	106
SBP	PC	.830**	1.000	.845**	-.256**	.528**	.200*	.131	.651**	.112	-.193*	-.174
	Sig. 2T	.000		.000	.008	.000	.040	.181	.000	.252	.047	.074
	N	106	106.00	106	106	106	106	106	106	106	106	106
DBP	PC	.791**	.845**	1.000	-.317**	.123	.081	.042	.496**	.026	-.277**	-.201*
	Sig. 2T	.000	.000		.001	.207	.411	.667	.000	.792	.004	.039
	N	106	106	106.00	106	106	106	106	106	106	106	106
RRI	PC	-.361**	-.256**	-.317**	1.000	.049	.180	.241*	-.091	.147	.361**	.328**
	Sig. 2T	.000	.008	.001		.618	.065	.013	.354	.132	.000	.001
	N	106	106	106	106.00	106	106	106	106	106	106	106
PP	PC	.341**	.528**	.123	.049	1.000	.139	.098	.404**	.094	-.057	-.068
	Sig. 2T	.000	.000	.207	.618		.156	.316	.000	.339	.563	.491
	N	106	106	106	106	106.00	106	106	106	106	106	106
Age	PC	.139	.200*	.081	.180	.139	1.000	.238*	.095	.744**	.235*	.170
	Sig. 2T	.155	.040	.411	.065	.156		.014	.330	.000	.015	.082
	N	106	106	106	106	106	106.00	106	106	106	106	106
Sex	PC	.112	.131	.042	.241*	.098	.238*	1.000	.053	.158	.097	-.008

	Sig. 2T	.255	.181	.667	.013	.316	.014		.592	.107	.321	.933
	N	106	106	106	106	106	106	106.00	106	106	106	106
BMI	PC	.511**	.651**	.496**	-.091	.404**	.095	.053	1.000	-.060	-.036	.009
	Sig. 2T	.000	.000	.000	.354	.000	.330	.592		.540	.715	.924
	N	106	106	106	106	106	106	106	106.00	106	106	106
PHV	PC	.013	.112	.026	.147	.094	.744**	.158	-.060	1.000	.165	.088
	Sig. 2T	.894	.252	.792	.132	.339	.000	.107	.540		.091	.367
	N	106	106	106	106	106	106	106	106	106.00	106	106
LF RRI	PC	-.226*	-.193*	-.277**	.361**	-.057	.235*	.097	-.036	.165	1.000	.611**
	Sig. 2T	.020	.047	.004	.000	.563	.015	.321	.715	.091		.000
	N	106	106	106	106	106	106	106	106	106	106.00	106
HF RRI	PC	-.199*	-.174	-.201*	.328**	-.068	.170	-.008	.009	.088	.611**	1.000
	Sig. 2T	.041	.074	.039	.001	.491	.082	.933	.924	.367	.000	
	N	106	106	106	106	106	106	106	106	106	106	106.00
TP RRI	PC	-.221*	-.195*	-.248*	.361**	-.066	.199*	.045	.004	.109	.807**	.954**
	Sig. 2T	.023	.045	.010	.000	.502	.041	.647	.969	.266	.000	.000
	N	106	106	106	106	106	106	106	106	106	106	106
LF/HF RRI	PC	.276**	.327**	.254**	-.286**	.150	.057	.000	.299**	.035	-.017	-.426**
	Sig. 2T	.004	.001	.009	.003	.124	.561	.995	.002	.725	.864	.000
	N	106	106	106	106	106	106	106	106	106	106	106
LF/TP RRI	PC	.257**	.296**	.221*	-.271**	.160	.055	.039	.219*	.037	.020	-.521**
	Sig. 2T	.008	.002	.023	.005	.102	.576	.690	.024	.710	.836	.000
	N	106	106	106	106	106	106	106	106	106	106	106
HF/TP RRI	PC	-.257**	-.296**	-.221*	.271**	-.160	-.055	-.039	-.219*	-.037	-.020	.521**
	Sig. 2T	.008	.002	.023	.005	.102	.576	.690	.024	.710	.836	.000
	N	106	106	106	106	106	106	106	106	106	106	106
LF SBP	PC	.224*	.273**	.107	-.104	.180	.048	.013	.392**	-.016	.215*	.100
	Sig. 2T	.021	.005	.274	.289	.064	.622	.892	.000	.874	.027	.308
	N	106	106	106	106	106	106	106	106	106	106	106
HF SBP	PC	-.062	-.002	-.075	-.023	.052	-.005	-.090	.096	.022	.157	.297**
	Sig. 2T	.525	.985	.445	.813	.600	.956	.358	.327	.823	.107	.002

	N	106	106	106	106	106	106	106	106	106	106	106
TP SBP	PC	.177	.234*	.074	-.094	.167	.040	-.010	.359**	-.008	.221*	.155
	Sig. 2T	.069	.016	.448	.335	.088	.682	.922	.000	.933	.023	.112
	N	106	106	106	106	106	106	106	106	106	106	106
LF/HF SBP	PC	.332**	.301**	.203*	-.128	.156	.056	.063	.293**	-.018	.030	-.230*
	Sig. 2T	.001	.002	.037	.192	.110	.567	.519	.002	.856	.762	.018
	N	106	106	106	106	106	106	106	106	106	106	106
LF/TP SBP	PC	.292**	.278**	.187	-.097	.120	.030	.024	.301**	-.037	.042	-.223*
	Sig. 2T	.002	.004	.055	.325	.220	.757	.806	.002	.708	.666	.022
	N	106	106	106	106	106	106	106	106	106	106	106
HF/TP SBP	PC	-.292**	-.278**	-.187	.097	-.120	-.030	-.024	-.301**	.037	-.042	.223*
	Sig. 2T	.002	.004	.055	.325	.220	.757	.806	.002	.708	.666	.022
	N	106	106	106	106	106	106	106	106	106	106	106
LF Gain	PC	-.263**	-.231*	-.201*	.449**	-.060	.174	.142	-.235*	.174	.474**	.439**
	Sig. 2T	.006	.017	.039	.000	.541	.075	.146	.015	.075	.000	.000
	N	106	106	106	106	106	106	106	106	106	106	106
HF Gain	PC	-.240*	-.245*	-.234*	.551**	-.063	.155	.096	-.204*	.109	.456**	.591**
	Sig. 2T	.013	.012	.016	.000	.521	.112	.326	.035	.264	.000	.000
	N	106	106	106	106	106	106	106	106	106	106	106

