

THE PENNSYLVANIA STATE UNIVERSITY  
SCHREYER HONORS COLLEGE

DEPARTMENT OF KINESIOLOGY

EVALUATION OF BLOOD PRESSURE ESTIMATION USING PULSE TRANSIT TIME  
DURING CHANGES IN PHYSIOLOGICAL STATUS

AMANDA SKLARSKY  
FALL 2018

A thesis  
submitted in partial fulfillment  
of the requirements  
for a baccalaureate degree  
in Science  
with honors in Kinesiology

Reviewed and approved\* by the following:

Dr. James Pawelczyk  
Associate Professor of Physiology and Kinesiology  
Thesis Supervisor

Dr. Jinger Gottschall  
Associate Professor of Kinesiology  
Honors Adviser

\* Signatures are on file in the Schreyer Honors College.

## ABSTRACT

The nation's leading cause of death since 1921 – Cardiovascular Disease (CVD) – is a pressing issue in society. Blood Pressure (BP) is a significant indicator of cardiovascular health and is thus central to much research. The issue lies in the fact that BP is generally not measured on a day-to-day basis, as the available forms of measurement are uncondusive to daily measurement (i.e. cuff-based, non-continuous, and/or invasive). Pulse Transit Time (PTT) – the time delay between blood ejection to the heart to arrival at a peripheral point – is a promising metric in overcoming this issue and has been incorporated in a few wearable medical devices to date.

This retrospective study aimed to determine whether PTT could withstand alterations in physiological status, specifically alterations in cardiac output and resistance. These changes were elicited via Cold Pressor Test (CPT) and Static Handgrip (SHG) protocols and were intended to reveal whether PTT is truly a reliable measurement that can be used in daily life by consumers of wearable medical devices.

The results showed that there was, in fact, a significant difference between conditions (CPT vs. SHG) in BP measurement. Thus, PTT may not be transferable across physiological conditions. In the form utilized in this investigation, PTT does not appear to be sufficiently accurate for use in wearable medical devices. However, the inverse relationship between PTT and BP was consistent with that of other research studies, so PTT may be useful in considering relative changes in BP. Further research might consider individualized calibration to overcome variability between subjects. Nevertheless, the significant difference between the physiological states calls into question the broad utility of estimations of BP from PTT. Estimates derived with this methodology should be interpreted conservatively.

## TABLE OF CONTENTS

LIST OF FIGURES .....	iii
LIST OF TABLES .....	iv
ACKNOWLEDGEMENTS .....	v
Chapter 1 Introduction .....	1
Chapter 2 Literature Review .....	4
Chapter 3 Methods .....	14
Chapter 4 Results .....	21
Chapter 5 Discussion .....	27
Appendix A Informed Consent Forms.....	32
BIBLIOGRAPHY .....	50

## LIST OF FIGURES

Figure 1: Kymograph, invented in 1847 by Carl Ludwig.....	5
Figure 2: a) The time delay between proximal and distal arterial pressure waveforms provides an estimation for Pulse Transit time. b) The inverse relationship between DBP and PTT <sup>24</sup> .....	8
Figure 3: PEP denoted at point D – Isovolumetric Contraction – in the Wigger Diagram and depicted in Phase 2a on bottom of image. During this time, the left ventricle contracts (see increase in pressure at point D), but ventricular volume is constant <sup>39</sup> . .....	9
Figure 4: Subject Characteristics .....	15
Figure 5: Blood Pressure, Heart Rate, and Pulse Transit Time vs. Time during the Static Handgrip Protocol .....	22
Figure 6: Blood Pressure, Heart Rate, and Pulse Transit Time vs. Time for the Cold Pressor Test Protocol .....	24
Figure 7: Relation between systolic blood pressure (SBP) and pulse transit time (PTT) .....	25
Figure 8: Scanadu Scout (left) and Heartisans <sup>TM</sup> watch (right) .....	27

**LIST OF TABLES**

Table 1: Regression analysis of SBP and PTT .....	26
Table 2: Regression equations during each autonomic state for the CPT and SHG paradigms.....	29

## **ACKNOWLEDGEMENTS**

I would like to sincerely thank my thesis supervisor, Dr. Pawelczyk, for mentoring me throughout the past two years. There was never a time I left his office without a new daunting challenge ahead of me, but through his guidance, there was no challenge that was insurmountable. I would also like to thank Dr. Nathan Garvin for all of his knowledge and assistance. Lastly, I would like to thank the wonderful people I am fortunate enough to call my family and friends for all of their love and support.

## Chapter 1

### Introduction

Cardiovascular Disease (CVD) has been the nation's leading cause of death since 1921<sup>1</sup>. As of 2017, the Centers for Disease Control and Prevention reports that CVD accounts for 1 in every 4 deaths in the United States<sup>16</sup>. Furthermore, the disease is the number one cause of death on a global level, claiming 17.3 million lives per year according to a 2015 American Heart Association report. To address this global issue, investigative studies have sought preventative solutions. Because blood pressure (BP) is a significant indicator of long-term cardiovascular health<sup>15</sup>, the medical community stresses the importance of maintaining a healthy blood pressure to lower the risk of developing CVD<sup>23</sup>.

Traditionally, sphygmomanometers (cuff-based methods) have been used to measure blood pressure. While the use of sphygmomanometers has been the “gold standard” for non-invasive determination of blood pressure since the pioneering work of Korotkoff in 1906, there are practical limitations to the use of cuff-based methods for BP measurement<sup>36</sup>. For instance, a sphygmomanometer cannot provide a continuous BP record – and thus cannot capture short-term BP changes – due to the 1-2 minute pause taken between BP measurements necessary to reduce error<sup>7</sup>. Moreover, the cuff itself tends to be bulky and interferes with everyday life.

Intra-arterial blood pressure monitoring provides direct measurement via the insertion of a cannula needle into an appropriate artery<sup>18</sup>. Although this method provides accurate *continuous* (beat-by-beat) BP measurement, the invasive nature of the method makes it unsuitable for everyday use.

In an age of wearable technology and rapid medical advancement, there has been a push in the medical device industry for the development of a cuff-less, continuous, noninvasive form of accurate blood pressure measurement<sup>9,15,17,19</sup>. Such a method would enable individuals to monitor BP on a regular basis and resultantly gain a more accurate depiction of overall state of health.

One method that overcomes both limitations is pulse transit time (PTT), the time required for the arterial pulse pressure wave to reach a peripheral point from the aortic valve<sup>31,39</sup>. PTT can be estimated as the time difference between the R wave in an electrocardiogram (ECG) – indicating depolarization of the ventricles – and the peak in photoplethysmogram (PPG) signal – indicating the arrival of blood at a peripheral artery<sup>21</sup>. Since blood pressure is directly proportional to the speed of the arterial pulse pressure wave, PTT has an inversely proportional relationship with BP<sup>39</sup>. Thus, an increase in BP corresponds with a relatively short PTT; conversely, a decrease in BP corresponds with a relatively long PTT<sup>39</sup>.

This relationship between PTT and BP has been verified in numerous studies including – but not limited to – those involving vasodilator and vasoconstrictor drugs, which alter vascular tone in a homogenous fashion<sup>8,32</sup>. However, PTT has not been reliably tested under a range of *physiological* conditions.