PC = Pearson correlation

2T = 2-Tailed

**. Correlation is significant at the 0.01 level

(2T)

*. Correlation is significant at the 0.05 level

(2T)

		TP RRI	LF/HF RRI	LF/TP RRI	HF/TP RRI	LF SBP	HF SBP	TP SBP	LF/HF SBP	LF/TP SBP	HF/TP SBP	LF Gain	HF Gain
hype	PC	-.221*	.276**	.257**	-.257**	.224*	-.062	.177	.332**	.292**	-.292**	-.263**	-.240*
	Sig. 2T	.023	.004	.008	.008	.021	.525	.069	.001	.002	.002	.006	.013
	N	106	106	106	106	106	106	106	106	106	106	106	106
SBP	PC	-.195*	.327**	.296**	-.296**	.273**	-.002	.234*	.301**	.278**	-.278**	-.231*	-.245*

	Sig. 2T	.045	.001	.002	.002	.005	.985	.016	.002	.004	.004	.017	.012
	N	106	106	106	106	106	106	106	106	106	106	106	106
DBP	PC	-.248*	.254**	.221*	-.221*	.107	-.075	.074	.203*	.187	-.187	-.201*	-.234*
	Sig. 2T	.010	.009	.023	.023	.274	.445	.448	.037	.055	.055	.039	.016
	N	106	106	106	106	106	106	106	106	106	106	106	106
RRI	PC	.361**	-.286**	-.271**	.271**	-.104	-.023	-.094	-.128	-.097	.097	.449**	.551**
	Sig. 2T	.000	.003	.005	.005	.289	.813	.335	.192	.325	.325	.000	.000
	N	106	106	106	106	106	106	106	106	106	106	106	106
PP	PC	-.066	.150	.160	-.160	.180	.052	.167	.156	.120	-.120	-.060	-.063
	Sig. 2T	.502	.124	.102	.102	.064	.600	.088	.110	.220	.220	.541	.521
	N	106	106	106	106	106	106	106	106	106	106	106	106
Age	PC	.199*	.057	.055	-.055	.048	-.005	.040	.056	.030	-.030	.174	.155
	Sig. 2T	.041	.561	.576	.576	.622	.956	.682	.567	.757	.757	.075	.112
	N	106	106	106	106	106	106	106	106	106	106	106	106
Sex	PC	.045	.000	.039	-.039	.013	-.090	-.010	.063	.024	-.024	.142	.096
	Sig. 2T	.647	.995	.690	.690	.892	.358	.922	.519	.806	.806	.146	.326
	N	106	106	106	106	106	106	106	106	106	106	106	106
BMI	PC	.004	.299**	.219*	-.219*	.392**	.096	.359**	.293**	.301**	-.301**	-.235*	-.204*
	Sig. 2T	.969	.002	.024	.024	.000	.327	.000	.002	.002	.002	.015	.035
	N	106	106	106	106	106	106	106	106	106	106	106	106
PHV	PC	.109	.035	.037	-.037	-.016	.022	-.008	-.018	-.037	.037	.174	.109
	Sig. 2T	.266	.725	.710	.710	.874	.823	.933	.856	.708	.708	.075	.264
	N	106	106	106	106	106	106	106	106	106	106	106	106
LF RRI	PC	.807**	-.017	.020	-.020	.215*	.157	.221*	.030	.042	-.042	.474**	.456**
	Sig. 2T	.000	.864	.836	.836	.027	.107	.023	.762	.666	.666	.000	.000
	N	106	106	106	106	106	106	106	106	106	106	106	106
HF RRI	PC	.954**	-.426**	-.521**	.521**	.100	.297**	.155	-.230*	-.223*	.223*	.439**	.591**
	Sig. 2T	.000	.000	.000	.000	.308	.002	.112	.018	.022	.022	.000	.000
	N	106	106	106	106	106	106	106	106	106	106	106	106
TP RRI	PC	1.000	-.306**	-.358**	.358**	.166	.277**	.207*	-.148	-.132	.132	.491**	.591**
	Sig. 2T		.001	.000	.000	.089	.004	.033	.130	.179	.179	.000	.000

	N	106.00	106	106	106	106	106	106	106	106	106	106	106
LF/HF RRI	PC	-.306**	1.000	.919**	-.919**	.117	-.243*	.044	.492**	.417**	-.417**	-.183	-.348**
	Sig. 2T	.001		.000	.000	.231	.012	.655	.000	.000	.000	.061	.000
	N	106	106.00	106	106	106	106	106	106	106	106	106	106
LF/TP RRI	PC	-.358**	.919**	1.000	-1.000**	.082	-.271**	.007	.460**	.418**	-.418**	-.190	-.392**
	Sig. 2T	.000	.000		.000	.404	.005	.944	.000	.000	.000	.051	.000
	N	106	106	106.00	106	106	106	106	106	106	106	106	106
HF/TP RRI	PC	.358**	-.919**	-1.000**	1.000	-.082	.271**	-.007	-.460**	-.418**	.418**	.190	.392**
	Sig. 2T	.000	.000	.000		.404	.005	.944	.000	.000	.000	.051	.000
	N	106	106	106	106.00	106	106	106	106	106	106	106	106
LF SBP	PC	.166	.117	.082	-.082	1.000	.523**	.980**	.473**	.471**	-.471**	-.457**	-.296**
	Sig. 2T	.089	.231	.404	.404		.000	.000	.000	.000	.000	.000	.002
	N	106	106	106	106	106.00	106	106	106	106	106	106	106
HF SBP	PC	.277**	-.243*	-.271**	.271**	.523**	1.000	.682**	-.296**	-.304**	.304**	-.219*	-.285**
	Sig. 2T	.004	.012	.005	.005	.000		.000	.002	.002	.002	.024	.003
	N	106	106	106	106	106	106.000	106	106	106	106	106	106
TP SBP	PC	.207*	.044	.007	-.007	.980**	.682**	1.000	.336**	.333**	-.333**	-.443**	-.321**
	Sig. 2T	.033	.655	.944	.944	.000	.000		.000	.000	.000	.000	.001
	N	106	106	106	106	106	106	106.00	106	106	106	106	106
LF/HF SBP	PC	-.148	.492**	.460**	-.460**	.473**	-.296**	.336**	1.000	.837**	-.837**	-.292**	-.034
	Sig. 2T	.130	.000	.000	.000	.000	.002	.000		.000	.000	.002	.732
	N	106	106	106	106	106	106	106	106.00	106	106	106	106
LF/TP SBP	PC	-.132	.417**	.418**	-.418**	.471**	-.304**	.333**	.837**	1.000	-1.000**	-.342**	-.010
	Sig. 2T	.179	.000	.000	.000	.000	.002	.000	.000		.000	.000	.918
	N	106	106	106	106	106	106	106	106	106.00	106	106	106
HF/TP SBP	PC	.132	-.417**	-.418**	.418**	-.471**	.304**	-.333**	-.837**	-1.000**	1.000	.342**	.010
	Sig. 2T	.179	.000	.000	.000	.000	.002	.000	.000	.000		.000	.918
	N	106	106	106	106	106	106	106	106	106	106.00	106	106

LF Gain	PC	.491**	-.183	-.190	.190	-.457**	-.219*	-.443**	-.292**	-.342**	.342**	1.000	.797**
	Sig. 2T	.000	.061	.051	.051	.000	.024	.000	.002	.000	.000		.000
	N	106	106	106	106	106	106	106	106	106	106	106.00	106
HF Gain	PC	.591**	-.348**	-.392**	.392**	-.296**	-.285**	-.321**	-.034	-.010	.010	.797**	1.000
	Sig. 2T	.000	.000	.000	.000	.002	.003	.001	.732	.918	.918	.000	
	N	106	106	106	106	106	106	106	106	106	106	106	106.00

PC = Pearson correlation

2T = 2-Tailed

**. Correlation is significant at the 0.01 level (2T)

*. Correlation is significant at the 0.05 level (2T)

Interactions

LF Interaction for BMI and BP category

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.291[a]	.085	.058	6.80382

a. Predictors: (Constant), newBMIinteraction, bmi, hype

ANOVA[b]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	436.472	3	145.491	3.143	.028[a]
	Residual	4721.777	102	46.292		
	Total	5158.249	105			

a. Predictors: (Constant), newBMIinteraction, bmi, hype

b. Dependent Variable: gainlfsb

Coefficients[a]

Model	Unstandardized Coefficients	Standardized Coefficients	t	Sig.

		B	Std. Error	Beta		
1	(Constant)	19.990	4.166		4.799	.000
	hype	-6.326	7.156	-.361	-.884	.379
	bmi	-.246	.208	-.183	-1.187	.238
	newBMIinteraction	.127	.298	.200	.428	.670

a. Dependent Variable: gainlfsb

HF Interaction for BMI and BP category

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.275[a]	.076	.048	11.08753

a. Predictors: (Constant), newBMIinteraction, bmi, hype

ANOVA[b]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	1025.205	3	341.735	2.780	.045[a]
	Residual	12539.189	102	122.933		
	Total	13564.394	105			

a. Predictors: (Constant), newBMIinteraction, bmi, hype

b. Dependent Variable: gainhfsb

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	22.953	6.788		3.381	.001
	hype	5.879	11.661	.207	.504	.615
	bmi	-.009	.338	-.004	-.026	.979
	newBMIinteraction	-.479	.485	-.464	-.988	.326

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	22.953	6.788		3.381	.001
	hype	5.879	11.661	.207	.504	.615
	bmi	-.009	.338	-.004	-.026	.979
	newBMIinteraction	-.479	.485	-.464	-.988	.326

a. Dependent Variable: gainhfsb

LF Interaction for BMI and SBP

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.258[a]	.066	.039	6.87113

a. Predictors: (Constant), BMIandSBPinteraction, LabFieldAveS, bmi

ANOVA[b]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	342.585	3	114.195	2.419	.071[a]
	Residual	4815.664	102	47.212		
	Total	5158.249	105			

a. Predictors: (Constant), BMIandSBPinteraction, LabFieldAveS, bmi

b. Dependent Variable: gainlfsb

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	33.886	25.657		1.321	.190
	bmi	-.472	1.146	-.350	-.412	.681
	LabFieldAveS	-.159	.258	-.212	-.614	.540

BMIandSBPinteraction	.003	.011	.260	.240	.811

a. Dependent Variable: gainlfsb

HF Interaction for BMI and SBP

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.270[a]	.073	.045	11.10465

a. Predictors: (Constant), BMIandSBPinteraction, LabFieldAveS, bmi

ANOVA[b]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	986.435	3	328.812	2.666	.052[a]
	Residual	12577.959	102	123.313		
	Total	13564.394	105			

a. Predictors: (Constant), BMIandSBPinteraction, LabFieldAveS, bmi

b. Dependent Variable: gainhfsb

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	6.923	41.465		.167	.868
	bmi	1.685	1.851	.770	.910	.365
	LabFieldAveS	.159	.418	.131	.381	.704
	BMIandSBPinteraction	-.018	.018	-1.092	-1.014	.313