The Moens-Korteweg (M-K) equation (see Eq1) relates PTT to BP by defining pulse wave velocity (PWV) – vessel length divided by PTT – as a function of density, vessel radius, vessel wall thickness, and the vascular wall elastic modulus<sup>38</sup>. Is PTT alone sufficient to yield a BP reading “accurate enough” to be incorporated in a reliable product in everyday life? In other words, can one ignore changes in arterial diameter and stiffness, as well as for the pre-ejection period (PEP), the time of isovolumetric contraction of the left ventricle before blood ejects



through the aorta, and still derive accurate estimation of blood pressure? One might hypothesize that failing to account for these factors would call into question the validity of BP readings measured via PTT; the degree of error created by these simplifications, however, is uncertain<sup>26</sup>.

The purpose of this study was to determine if the relationship between PTT and BP is reliable 1) *within* an individual with higher sympathetic activation invoked through physiological states (rest, Static Handgrip (SHG) Exercise, Cold Pressor Test (CPT), and Post-Exercise Circulatory Arrest (PECA)) and 2) *between* individuals undergoing those same physiological conditions. If the PTT-BP relationship is unchanged by these varying states in different subjects, perhaps factors such as PEP and differences in arterial diameter and stiffness could be considered negligible and steps can be taken towards the implementation of PTT in a wearable device.

**Thesis Statement (stated as the null hypothesis):** PTT, measured as the time from the R-wave of the ECG to the peak of the PPG, can be used to estimate systolic blood pressure only when physiological status (e.g. heart rate and sympathetic activation) is known.

## **Chapter 2**

### **Literature Review**

#### **The Pressing Issue of Hypertension**

Hypertension, defined as an average blood pressure of at least 140/90 mmHg, affects 25-43% of the world's adult population<sup>29</sup>. If left untreated, the prolonged strain on the vessel walls contributes to Cardiovascular Disease (CVD), an umbrella term for a list of conditions that comprise the leading cause of death in the United States. Two of the conditions falling under this umbrella, ischemic heart disease and stroke, are the world's biggest killers<sup>43</sup>.

Hypertension is both a primary and secondary risk factor for CVD. Risk of developing a variety of conditions categorized under CVD – such as stroke, coronary artery disease, heart failure, atrial fibrillation, and peripheral vascular disease – is increased by the presence of hypertension.

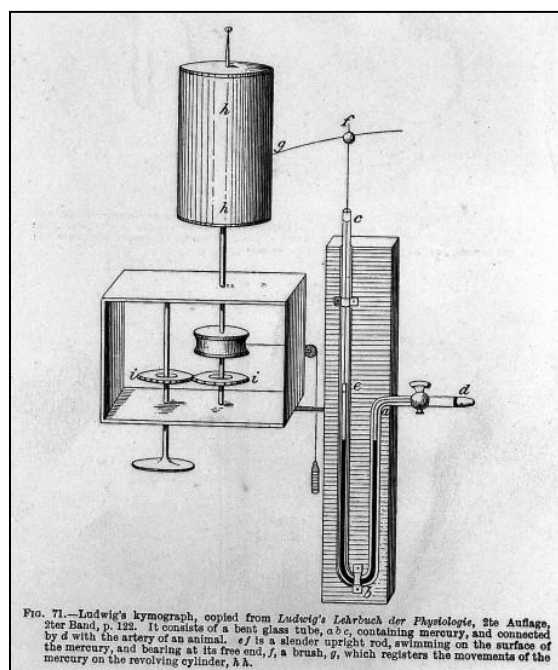
Needless to say, the consequences of developing and maintaining hypertension are severe; as such, there has been a recent increased demand for blood pressure monitoring devices.

#### **Existing Blood Pressure Measurement Methods**

The global market for devices that monitor blood pressure is projected to increase at a compound annual growth rate of 7.27% between 2018 and 2022<sup>22</sup>. However, the growth of blood pressure monitoring devices in the past has been quite slow relative to current projected growth rates.

The first documented measurement of blood pressure was in 1733 by Stephen Hales, who measured blood flow through a glass tube attached to a pipe and inserted into the artery of a

horse<sup>6,44</sup>. The next major milestone in blood pressure measurement was not until 1828, when Jean Leonard Marie Poiseuille, known as one of the first “physician physicists,” measured blood pressure by inserting a cannula filled with potassium carbonate into an artery and attaching it to a mercury manometer. With each heartbeat, blood pressure was measured by the amount of blood displaced the mercury in the manometer. This technique was enhanced in 1847 by Carl Ludwig, inventor of the kymograph (See Figure 1)<sup>6,44</sup>. By attaching a float pen to a revolving drum, each pulse (resulting in movement of the mercury) created a graphical depiction of that pulse.



**Figure 1: Kymograph, invented in 1847 by Carl Ludwig**

*Noninvasive* measurements of blood pressure were not introduced until the mid-late 1800s. Samuel Siegfried Karl Ritter von Basch and Pierre Potain conducted a series of improvements upon Etienne Jules Marey’s methods and measured blood pressure by occluding the arm in a water-filled chamber, placing a rubber bag around a manometer bulb, and inflating the bag with air.

The first use of a cuff to occlude the arm was Scipione Riva-Rocci in 1896<sup>6,44</sup>. The cuff was placed around the arm, and the pressure was increased until the radial pulse disappeared. At this point, the cuff was released, and the pressure at which the pulse returned was considered equivalent to systolic pressure. The identification of diastolic pressure, however, was not possible until 1905 when Nikolai Korotkoff discovered specific changes in sound (commonly known as Korotkoff sounds) as blood flow transitioned from turbulent to laminar with cuff deflation<sup>6,44</sup>.

Although integral to modern-day advancements, all the aforementioned methods of blood pressure measurement exhibit limits to practical and everyday use. Invasive measurements come with risk of infection and other complications, and the bulky cuff and quiet atmosphere necessary for the Riva-Rocci method with the supplement of Korotkoff sounds is impractical for everyday monitoring of blood pressure. Additionally, the Riva-Rocci and Korotkoff methods do not allow for a continuous measurement of blood pressure.

The Finapres device was introduced in the 1970's and allowed for the measurement of arterial pressure in the finger via infrared light transmission. It successfully implements the technique described by the Czechoslovakian researcher Jan Peňáz in 1967. A cuff placed around the finger connected to a fast servo pump applies varying degrees of pressure exactly opposite to blood pressure<sup>27</sup>. The constancy of near infra-red light transmitted across a digital artery is used to assure that the arterial volume is clamped by the servo pump. Under this set of conditions, the cuff pressure is related to blood pressure<sup>42</sup>. This method of blood pressure measurement has been proven to achieve errors within AAMI limits; however, the use of the cuff makes measuring BP cumbersome<sup>33</sup>.

Similarly, the 1990's were marked by the advent of arterial tonometry – a method in which an array of pressure sensors is placed against the superficial radial artery at the wrist – as a method of noninvasive, continuous blood pressure measurement<sup>20</sup>. Relatively inexpensive piezoelectric pressure sensors are used to measure oscillations of the pulse with considerable accuracy so long as the sensor array applanates the artery that is perpendicular to the wall tension. Although this method provides a continuous and noninvasive measurement of blood pressure, it is cumbersome and somewhat difficult to utilize properly. It is also highly sensitive to motion artifact, thus making it impractical for everyday continuous use<sup>24</sup>.

In short, none of the existing forms of blood pressure measurement provide a method that is simultaneously noninvasive, continuous, and ultra-convenient (i.e. suitable for today's mobile health revolution).