a. Dependent Variable: gainhfsb

Appendix H
Raw data

ID	BP category	Gender	Age	Height	Weight	BMI	PHV	SBP
A1048	0	0	11.85	150.0	39.4	17.51	-2.18	92.50
A1067	0	0	11.65	149.3	42.4	19.02	-2.65	87.17
A1127	0	0	12.70	161.0	42.9	16.55	-1.29	87.67
A1138	0	0	13.85	149.1	36.1	16.24	-1.04	84.50
A1141	0	0	14.01	160.2	66.0	25.72	-1.34	93.67
A1291	0	0	14.34	169.1	52.2	18.26	-0.22	91.17
A1365	0	0	13.33	156.1	40.6	16.66	-1.20	93.50
A1408	0	0	12.63	166.8	49.6	17.83	-1.10	92.00
A1441	0	0	13.14	155.5	50.8	21.01	-1.68	86.00
A148	0	0	12.67	151.3	40.7	17.78	-1.82	97.67
A1497	1	0	12.51	157.4	90.3	36.45	-2.98	113.50
A1543	0	1	13.56	173.8	51.7	17.12	-0.45	88.33
A1565	0	0	12.30	155.5	40.2	16.63	-1.62	94.67
A1570	0	0	12.28	159.8	63.9	25.02	-2.23	92.83
A1602	0	0	12.20	151.5	47.6	20.74	-2.33	86.83
A1622	0	1	13.74	155.9	56.6	23.29	-1.36	97.50
A1673	0	1	13.76	164.7	49.9	18.40	-0.91	95.67
A281	1	0	12.81	149.7	38.7	17.27	-1.64	107.17
A329	0	0	11.77	168.3	68.8	24.29	-2.16	99.50
A490	0	1	12.14	157.0	45.1	18.30	-1.92	89.83
A492	0	0	12.13	157.2	49.1	19.87	-2.06	88.67
A609	0	0	12.56	159.6	53.0	20.81	-1.65	93.83
A61	0	0	11.91	150.8	34.5	15.17	-2.21	86.67
A661	1	1	14.35	170.5	68.2	23.46	0.65	109.67
A687	0	1	12.44	155.9	43.7	17.98	-1.96	81.67
A693	0	1	12.17	163.0	49.9	18.78	-1.71	86.67
A728	1	1	12.62	167.5	48.0	17.11	-1.66	115.33
A759	0	0	13.26	167.5	57.8	20.60	-0.98	88.50
A871	0	0	12.97	161.0	42.3	16.32	-1.14	90.50
A872	1	1	13.76	145.2	38.5	18.26	-2.40	98.83
A886	0	0	12.95	145.7	36.4	17.15	-1.92	85.50
A890	0	0	13.25	154.9	50.9	21.21	-1.53	97.67
B1078	1	0	12.05	158.4	61.1	24.35	-2.33	108.17
B1090	0	0	11.57	139.9	37.6	19.21	-2.93	82.33
B1099	0	1	12.34	157.6	46.0	18.52	-2.33	88.33
B1128	0	0	12.96	163.6	39.8	14.87	-0.92	93.00
B113	0	0	13.98	168.7	59.2	20.80	-0.51	94.50
B1180	1	0	14.17	167.5	83.1	29.62	-1.36	106.00
B1211	0	0	12.53	134.0	28.5	15.87	-2.61	92.67
B1257	0	0	12.07	154.4	50.3	21.10	-1.94	88.33

B1259	0	1	12.22	173.5	87.6	29.10	-1.28	106.00
B1389	0	1	12.35	150.9	37.5	16.47	-2.27	82.17
B1421	0	0	13.47	165.4	60.5	22.11	-1.23	94.67
B1506	0	0	12.32	156.4	62.6	25.59	-2.34	89.83
B1544	0	0	13.08	148.6	43.8	19.84	-1.94	96.83
B159	0	1	12.40	165.7	63.6	23.16	-1.36	97.33
B160	1	0	11.65	155.3	60.2	24.96	-2.60	109.50
B1618	0	0	12.87	157.7	77.3	31.08	-2.55	96.33
B1651	0	0	11.88	153.5	59.0	25.04	-2.61	89.00
B1680	0	0	12.13	137.6	35.9	18.96	-2.82	88.50
B1688	0	0	11.96	162.5	50.1	18.97	-1.71	92.83
B1694	0	1	11.80	154.5	37.0	15.50	-2.37	88.00
B1696	0	0	12.05	146.0	34.4	16.14	-2.34	88.17
B173	0	0	13.79	172.3	50.1	16.88	-0.04	88.50
B197	0	1	14.12	174.5	60.8	19.97	-0.57	84.67
B221	0	0	12.96	159.3	61.1	24.08	-1.69	90.67
B240	1	1	13.58	164.2	67.5	25.04	-0.88	111.83
B288	0	0	11.43	134.2	29.2	16.21	-3.19	84.67
B344	0	1	11.76	147.8	42.5	19.46	-2.84	95.67
B568	0	1	12.20	171.8	47.0	15.92	-1.75	91.17
B576	0	1	11.86	147.8	36.8	16.85	-2.70	86.67
B579	0	0	11.75	168.2	60.2	21.28	-1.89	94.67
B645	0	1	13.42	171.4	94.0	32.00	-0.48	106.00
B669	0	0	12.45	155.0	40.0	16.65	-1.62	84.83
B69	1	0	13.52	168.8	59.9	21.02	-0.86	108.83
B728	0	0	11.48	154.3	59.7	25.08	-2.79	88.00
B878	0	1	14.12	167.2	57.8	20.68	-4.19	98.50
B899	1	1	13.47	160.9	93.5	36.12	-1.39	112.67
B904	0	1	13.07	162.2	49.1	18.66	-1.62	86.50
B910	0	0	13.20	167.4	55.1	19.66	-0.82	97.50
B921	0	1	12.22	167.0	53.9	19.33	-1.39	91.17
B937	0	1	13.95	164.3	54.1	20.04	-1.08	98.00
B944	0	0	12.89	158.7	62.8	24.93	-1.92	88.33
B957	0	0	13.22	167.8	54.4	19.32	-1.01	88.33
B980	0	0	12.29	155.0	41.1	17.11	-1.87	90.67
B992	0	1	12.28	160.7	54.0	20.91	-1.81	90.00
B994	0	0	11.21	137.6	38.6	20.39	-3.28	84.67
C115	0	1	14.32	167.6	80.1	28.52	-0.34	88.00
C139	1	1	13.77	165.7	60.4	22.00	-0.59	105.17
C22	0	1	14.31	161.3	48.2	18.53	-0.94	89.67
C62	0	1	12.84	162.4	54.0	20.47	-1.79	85.50
C7	0	1	13.99	168.0	46.6	16.51	-0.92	89.17
D108	0	0	12.01	153.5	48.0	20.37	-2.23	94.00
D1116	1	1	13.13	150.3	67.6	29.92	-1.86	108.33

D266	0	0	14.08	166.3	45.7	16.52	-0.22	87.00
D300	1	1	14.49	165.5	67.0	24.46	-0.85	106.67
D534	1	1	14.09	172.4	124.6	41.92	-0.37	125.33
D686	0	1	12.51	150.7	47.1	20.74	-2.13	89.50
D704	0	0	12.52	155.0	47.0	19.56	-1.93	84.83
E1137	1	0	12.54	154.7	48.6	20.31	-1.97	107.33
E199	0	0	13.22	157.9	55.9	22.42	-1.57	91.83
E231	0	0	12.87	158.0	50.3	20.15	-1.46	94.67
E236	1	0	12.81	164.1	100.1	37.17	-2.82	114.17
E307	1	0	11.58	142.3	43.0	21.24	-2.93	100.17
E315	0	0	11.58	146.9	47.7	22.10	-2.77	90.67
E396	1	1	13.51	177.1	66.0	21.04	-0.50	119.17
E442	0	1	13.36	161.6	43.0	16.47	-2.01	90.17
E443	0	0	13.02	152.3	32.5	14.01	-1.43	83.00
E544	0	0	14.33	167.7	46.0	16.36	-0.01	87.17
E635	1	0	11.87	149.0	69.0	31.08	-3.18	117.67
E639	0	1	11.62	138.5	33.0	17.20	-3.18	84.83
E708	0	0	13.33	169.1	50.9	17.80	-0.74	99.00
E828	1	0	11.90	165.1	85.4	31.33	-2.76	107.50
E871	0	0	13.68	158.9	47.0	18.61	-0.98	87.83
E876	0	0	13.54	156.0	47.1	19.35	-1.22	97.83
E927	0	1	12.61	151.2	39.6	17.32	-2.03	92.33

ID	DBP	MAP	RRI	PP	LF RRI	HF RRI	TP RRI	LF/HF RRI
A1048	52.67	65.94	861.89	36.67	403.61	581.98	985.59	0.69
A1067	46.00	59.72	729.32	38.33	732.94	1584.92	2317.86	0.46
A1127	51.83	63.78	774.60	38.00	287.76	429.68	717.43	0.67
A1138	48.67	60.61	749.44	36.33	284.11	507.30	791.40	0.56
A1141	57.17	69.33	874.09	35.00	1792.91	7215.56	9008.47	0.25
A1291	59.33	69.94	769.00	31.67	1211.54	543.07	855.03	0.57
A1365	57.00	69.17	1027.17	36.33	1211.54	1328.92	1894.79	0.43
A1408	53.17	66.11	859.31	35.00	1211.54	246.17	710.53	1.89
A1441	54.67	65.11	793.29	33.33	334.68	628.36	963.04	0.53
A148	57.67	71.00	651.34	40.33	522.38	719.18	1241.55	0.73
A1497	72.33	86.06	701.30	35.67	1220.19	626.87	1847.06	1.95
A1543	47.83	61.33	1059.45	42.00	1109.33	1293.31	2402.64	0.86
A1565	61.33	72.44	766.85	31.67	846.22	1351.32	2197.55	0.63
A1570	56.83	68.83	666.97	32.33	255.55	188.64	444.19	1.35
A1602	49.17	61.72	806.47	34.67	712.47	702.38	1414.85	1.01
A1622	54.83	69.06	916.07	38.67	518.25	451.80	970.05	1.15
A1673	48.50	64.22	860.72	48.33	678.17	852.68	1530.85	0.80
A281	69.83	82.28	583.13	31.67	86.45	56.20	142.66	1.54

A329	60.50	73.50	832.90	42.00	641.63	562.58	1204.21	1.14
A490	51.67	64.39	954.63	36.00	313.12	1522.04	1835.16	0.21
A492	55.00	66.22	661.49	33.00	284.01	330.22	614.23	0.86
A609	58.50	70.28	933.29	32.00	1124.98	1563.71	2688.69	0.72
A61	51.00	62.89	739.09	30.00	324.42	432.81	757.23	0.75
A661	76.17	87.33	607.78	30.33	595.37	1280.15	1875.52	0.47
A687	53.00	62.56	862.59	30.67	239.22	650.84	890.06	0.37
A693	52.67	64.00	885.36	34.67	808.66	1655.81	2464.47	0.49
A728	74.33	88.00	646.46	35.67	431.01	272.98	703.98	1.58
A759	55.17	66.28	819.43	34.00	312.00	89.34	401.34	3.49
A871	54.00	66.17	819.43	34.00	1493.33	1455.26	2948.59	1.03
A872	64.00	75.61	717.94	32.00	567.55	493.50	1061.05	1.15
A886	55.67	65.61	689.10	34.00	596.08	506.68	1102.76	1.18
A890	62.83	74.44	820.31	34.00	339.59	429.82	769.42	0.79
B1078	65.50	79.72	734.70	44.67	915.53	1205.41	2120.94	0.76
B1090	47.67	59.22	929.50	38.00	651.60	1061.96	1713.56	0.61
B1099	61.33	70.33	790.64	29.00	590.02	479.87	1069.89	1.23
B1128	61.00	71.67	708.20	34.33	740.98	875.17	1616.15	0.85
B113	61.33	72.39	741.77	33.00	187.26	316.99	504.25	0.59
B1180	76.83	86.56	619.94	32.33	96.62	64.16	160.78	1.51
B1211	59.17	70.33	794.18	34.67	1657.09	2114.90	3771.99	0.78
B1257	50.00	62.78	675.40	39.00	609.86	301.60	911.47	2.02
B1259	63.50	77.67	768.65	40.00	223.01	63.72	286.74	3.50
B1389	55.17	64.17	805.91	21.67	937.16	514.61	1451.77	1.82
B1421	47.83	63.44	838.59	42.33	1191.42	1210.50	2401.91	0.98
B1506	54.00	65.94	818.64	35.00	443.02	988.25	1431.27	0.45
B1544	64.17	75.06	696.13	26.33	975.73	247.83	1223.56	3.94
B159	59.83	72.33	918.44	36.67	1225.91	713.49	1939.41	1.72
B160	75.00	86.50	835.93	43.67	302.82	253.94	556.75	1.19
B1618	64.50	75.11	781.81	30.00	786.20	2686.93	3473.13	0.29
B1651	53.50	65.33	698.72	24.33	178.18	216.83	395.02	0.82
B1680	51.83	64.06	715.66	36.33	426.48	209.35	635.84	2.04
B1688	57.67	69.39	684.91	32.00	334.19	308.42	642.61	1.08
B1694	58.00	68.00	738.91	23.00	633.78	768.01	1401.78	0.83
B1696	51.17	63.50	554.41	36.67	442.01	235.22	677.23	1.88
B173	50.00	62.83	715.92	34.00	731.44	225.53	956.97	3.24
B197	50.17	61.67	814.35	32.00	908.74	459.08	1367.82	1.98
B221	55.17	67.00	810.96	34.67	546.10	487.19	1033.29	1.12
B240	69.33	83.50	642.29	41.67	245.95	110.20	356.15	2.23
B288	51.33	62.44	738.23	33.00	349.01	589.52	938.53	0.59
B344	53.83	67.78	634.48	44.00	564.37	357.06	921.43	1.58
B568	57.83	68.94	987.03	34.00	684.11	751.33	1435.44	0.91