### **Physiological Factors that Influence Blood Pressure**

The balance between cardiac output and peripheral vascular resistance defines blood pressure. A relatively high cardiac output (as is seen during exercise) or a relatively high peripheral resistance (as is seen in chronic-stage hypertensive patients) will increase high blood pressure<sup>2</sup>. Peripheral resistance may increase semi-permanently if the vascular walls remodel such that the vessel walls thicken over time<sup>2</sup>. The most common example is aging, which stiffens the vessels and reduces compliance (the ability of a vessel to expand and contract in response to changes in pressure)<sup>12</sup>. Related factors that influence peripheral resistance – and thus influence blood pressure – include blood vessel diameter, blood viscosity, and vessel length. All of these factors affect the propagation of the arterial pressure through the vascular tree and the average blood pressure. In this simultaneous effect on pulse propagation and blood pressure, one finds the theoretical basis for a more practical and portable method of blood pressure measurement.

## What is Pulse Transit Time?

The time the pulse pressure waveform takes to propagate through the arterial tree – from one arterial site to another – is called *pulse transit time*<sup>39</sup>. The pulse pressure waveform, a direct effect of blood ejection from the heart, actually moves with a much greater velocity than the velocity of blood itself. Figure 2a provides a visual representation of the movement of the pressure wave. Pulse transit time is inversely proportional to blood pressure (see Figure 2b), whereas the speed of the waveform is directly proportional to blood pressure. PTT is shorter with a higher blood pressure, which is associated with a greater pulse wave velocity (PVW) and vascular tone, as well as stiffer arterial walls<sup>31</sup>. Low blood pressure, on the other hand, is associated with a longer PTT and a decrease in PVW, vascular tone, and arterial stiffness<sup>24</sup>.

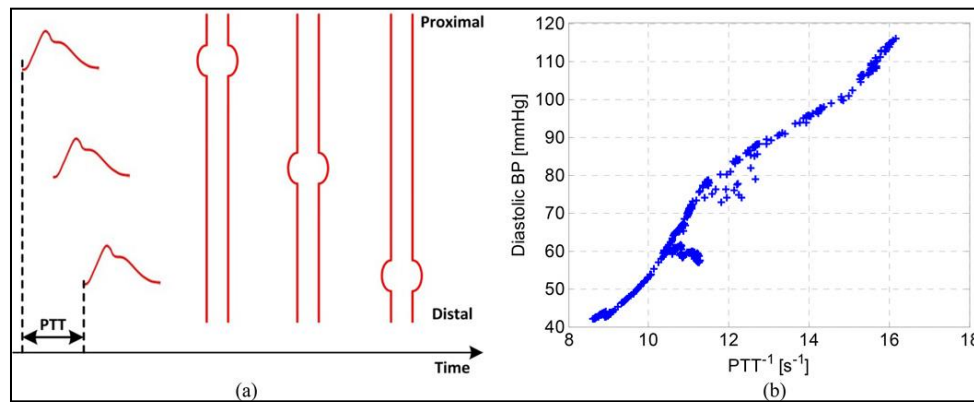
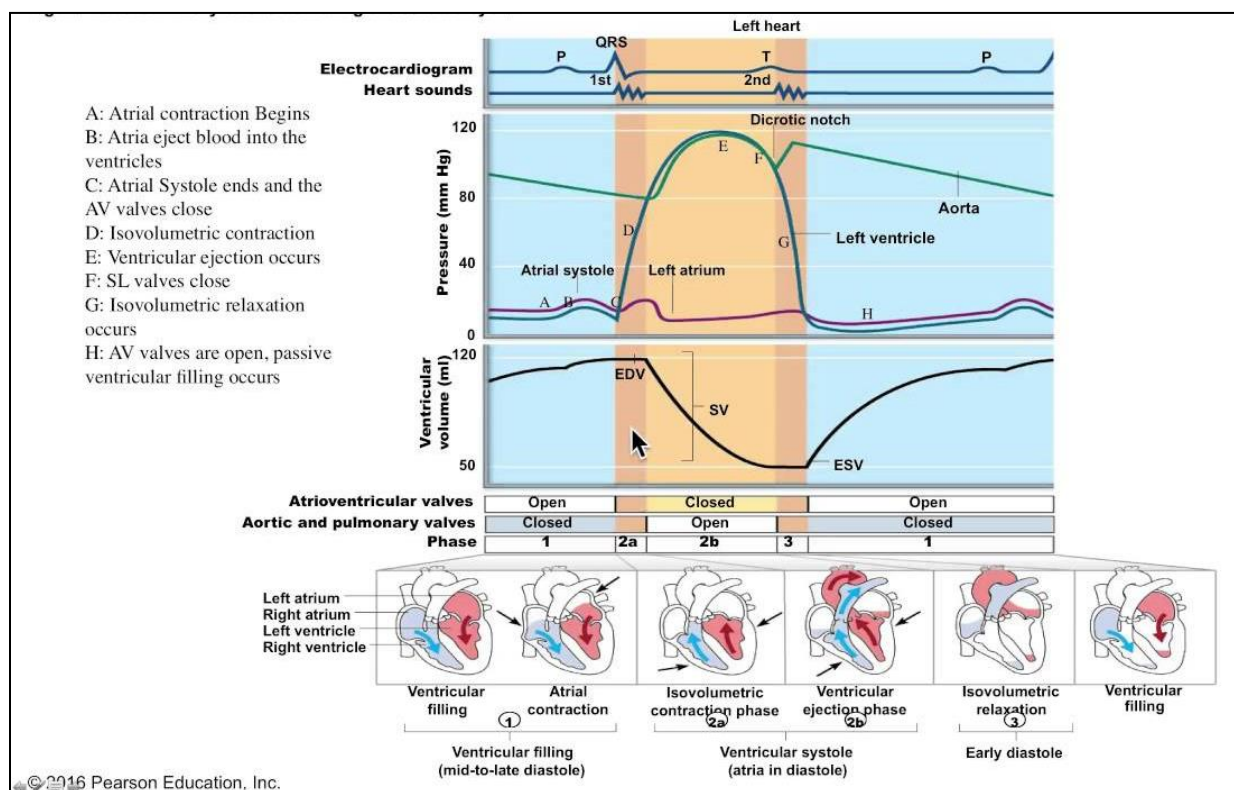


Figure 2: a) The time delay between proximal and distal arterial pressure waveforms provides an estimation for Pulse Transit time. b) The inverse relationship between DBP and PTT<sup>24</sup>

## Factors that Influence Pulse Transit Time

The first of several factors affecting PTT is the *pre-ejection period (PEP)* – the time of isovolumetric contraction of the left ventricle before blood ejects through the aorta (see Figure 3)<sup>34</sup>. The PEP does not represent the time between the exit of blood from the aorta to its arrival at a peripheral point (PTT); however, it is often erroneously included in the measurement of PTT obtained through ECG and PPG. The PEP varies with cardiac electrical and mechanical

properties and is thus variable in each individual and with each individual's heartbeat. Hence, inclusion of the PEP increases the duration and variability of the PTT estimation.



**Figure 3: PEP denoted at point D – Isovolumetric Contraction – in the Wigger Diagram and depicted in Phase 2a on bottom of image. During this time, the left ventricle contracts (see increase in pressure at point D), but ventricular volume is constant<sup>40</sup>.**

Additionally, differences in *Ventricular Stroke Volume* - the volume of blood pumped from the left ventricle per heartbeat – affect PTT. This parameter can be obtained by subtracting end-systolic volume from end-diastolic volume. A greater stroke volume means a larger amount of blood is ejected from the heart and PTT decreases as a result.

There are a number of factors which may affect stroke volume– and thus erroneously alter the measurement of PTT:

- Ventricular preload (the filling of the ventricle during diastole)
  - An increase in ventricular preload causes a decrease in PEP due to the resultant increased contractility elicited by an increase in ventricular preload. Moreover,

by allowing more blood to accumulate before ejection, an increase in preload causes an increase in stroke volume<sup>3</sup>.