B576	46.83	60.11	763.96	39.00	1823.42	1462.42	3285.84	1.25
B579	61.00	72.22	767.72	37.00	233.71	176.76	410.47	1.32
B645	62.17	76.78	895.75	40.67	451.47	1870.08	2321.55	0.24
B669	50.00	61.61	775.72	37.67	211.44	164.97	376.41	1.28
B69	65.00	79.61	715.99	43.33	605.90	2495.86	3101.76	0.24
B728	47.17	60.78	774.82	41.33	807.34	1775.67	2583.02	0.45
B878	56.33	70.39	975.13	38.33	556.91	687.80	1244.71	0.81
B899	66.67	82.00	616.81	43.67	95.33	29.32	124.65	3.25
B904	56.83	66.72	878.45	21.33	1634.68	1433.58	3068.26	1.14
B910	63.50	74.83	1010.95	34.67	896.58	987.67	1884.25	0.91
B921	61.17	71.17	799.54	30.00	518.96	505.23	1024.18	1.03
B937	53.50	68.33	852.79	41.00	1240.47	962.99	2203.46	1.29
B944	52.00	64.11	912.74	32.33	1711.27	2462.71	4173.98	0.69
B957	61.67	70.56	850.82	31.00	462.09	772.82	1234.91	0.60
B980	55.17	67.00	714.85	41.33	248.07	159.57	407.64	1.55
B992	53.33	65.56	805.01	36.33	180.99	272.23	453.21	0.66
B994	54.67	64.67	693.27	33.67	264.11	376.91	641.02	0.70
C115	47.83	61.22	953.38	34.00	2100.20	2488.09	4588.30	0.84
C139	68.67	80.83	978.40	39.00	383.83	605.79	989.62	0.63
C22	55.67	67.00	857.61	32.33	745.32	926.90	1672.23	0.80
C62	49.50	61.50	849.57	37.67	2650.48	1854.94	4505.43	1.43
C7	49.33	62.61	1011.72	43.00	451.91	616.76	1068.67	0.73
D108	58.17	70.11	698.93	36.33	1.78	7.48	9.26	0.24
D1116	69.00	82.11	688.17	47.50	343.96	198.88	542.84	1.73
D266	46.00	59.67	789.97	38.00	1724.01	797.30	2521.31	2.16
D300	58.17	74.33	773.72	46.00	399.11	271.15	670.25	1.47
D534	72.50	90.11	829.00	56.33	1049.24	508.12	1557.36	2.06
D686	57.67	68.28	895.79	28.00	449.35	456.84	906.19	0.98
D704	53.17	63.72	816.25	27.00	438.06	657.65	1095.71	0.67
E1137	72.17	83.89	642.18	32.50	85.25	192.99	278.24	0.44
E199	58.83	69.83	755.23	34.67	211.81	190.78	402.59	1.11
E231	57.00	69.56	774.31	40.67	586.57	925.24	1511.81	0.63
E236	69.33	84.28	697.55	45.00	878.37	224.96	1103.33	3.90
E307	72.33	81.61	738.67	24.67	413.82	118.33	532.15	3.50
E315	59.33	69.78	927.54	30.00	373.36	404.61	777.98	0.92
E396	81.67	94.17	698.98	42.50	222.91	159.09	382.00	1.40
E442	53.17	65.50	848.21	38.33	519.41	1040.17	1559.58	0.50
E443	49.67	60.78	831.12	35.67	750.00	2452.91	3202.91	0.31
E544	55.33	65.94	784.05	28.33	600.07	362.04	962.11	1.66
E635	78.50	91.56	803.92	55.00	126.82	52.09	178.91	2.43
E639	57.83	66.83	689.79	26.00	211.21	785.13	996.35	0.27
E708	57.33	71.22	739.94	35.33	155.47	93.02	248.49	1.67

E828	71.17	83.28	745.62	34.33	361.57	340.44	702.02	1.06
E871	59.00	68.61	805.75	27.33	1777.44	2970.93	4748.37	0.60
E876	60.83	73.17	835.48	40.00	1006.56	404.68	1411.24	2.49
E927	59.50	70.44	772.94	31.67	1482.42	1726.49	3208.92	0.86