- Afterload or aortic diastolic pressure (the pressure with which ventricular pressure must exceed in order for the aortic valve to open)
  - An increase in aortic diastolic pressure increases the length of the PEP due to the higher ventricular pressure that must be reached before the opening of the aortic valve and subsequent ejection of blood<sup>25</sup>. Again, an increase in afterload causes an increase in stroke volume because the greater pressure allows for a greater volume of blood to be ejected.
- Vascular tone / Alpha-adrenergic Effects (Alpha receptors, located on the arteries, constrict vascular smooth muscle when stimulated)
  - Adrenaline and noradrenaline infusion following beta-adrenergic blockade results in an increase in the PEP<sup>25</sup>.

Ultimately, the time it takes for the blood to reach a peripheral point from its exit from the heart (PTT) is correlated with BP, not the PEP; therefore, failing to account for these variables may result in an erroneous BP measurement.

### **Measurement of Pulse Transit Time**

PTT can be estimated as the interval in time between the R-wave of the ECG and a PPG signal<sup>11</sup>. To relate PTT to BP, however, pulse wave velocity (PWV) must also be calculated<sup>28</sup>. This is achieved via the Moens-Korteweg (M-K) equation (see Equation 1 below), where “C” is compliance – the change in the vessel cross-sectional area divided by the change in pressure of the vessel ( $\frac{dA}{dP}$ ), “L” is a constant representing the pressure required to accelerate blood ( $\frac{\rho}{A}$ ), “p”



is blood density, “A” is the cross-sectional area of the vessel, “E” is the elastic modulus, “h” is the vessel wall thickness, and “r” is the lumen radius<sup>24</sup>.

$$PWV = \frac{1}{\sqrt{L \cdot C}} = \sqrt{\frac{AdP}{\rho dA}} = \sqrt{\frac{Eh}{2r\rho}} \quad [Eq1]^{24}$$

PWV is then transformed to PTT via Equation 2.

$$PTT = 1\sqrt{LC(P)} \quad [Eq2]^{24}$$

### Limitations of PTT Approach

Pulse wave velocity – and thus PTT – is defined using the Moens-Korteweg (M-K) equation (see above), which assumes that arterial stiffness and diameter remain unchanged<sup>24</sup>. However, arterial stiffness does in fact change with factors such as age, disease, caffeine use and alterations in sympathoadrenal state. With increased vessel wall stiffness (decreased compliance), PWV increases. Similarly, arterial diameter changes over the cardiac cycle and is regulated by the contraction or relaxation of the vascular smooth muscle. Failing to account for changes in arterial stiffness and diameter could negatively impact an estimation of blood pressure from PTT. That said, if factors affected by aging such as arterial elasticity were to be accounted for periodically, this intermittent recalibration would improve the utility of PTT for chronic, ambulatory BP monitoring. Unknown is the impact of *physiological* variation in vascular tone on PTT and BP estimation.

Yet another delimitation for PTT is its failure to account for the pre-ejection period (PEP)<sup>24</sup>. As mentioned previously, incorrectly including this short time interval in the

measurement of PTT alters the validity of its corresponding blood pressure measurement. The degree of error which PEP causes, however, is unclear.

### **Methods to Perturb PTT and Blood Pressure**

While a number of studies have proven PTT can accurately estimate BP when vascular tone and BP are perturbed by intravenous drugs, studies establishing the accuracy of PTT estimation of BP under a variety of physiological conditions are limited. Because BP is affected by such influences during everyday life, and because PTT will be utilized in everyday wearable devices, PTT estimation of BP must be tested thoroughly under a range of such conditions. Here we consider two classic paradigms to perturb BP physiologically: static handgrip (SHG), with post-exercise circulatory arrest (PECA), and cold pressor test (CPT).

#### Static Handgrip (SHG) Exercise and Post-Exercise Circulatory Arrest (PECA)

SHG has been utilized in numerous studies to investigate patterns in cardiovascular response<sup>14</sup>. Reliably, SHG increases systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) proportional to the degree and duration of the SHG exercise<sup>14</sup>.

Moreover, post-exercise circulatory arrest (PECA) has been studied extensively in conjunction with SHG<sup>14,35</sup>. By preventing blood flow to the contracting muscles, metabolites are trapped in the muscle interstitial space, eliciting the exercise pressor reflex to keep BP elevated while heart rate (HR) returns to a resting level. Because we wished to evaluate the PTT-BP relationship under several conditions, it was pertinent to obtain data from periods of increased cardiac output and elevated blood pressure (SHG Exercise), normal cardiac output and elevated blood pressure (PECA), and normal cardiac output and normal blood pressure (resting state).

### Cold Pressor Test (CPT)

CPT has been utilized in physiological studies to evaluate cardiac function and its corresponding BP response<sup>41</sup>. The activation of peripheral thermo/nociceptors elicits a large BP response with little change in HR<sup>14</sup>. Thus, the analysis of data from the CPT protocol permits the evaluation of the PTT-BP relationship under another physiological state where blood pressure is elevated.

### **Statement of the Problem**

The utility of BP estimation using PTT has not been extensively evaluated under physiological conditions. Accordingly, we evaluated the slope of the SBP-PTT relation during the conditions of rest, SHG, PECA, and CPT to determine if the relation was generalizable to a wide range of physiological states.

## **Chapter 3**

### **Methods**

#### **Part 1: Introduction and Population Characteristics**

This thesis is a retrospective study of the Static Handgrip (SHG) and Cold Pressor Test (CPT) protocols of Dr. Nathan Garvin's 2017 Dissertation, "Association of Variability in Cardiovascular Responsiveness to Reflex Activation of the Autonomic Nervous System with Genetics of Peripheral Sensory Receptors." This dissertation included five different autonomic tests. For the purpose of this thesis, protocols that elicited only modest changes in blood pressure (hypercapnic, hyperoxic rebreathing, immersion of the hand in warm water, and rhythmic handgrip exercise) were excluded. The two protocols that were included – static handgrip exercise with post-exercise circulatory arrest and cold pressor test – were delivered in randomized order during a single laboratory visit of approximately four hours duration. To ensure sufficient recovery time, 15 minutes of rest was included in between each protocol. The author aided in the data collection and primary analysis for these protocols from August 2016 to May 2017. The secondary analysis presented here was designed, implemented, analyzed and interpreted by the author.

The study population for this study was composed of subset of 17 individuals of the original study. Subjects were recruited from the University population of undergraduate students. They were excluded if they were training for competition (recreationally active volunteers were included). Additional exclusion criteria included oral contraceptive use; self-report of smoking within the last 30 days, use of blood pressure medication or any drug that might affect blood

pressure regulation; history of asthma, asthma symptoms or lung disease other than asthma; history of hypertension, resting tachycardia, or a body mass index (BMI) of  $\geq 30$  kg/m<sup>2</sup>. The selected subjects had the following characteristics:

	Low	High	p-value
n	14	17	
Gender*- M:F	9:5	12:5	
Gender*- M=1	0.64	0.71	0.720
Age* (years)	22.9 (0.7)	21.6 (0.7)	0.228
Height (m)	1.72 (0.03)	1.73 (.02)	0.762
Weight (kg)	68.9 (4.0)	71.9 (2.9)	0.537
BMI (kg/m <sup>2</sup> )	23.1 (0.7)	24.0 (0.6)	0.373
Handedness*- R:L	13:1	16:1	
Handedness*- R=1	0.93 (0.1)	0.94 (0.1)	0.892
Caffeine Drinks/Wk*	6.8 (2.1)	5.6 (1.2)	0.621
Alcohol Drinks/Wk*	6.1(1.6)	9.1 (2.4)	0.350
1 parent HTN*- Y:N	7:7	7:10	
1 parent HTN*- Y=1	0.50	0.41	0.637
2 parents HTN*- Y:N	2:12	1:17	
2 parents HTN*- Y=1	0.14	0.06	0.448
HR (BPM)	63 (2)	59 (2)	0.256
Brachial BP			
SBP (mmHg)	114 (3)	120 (2)	0.118
MAP (mmHg)	83 (2)	86 (2)	0.224
DBP (mmHg)	67 (2)	70 (1)	0.170

**Figure 4: Subject Characteristics**

The remaining subjects were not selected either because of data dropouts or transient interruptions in the quality of the blood pressure or electrocardiographic recordings that rendered them unsuitable for pulse-transit time analysis.