ID	LF/TP RRI	HF/TP RRI	LF SBP	HF SBP	TP SBP	LF/HF SBP	LF/TP SBP	HF/TP SBP
A1048	0.41	0.59	4.11	0.88	4.99	4.69	0.82	0.18
A1067	0.32	0.68	6.88	3.10	9.98	2.22	0.69	0.31
A1127	0.40	0.60	10.68	8.53	19.21	1.25	0.56	0.44
A1138	0.36	0.64	1.68	1.65	3.33	1.02	0.51	0.49
A1141	0.20	0.80	2.60	2.04	4.64	1.28	0.56	0.44
A1291	0.36	0.64	1.47	2.06	3.52	0.71	0.42	0.58
A1365	0.30	0.70	2.08	0.30	2.39	6.92	0.87	0.13
A1408	0.65	0.35	4.87	1.05	5.92	4.63	0.82	0.18
A1441	0.35	0.65	11.66	1.67	13.32	6.99	0.87	0.13
A148	0.42	0.58	2.57	1.44	4.01	1.79	0.64	0.36
A1497	0.66	0.34	10.20	1.57	11.77	6.50	0.87	0.13
A1543	0.46	0.54	2.46	0.83	3.29	2.98	0.75	0.25
A1565	0.39	0.61	9.30	1.97	11.27	4.72	0.83	0.17
A1570	0.58	0.42	4.64	2.34	6.98	1.98	0.66	0.34
A1602	0.50	0.50	6.63	1.40	8.04	4.73	0.83	0.17
A1622	0.53	0.47	9.31	0.69	10.00	13.47	0.93	0.07
A1673	0.44	0.56	2.22	1.73	3.95	1.28	0.56	0.44
A281	0.61	0.39	3.26	0.95	4.21	3.43	0.77	0.23
A329	0.53	0.47	4.43	0.53	4.96	8.30	0.89	0.11
A490	0.17	0.83	0.78	1.20	1.98	0.65	0.39	0.61
A492	0.46	0.54	3.32	1.75	5.07	1.90	0.66	0.34
A609	0.42	0.58	2.90	0.75	3.65	3.86	0.79	0.21
A61	0.43	0.57	3.79	0.81	4.60	4.69	0.82	0.18
A661	0.32	0.68	5.96	1.59	7.55	3.74	0.79	0.21
A687	0.27	0.73	0.74	0.50	1.24	1.48	0.60	0.40
A693	0.33	0.67	9.49	2.39	11.88	3.97	0.80	0.20
A728	0.61	0.39	15.52	1.90	17.42	8.17	0.89	0.11
A759	0.78	0.22	2.87	0.31	3.18	9.18	0.90	0.10
A871	0.51	0.49	3.42	1.87	5.29	1.82	0.65	0.35
A872	0.53	0.47	3.27	0.60	3.87	5.42	0.84	0.16
A886	0.54	0.46	3.80	1.01	4.81	3.74	0.79	0.21
A890	0.44	0.56	6.00	1.34	7.33	4.49	0.82	0.18
B1078	0.43	0.57	9.46	0.80	10.26	11.88	0.92	0.08
B1090	0.38	0.62	0.69	0.32	1.00	2.16	0.68	0.32
B1099	0.55	0.45	3.85	2.64	6.48	1.46	0.59	0.41

B1128	0.46	0.54	3.17	1.60	4.77	1.99	0.67	0.33
B113	0.37	0.63	7.91	1.39	9.29	5.71	0.85	0.15
B1180	0.60	0.40	5.46	1.88	7.34	2.90	0.74	0.26
B1211	0.44	0.56	14.56	3.59	18.15	4.05	0.80	0.20
B1257	0.67	0.33	5.83	0.62	6.45	9.39	0.90	0.10
B1259	0.78	0.22	4.72	1.09	5.81	4.35	0.81	0.19
B1389	0.65	0.35	2.23	0.96	3.19	2.32	0.70	0.30
B1421	0.50	0.50	16.31	3.05	19.36	5.35	0.84	0.16
B1506	0.31	0.69	2.93	0.70	3.63	4.20	0.81	0.19
B1544	0.80	0.20	1.11	0.13	1.23	8.66	0.90	0.10
B159	0.63	0.37	9.88	3.87	13.75	2.55	0.72	0.28
B160	0.54	0.46	4.28	1.56	5.84	2.75	0.73	0.27
B1618	0.23	0.77	7.26	2.97	10.22	2.45	0.71	0.29
B1651	0.45	0.55	11.77	1.84	13.61	6.38	0.86	0.14
B1680	0.67	0.33	10.65	1.58	12.22	6.75	0.87	0.13
B1688	0.52	0.48	2.69	3.91	6.61	0.69	0.41	0.59
B1694	0.45	0.55	4.97	1.71	6.68	2.91	0.74	0.26
B1696	0.65	0.35	2.74	0.86	3.61	3.19	0.76	0.24
B173	0.76	0.24	5.20	1.18	6.38	4.40	0.81	0.19
B197	0.66	0.34	4.90	0.94	5.84	5.20	0.84	0.16
B221	0.53	0.47	3.86	0.66	4.52	5.88	0.85	0.15
B240	0.69	0.31	10.84	0.72	11.55	15.06	0.94	0.06
B288	0.37	0.63	4.78	1.52	6.30	3.14	0.76	0.24
B344	0.61	0.39	6.49	0.90	7.40	7.18	0.88	0.12
B568	0.48	0.52	0.83	1.09	1.92	0.76	0.43	0.57
B576	0.55	0.45	5.34	0.84	6.18	6.36	0.86	0.14
B579	0.57	0.43	3.35	0.47	3.82	7.12	0.88	0.12
B645	0.19	0.81	22.83	5.42	28.25	4.21	0.81	0.19
B669	0.56	0.44	3.98	1.22	5.21	3.26	0.77	0.23
B69	0.20	0.80	11.04	4.55	15.59	2.43	0.71	0.29
B728	0.31	0.69	7.58	2.91	10.49	2.60	0.72	0.28
B878	0.45	0.55	3.59	1.77	5.36	2.03	0.67	0.33
B899	0.76	0.24	5.76	0.69	6.44	8.38	0.89	0.11
B904	0.53	0.47	13.11	1.40	14.51	9.39	0.90	0.10
B910	0.48	0.52	1.25	0.43	1.68	2.93	0.75	0.25
B921	0.51	0.49	2.02	0.92	2.94	2.20	0.69	0.31
B937	0.56	0.44	2.70	0.49	3.20	5.46	0.85	0.15
B944	0.41	0.59	12.05	5.36	17.40	2.25	0.69	0.31
B957	0.37	0.63	5.47	0.66	6.13	8.27	0.89	0.11
B980	0.61	0.39	1.71	1.31	3.02	1.30	0.57	0.43
B992	0.40	0.60	1.38	0.64	2.02	2.15	0.68	0.32
B994	0.41	0.59	1.10	0.66	1.77	1.66	0.62	0.38