## **Part 2: Standard Pre-Examination Procedure**

Prior to the day of the study, subjects abstained from: rigorous exercise for 24 hours and caffeine and alcohol use for 12 hours. Moreover, they reported to the laboratory in the morning

after an overnight fast. To reduce the effects of circadian rhythms on resting BP, subjects began all procedures in the morning. After completing voluntary and written informed consent (approved by Penn State Institutional Review Board; see Appendix), subjects reclined on a bed in a 30° head-up and 20° legs-up position in a dimly lit, quiet, ambient temperature (22° C) room. Subjects remained in this state for a minimum of 15 minutes before the testing began.

Instrumentation included ECG electrodes for heart rate, a finger cuff for beat-to-beat determination of blood pressure using optoplethysmography (method of Peñáz) and microelectrodes for recording of muscle sympathetic nerve activity from the common or superficial peroneal nerve. Only the ECG and blood pressure data were used in this thesis.

### **Part 3: Static Handgrip (SHG) Exercise and Post-Exercise Circulatory Arrest (PECA)**

#### SHG Preparation:

A handgrip dynamometer was arranged to allow the subject to abduct their dominant arm 90° from midline onto a level tabletop supporting the dynamometer. The height of the table was adjusted so that the arm was level with the mid-axillary line. The greatest of three attempts – with a one-minute pause in between attempts – was recorded as the Maximum Voluntary Contraction (MVC). Afterwards, a 3-lead ECG monitor – to measure HR – and an Omron HEM-705CP and Finometer Midi FMS – to measure BP – were attached for data collection. Additionally, a blood pressure cuff of 10 cm width was wrapped around the upper arm of the subject's dominant hand in preparation for PECA.

Once the subjects were properly positioned and equipment was accurately recording, each component of the protocol was reviewed aloud. Subjects were instructed to breathe normally and relax all muscles, except for those involved in the handgrip.

SHG Protocol:

The protocol had the following structure: 5 minutes of rest (following the 15-minute period of unrecorded rest), 3 minutes of SHG at 30% MVC, inflation of the occlusion cuff on the exercising arm to 250 mmHg 5 seconds before the end of exercise, 2 minutes of PECA, and 3 minutes of recovery. A visual pain scale was presented to the subject where zero meant no pain, and ten meant the worst pain imaginable; subjects ranked their perceived pain twice during the 5 minutes of rest and once every minute for the remainder of the protocol.

Continuous BP measurement commenced 5 minutes prior to the onset of exercise. During this period of rest 5 minutes before to the start of exercise, subjects were instructed to rest their hand near the dynamometer; 20-30 seconds prior to the onset of SHG Exercise, the dynamometer was loosely placed in the subject's hand.

As the 3 minutes of exercise commenced, subjects referenced a monitor that displayed their target handgrip force and their real-time force exerted on the dynamometer. Subjects were verbally encouraged to maintain 30% of MVC during the 3 minutes of exercise, and the trial was omitted if the subject failed to maintain at least an average of 27% MVC or if the subject readjusted their grip on the device.

The occlusion cuff was set to 250 mmHg (or 50 mmHg more than the greatest SBP measurement during exercise). The cuff was inflated 5 seconds prior to the cessation of exercise and was maintained throughout the two-minute duration of PECA. During PECA subjects were instructed to release the dynamometer and rest their arm on the table, maintain a regular breathing pattern without talking, and to remain still.

Following the 3 minutes of exercise and 2 minutes of PECA, the cuff was released, and subjects maintained a relaxed, quiet state during a recovery period of 3 minutes. Perceived pain ranking and BP and HR monitoring continued throughout these 3 minutes.

#### **Part 4: Cold Pressor Test (CPT)**

Subjects were instrumented identically to the SHG protocol. After a 3-minute period of rest, the subject's hand was removed from the bed and lowered into a bucket containing a slurry of crushed ice and water. Temperature of the ice bath was recorded continuously and remained at 3.0-3.5°C by the addition of ice as needed. A small aerator was included in the bucket to keep the water stirred to prevent a boundary layer of warm water forming around the subject's hand. This position was maintained for 3 minutes.

During this time of cold water immersion, subjects were instructed to remain as motionless as possible and keep all muscles relaxed – especially those of the arm, hand, and fingers. Just as in the SHG protocol, subjects recorded their sensation on a visual pain scale of 0 (no pain) to 10 (worst pain imaginable); subjects ranked their pain twice during the 5 minutes of rest and once every minute thereafter.

After the 3 minutes of cold water immersion, the subject's arm was removed from the water by an investigator and placed on a towel laid across the subject's abdomen. Then, the subject completed 3 minutes of quiet rest to record physiological data during recovery.

#### **Part 5: Data Recording and Analysis**

Analog ECG and blood pressure recordings were computer sampled at 1000 Hz and stored for offline analysis (ADInstruments PowerLab 16/30 V5.5.6 and LabChart 7; Castle Hill,



Australia). Recordings were visually inspected for artifact or data dropouts and were excluded if they were not amenable to pulse-transit time analysis.

Static Handgrip and Cold Pressor Test data on the 17 subjects used in this retrospective study was extracted from LabChart and converted into Excel using LabView (National Instruments). The R-wave of the ECG was identified as a trigger and the minimum, maximum and average of blood pressure between R-wave triggers was used to determine beat-to-beat systolic (SBP), diastolic (DBP), and mean arterial (MAP) blood pressure, respectively. Furthermore, the following parameters were calculated: Start Time (sec), End Time (sec), Duration (sec), and HR (beat/min).

To determine pulse transit time (PTT), the times at peak ECG (i.e., the R wave) and BP (i.e., SBP) were identified by selecting the “active point” from the respective source channel in LabView. In the event that the software erroneously associated an ECG value with a BP value (e.g., a BP time that occurred *before*, rather than after, the ECG), the correct BP time was manually extracted from the raw data. The ECG and BP max times were copied into Excel documents and PTT was calculated on a beat-to-beat basis as the difference between BP max time and ECG max time with a resolution of 1 msec.

HR, BP, and PTT data were stored in separate Excel sheets for each subject and protocol. Data were then averaged in 30 sec bins (Excel AVG function) and coded by protocol for subsequent statistical analysis.

## **Part 6: Statistical Analysis**

The binned data were aggregated in a single file that was coded for subject, protocol, protocol phase, and time and imported into Minitab 18.1. Each variable (HR, SBP, DBP, MAP and PTT) were averaged across subjects at each time point for each protocol. Analysis-of-

variance with repeated measures was used to analyze the temporal changes in each variable during each protocol. Main effects were probed with post hoc t-tests to identify differences from control using a Bonferonni correction for multiple comparisons.