C115	0.46	0.54	6.44	1.55	7.98	4.16	0.81	0.19
C139	0.39	0.61	2.22	0.73	2.95	3.06	0.75	0.25
C22	0.45	0.55	3.04	0.73	3.77	4.18	0.81	0.19
C62	0.59	0.41	12.84	2.02	14.86	6.37	0.86	0.14
C7	0.42	0.58	1.42	0.23	1.65	6.28	0.86	0.14
D108	0.19	0.81	1.43	0.65	2.08	2.20	0.69	0.31
D1116	0.63	0.37	11.06	0.89	11.95	12.44	0.93	0.07
D266	0.68	0.32	11.49	1.21	12.70	9.47	0.90	0.10
D300	0.60	0.40	7.76	1.34	9.10	5.80	0.85	0.15
D534	0.67	0.33	9.71	1.85	11.56	5.25	0.84	0.16
D686	0.50	0.50	2.47	0.51	2.98	4.84	0.83	0.17
D704	0.40	0.60	15.65	2.00	17.65	7.80	0.89	0.11
E1137	0.31	0.69	6.71	1.50	8.21	4.48	0.82	0.18
E199	0.53	0.47	1.83	0.74	2.58	2.46	0.71	0.29
E231	0.39	0.61	1.70	1.57	3.27	1.09	0.52	0.48
E236	0.80	0.20	21.39	1.97	23.36	10.85	0.92	0.08
E307	0.78	0.22	3.69	0.29	3.99	12.56	0.93	0.07
E315	0.48	0.52	1.73	0.56	2.30	3.07	0.75	0.25
E396	0.58	0.42	0.25	0.08	0.33	2.99	0.75	0.25
E442	0.33	0.67	2.20	1.80	4.00	1.22	0.55	0.45
E443	0.23	0.77	3.80	1.72	5.52	2.21	0.69	0.31
E544	0.62	0.38	1.94	1.26	3.20	1.54	0.61	0.39
E635	0.71	0.29	7.52	1.40	8.92	5.38	0.84	0.16
E639	0.21	0.79	3.30	1.15	4.44	2.88	0.74	0.26
E708	0.63	0.37	1.65	0.78	2.43	2.13	0.68	0.32
E828	0.52	0.48	4.15	1.40	5.55	2.96	0.75	0.25
E871	0.37	0.63	1.32	0.96	2.28	1.37	0.58	0.42
E876	0.71	0.29	4.36	0.86	5.22	5.05	0.83	0.17
E927	0.46	0.54	3.23	2.42	5.66	1.33	0.57	0.43

ID	LF Gain	HF Gain	BMI Categories (1=NW, 2=OW, 3=OB)	Parent with HBP (1=1parent 2=both)
A1048	11.03	24.06	1	1
A1067	11.44	19.32	1	0
A1127	7.49	7.10	1	0
A1138	14.40	16.50	1	0
A1141	26.26	57.64	2	0
A1291	16.29	13.54	1	0
A1365	23.18	61.68	1	0
A1408	12.42	12.36	1	0
A1441	5.77	18.57	1	0
A148	15.89	17.97	1	1

A1497	13.76	13.29	3	1
A1543	24.80	35.17	1	0
A1565	13.95	25.15	1	0
A1570	9.73	8.67	2	0
A1602	10.93	20.23	1	0
A1622	8.20	24.18	2	0
A1673	18.68	21.44	1	0
A281	3.79	6.72	1	0
A329	15.90	30.88	2	0
A490	31.22	36.62	1	1
A492	9.26	13.39	1	0
A609	18.98	39.08	1	0
A61	9.08	19.40	1	0
A661	14.05	25.10	1	0
A687	17.09	32.13	1	0
A693	8.21	23.78	1	0
A728	5.82	11.34	1	0
A759	10.88	16.69	1	0
A871	18.75	23.36	1	0
A872	16.79	26.88	1	0
A886	15.49	19.89	1	0
A890	6.13	15.31	1	0
B1078	16.81	35.09	2	0
B1090	35.71	52.53	1	0
B1099	14.53	10.61	1	0
B1128	20.91	20.84	1	0
B113	9.00	13.55	1	0
B1180	4.82	5.05	3	1
B1211	12.44	21.47	1	0
B1257	12.55	17.94	1	0
B1259	5.82	6.53	3	0
B1389	17.89	18.67	1	0
B1421	11.69	17.93	1	0
B1506	12.40	33.85	0	0
B1544	29.68	35.62	1	0
B159	11.58	9.79	2	0
B160	7.40	12.15	3	0
B1618	13.91	26.25	3	0
B1651	4.10	8.99	2	0
B1680	6.68	12.61	1	0
B1688	10.72	8.69	1	1
B1694	12.53	18.59	1	0

B1696	13.23	13.69	1	0
B173	10.58	11.86	1	0
B197	16.05	20.62	1	1
B221	16.87	22.98	2	1
B240	5.95	10.04	2	0
B288	10.72	19.02	1	0
B344	10.71	17.41	1	0
B568	22.75	19.42	1	0
B576	20.95	36.12	1	1
B579	10.71	17.65	2	0
B645	10.31	17.43	3	0
B669	7.33	10.27	1	1
B69	13.14	21.46	2	0
B728	12.90	24.30	3	0
B878	12.90	18.01	2	0
B899	3.48	5.85	3	1
B904	10.36	22.79	1	0
B910	29.29	41.67	1	0
B921	15.22	21.13	1	0
B937	24.09	43.47	1	0
B944	15.38	20.09	2	0
B957	10.66	26.86	1	0
B980	12.55	8.76	1	0
B992	12.79	18.07	1	
B994	18.29	21.60	2	0
C115	27.28	37.29	3	0
C139	15.76	26.37	2	0
C22	19.08	32.05	1	0
C62	18.16	26.06	1	0
C7	21.13	46.09	1	0
D108	1.51	3.25	1	1
D1116	6.85	13.60	3	0
D266	13.69	23.17	1	0
D300	7.48	12.58	2	0
D534	14.70	13.90	3	0
D686	18.98	26.16	1	0
D704	5.77	16.08	1	0
E1137	1.88	10.47	1	1
E199	14.91	15.86	2	0
E231	26.55	22.68	1	0
E236	7.96	9.64	3	1
E307	13.43	17.41	1	

E315	12.67	25.50	2	
E396	31.64	37.83	1	0
E442	16.41	23.26	1	0
E443	20.24	35.73	1	0
E544	16.25	15.13	1	0
E635	4.41	5.12	3	0
E639	12.71	22.84	1	0
E708	9.74	10.32	1	1
E828	11.02	15.30	3	0
E871	33.89	49.10	1	0
E876	16.42	21.63	1	1
E927	21.98	22.19	1	0