To test the hypothesis that PTT would predict blood pressure across a range of autonomic stimuli, a linear regression was performed where SBP was the dependent variable, PTT was the independent variable. Autonomic test (denoted as “condition”) and protocol phase (denoted as “PCode”) were included as categorical variables in the analysis. If, for example, the autonomic test was not a statistically significant contributor to the overall model then the SBP-PTT relation could be considered stable, independent of autonomic state.

In all cases, statistical significance was established when  $P < 0.05$ . Data are presented as mean  $\pm$  SE.

## Chapter 4

### Results

Subjects completed the two protocols without incident. The primary data are presented below, followed by the analysis of pulse transit time.

#### **Part 1: Static Handgrip with PECA**

At rest, hemodynamic conditions were stable. SBP was  $137 \pm 3$  mmHg, DBP was  $70 \pm 2$ , and HR was  $62 \pm 2$  beat/min. As expected, SHG elicited a concomitant rise in BP and HR, reaching a peak of  $185 \pm 6$  mmHg,  $105 \pm 4$  mmHg and  $89 \pm 3$  beat/min, respectively, during the third minute of exercise (all  $P < 0.01$  vs. rest). Once SHG ended and PECA began, both BP and HR decreased to  $172 \pm 4$  mmHg,  $94 \pm 3$  mmHg and  $66 \pm 5$  beat/min, respectively. Nevertheless, BP remained significantly greater than control, as expected. When the occluding cuff was released, BP returned rapidly to control values.

The change in PTT was directionally opposite to that of blood pressure, decreasing from  $277 \pm 5$  to  $259 \pm 8$  msec during SHG, and recovering to  $267 \pm 8$  msec during PECA.

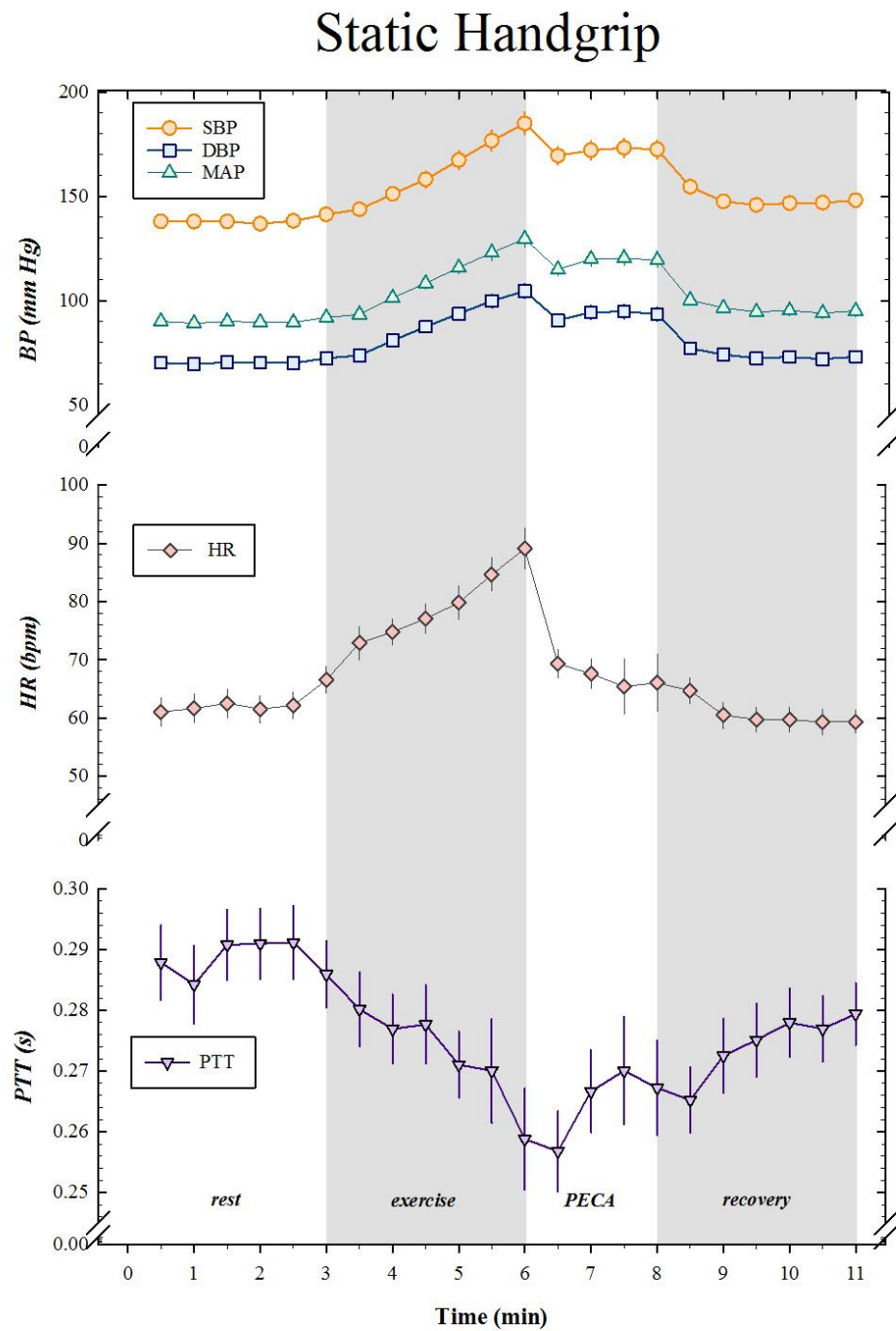


Figure 5: Blood Pressure, Heart Rate, and Pulse Transit Time vs. Time during the Static Handgrip Protocol

**Part 2: Cold Pressor Test**

At rest, hemodynamic conditions were stable. SBP was  $132 \pm 3$  mmHg, DBP was  $67 \pm 2$  and HR was  $61 \pm 3$  beat/min. However, HR tended to increase in the last minute prior to CPT; probably an anticipatory response to the ice water bath. Once CPT began, there was a prompt increase in HR to  $72 \pm 3$  beat/min during the first minute but this increase was not maintained over the duration of the test. The increase in blood pressure was slower, reaching a peak of  $162 \pm 4$  mmHg and  $92 \pm 3$  mmHg during the third minute of CPT ( $P < 0.01$  vs. rest). When CPT ended, both BP and returned rapidly to control values.

Like the SHG condition, PTT during CPT was inversely related to blood pressure. PTT decreased from  $287 \pm 6$  to  $274 \pm 6$  sec during the first two minutes of CPT and did not change significantly for the remainder of caloric stimulation, but it returned to control values during the recovery period.

# Cold Pressor Test

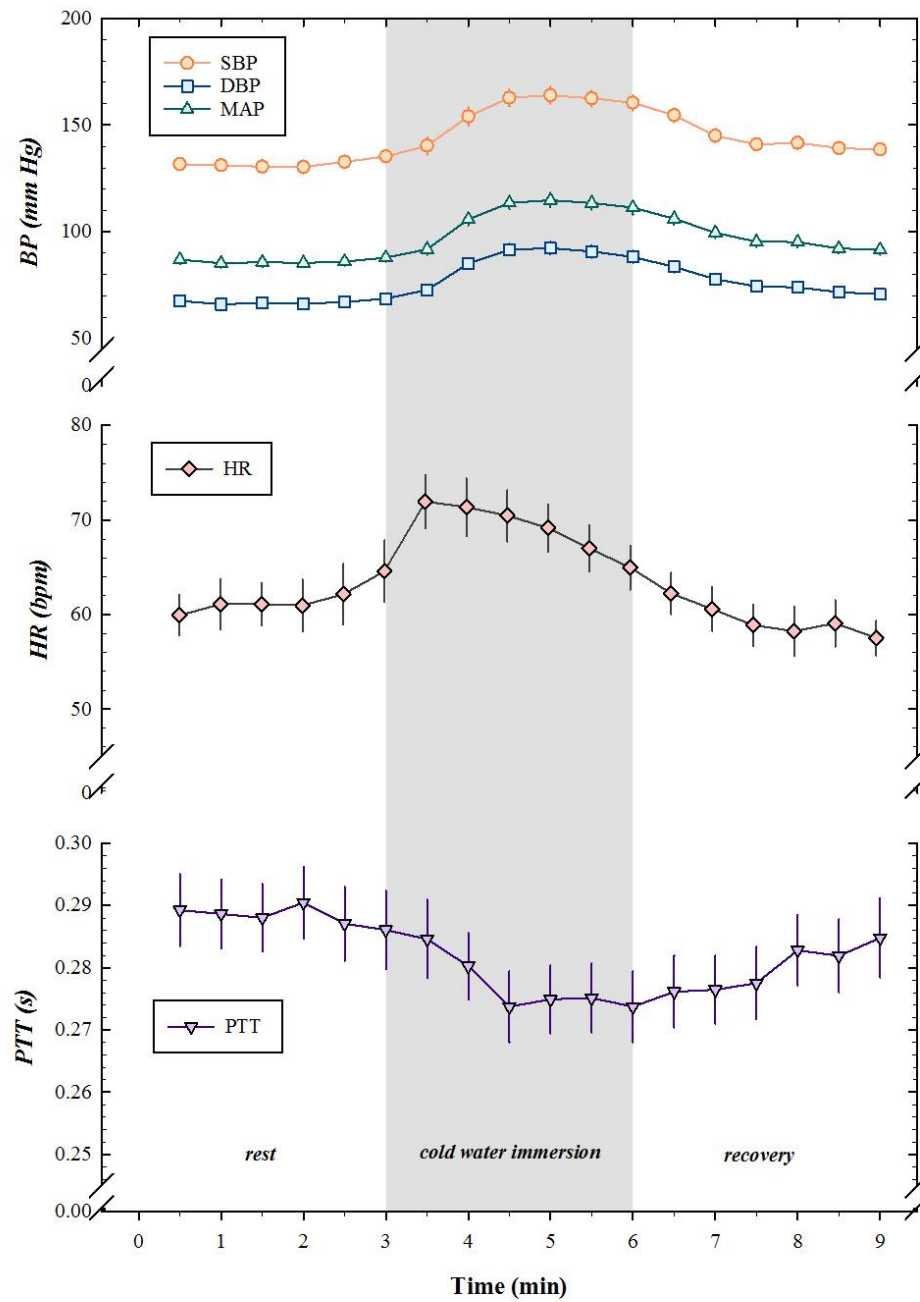
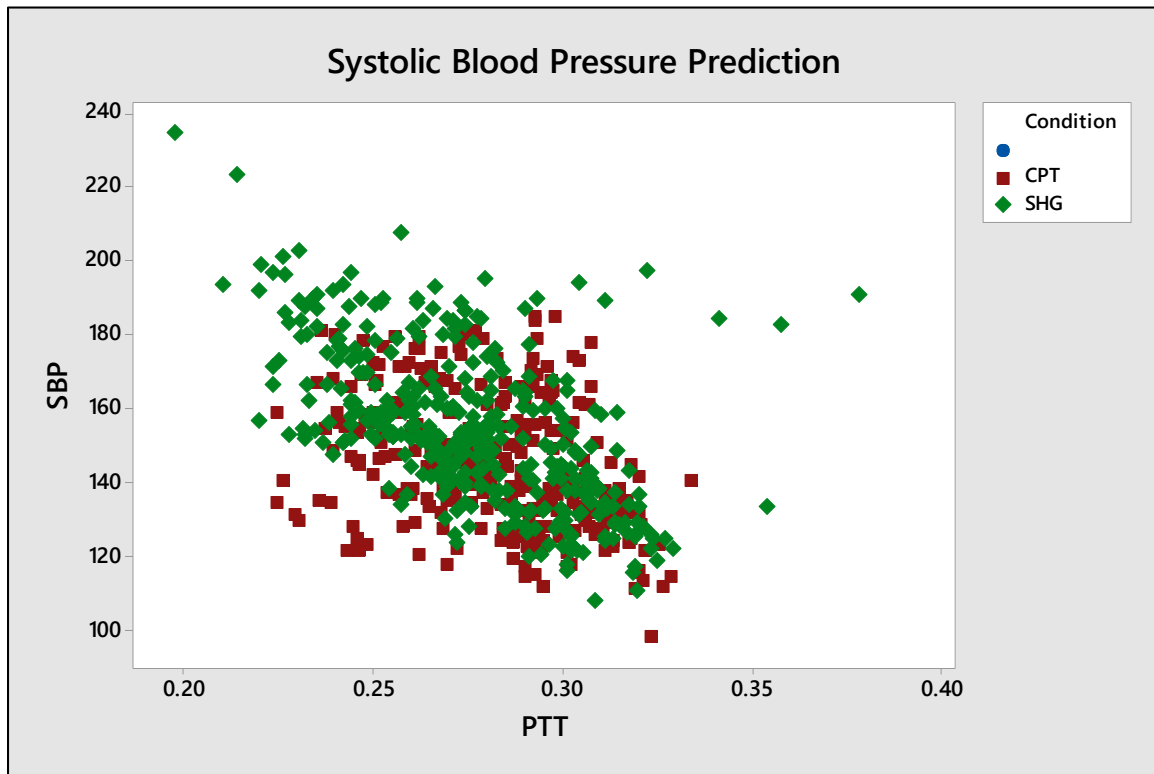


Figure 6: Blood Pressure, Heart Rate, and Pulse Transit Time vs. Time for the Cold Pressor Test Protocol

### Part 3: Prediction of SBP from PTT

Regression analysis was restricted to SBP and PTT. Although other BP parameters such as DBP and MAP could have been used, I considered SBP to be most appropriate because the systolic pressure wave is generated by ventricular contraction and is therefore best associated with ventricular depolarization (R wave of the ECG).

Figure 7 depicts the SBP-PTT relation. As expected, it was inverse, such that a greater PTT was associated with lower SBP. Visual inspection did not indicate any obvious difference between the SHG and CPT conditions.



**Figure 7: Relation between systolic blood pressure (SBP) and pulse transit time (PTT)**

Results of the regression analysis are presented in Table 1. The overall model was statistically significant ( $P < 0.0001$ ) with an adjusted  $R^2$  of 0.52. Indeed, PTT was the largest contributor to the model. However, both Pcode, a categorical dummy variable that indicated the

phase of each test (Rest, SHG, PECA and Recovery for SHG; Rest, CPT and Recovery for CPT) and Condition, a categorical dummy variable that coded each autonomic test, were significantly different ( $P < 0.0001$  and  $P < 0.001$ , respectively). This indicates that PTT may not, in fact, be generalizable across the multiple physiological conditions an individual experiences in everyday life. The implications of this finding are discussed in the next section.

**Table 1: Regression analysis of SBP and PTT**

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Regression	7	143930	20561.4	102.11	0.000
PTT	1	36156	36155.7	179.55	0.000
Pcode	5	61269	12253.8	60.85	0.000
Condition	1	2092	2091.9	10.39	0.001
Error	663	133510	201.4		
Lack-of-Fit	628	130981	208.6	2.89	0.000
Pure Error	35	2529	72.2		
Total	670	277440			



## Chapter 5

### Discussion

The goal of this study was to determine if PTT could be used as the basis of a valid form of cuffless, continuous, noninvasive BP measurement. Since the Pcode and Condition variables accounted for a portion of the variance in the model, the results indicate that PTT – and the generalizations made by the M-K Equation – may not be sufficient to estimate BP in a wearable device under a variety of everyday scenarios.

However, two notable medical devices are currently utilizing the PTT approach: the Scandu Scout (though the FDA required deactivation of the Scanadu Scout by May 15, 2017 after a 5-year clinical trial) and the Heartisans Watch (available through foreign distributors, but not currently approved by the FDA)<sup>17,30</sup>. Although the implementation differs somewhat, the devices share some common features:

- Highly portable and designed for “mobile health” applications
- Measurement of PTT from ECG origin to the Pulse Wave occurrence
- Utilization of aforementioned assumptions of the M-K Equation to derive blood pressure



Figure 8: Scanadu Scout (left) and Heartisans™ watch (right)

When viscosity of blood, cross-sectional area of the vessel and wall thickness are constant, the simplified form of the M-K equation should be valid. Over relatively brief periods of time (less than one week), when vascular remodeling would not be expected to be an important factor in vascular architecture or function, these assumptions are probably reasonable. As discussed above, the assumption of a constant elastic modulus, however, is more problematic, as it can be affected by both the composition of the vascular wall in the long term and sympathetic tone in the short term. It is the dynamic conditions of changing autonomic state that afforded the opportunity to directly evaluate the validity of this simplification.

If PTT is a reliable estimate of BP under a range of physiological conditions – and is suitable to be incorporated in wearable devices – we expect it to be generalizable over these stresses. Throughout this study, vascular resistance and tone were modified by the changes in sympathetic stimuli. If these stimuli did not affect the elastic modulus appreciably, then neither the Pcode nor Condition variable should have accounted for any significant portion of the variance in the regression model. Alternatively, a significant contribution of either variable to the model would call into question the assumptions made by the M-K equation, and subsequently, the assumptions made by these devices.

It was disappointing to find there was a significant difference between the SBP-PTT relation for the two within condition (SHG and PECA) and two between condition (SHG and CPT) changes in autonomic tone. This finding suggests that the simplifications in the M-K Equation needed to employ PTT in these devices is inappropriate, hindering the progress of the development of a revolutionary device with the power to *accurately* measure BP over the range of physiological conditions a consumer might encounter in everyday life.

The simplified form of the M-K equation has been verified under pharmacological conditions. Sharwood-Smith et al. (2006) tested this method during infusions of vasopressor and vagolytic agents and found PTT is related to arterial pressure changes and that this relationship is the same in normotensive subjects as well as those with pregnancy-induced hypertension (PIH)<sup>32</sup>. Our approach was different in that it utilized *physiological* stress to change sympathetic activity. Our logic was twofold: 1) these stresses are more representative of changes in sympathetic activity during activities of daily living; 2) they are dependent on intra- and inter-individual variation in responses. The significant main effects of subject and autonomic state indicate that a simplified form of the M-K equation that only considers PTT probably introduce error in BP estimation.

We are not alone in concluding that PTT is not sufficiently accurate for blood pressure estimation. Wang et al (2014) incorporated HR in their estimates of blood pressure<sup>38</sup>. Their logic, to a first approximation, is reasonable: Under many circumstances, HR is a biomarker of sympathetic activation (and therefore vascular tone). However, during the PECA condition, BP remains elevated, yet HR returns to control (or slightly below control) levels. This finding has been explained by the activation of metabolically-sensitive muscle afferents in skeletal muscle which elicit reflex increases in sympathetic activity to skeletal muscle, opposed by arterial baroreflexes and the lack of central command which lowers HR. Thus, HR alone is not sufficient to employ as a biomarker of sympathetic activation.

It is becoming apparent that more research on PTT under a range of physiological conditions may be necessary. Specifically, adjustments should be made for all assumptions of the M-K equation, including changes in arterial stiffness and vascular diameter. Furthermore, error

introduced by including the PEP in our PTT measurement must be considered; dynamic variation in PEP can easily reach  $\pm 5$  msec under physiological conditions<sup>37</sup>.

Table 2, a summary of the regression equations for each condition, offers some insight on the magnitude of the potential error in these heightened autonomic states. Conditions shown on the left are representative of low sympathetic activation (rest and recovery). Conditions on the right represent high sympathetic activation.

**Table 2: Regression equations during each autonomic state for the CPT and SHG paradigms**

Condition	Pcode				Condition	Pcode			
CPT	CRcvry	SBP	=	226.30 - 295.2 PTT	CPT	Cold	SBP	=	239.19 - 295.2 PTT
CPT	Rest	SBP	=	217.05 - 295.2 PTT	SHG	EX	SBP	=	244.03 - 295.2 PTT
SHG	Rest	SBP	=	223.50 - 295.2 PTT	SHG	PECA	SBP	=	250.06 - 295.2 PTT
SHG	XRcvry	SBP	=	229.29 - 295.2 PTT					

From the regression analysis, the standard error of the intercept estimate was 8.4 mmHg, or 3.4%. What is the physiological significance of this finding? Of note is the fact that the intercept (the point of zero PTT) clusters at 226 mmHg when sympathetic activation is low. In contrast, the intercepts for the three conditions with elevated sympathetic vascular tone cluster at 245 mmHg. The difference – approximately 19 mmHg – suggests that differences in sympathetic tone are of both statistical significance and functional importance to blood pressure estimation. Since hypertension is classified in stages that differ by 10 mmHg, this error in estimation could affect blood pressure management or treatment dramatically.

We must also consider the possibility that a portion of the variation in the model resulted from errors confined to this study (i.e. factors that may be accounted for in other studies and in devices such as the Scandu Scout and Heartisans Watch). Unfortunately, the algorithms for these

devices are not in the public domain and have not been released by the companies producing the devices. Neither the FDA nor Scanadu provided a rationale for ending development of the Scanadu Scout after the initial clinical trial.

Further research on the validity of the PTT method of BP estimation might incorporate a state of autonomic tone. Additionally, since individual calibration may be needed to address independent factors such as body size, further research should consider how PTT varies with factors such as height and weight.

A consumer-friendly, mobile device that measures blood pressure both accurately and frequently will have major implications in the world of cardiovascular health; it seems, however, that more research is necessary before we achieve this major medical milestone. That being said, the results from this investigation evidence an inverse relationship between SBP and PTT, which is consistent with other published studies. Therefore, PTT remains a potentially useful measure to consider relative changes in BP, but derivations from PTT should be considered conservatively until changes in vascular tone can be incorporated. To improve the accuracy of estimation, future research should focus on techniques to calibrate individual responses to minimize between subjects' variability, and to identify changes in sympathetic activation without user intervention.

## Appendix A

### Informed Consent Forms

#### CONSENT FOR RESEARCH The Pennsylvania State University

Title of Project: Autonomic Phenotyping of Healthy Men and Women

Principal Investigator: *James A Pawelczyk*

Address: 107 Noll Laboratory, Pennsylvania State University, University Park, PA 16802

Telephone Number: 814-865-3453

Subject's Printed Name: \_\_\_\_\_

**We are asking you to be in a research study. This form gives you information about the research.**

**Whether or not you take part is up to you. You can choose not to take part. You can agree to take part and later change your mind. Your decision will not be held against you.**

**Please ask questions about anything that is unclear to you and take your time to make your choice.**

#### 1. Why is this research study being done?

This research is being done to find out more about people with *different* blood pressure responses to the same tests. We will use a variety of blood pressure raising stimuli to record individual responses. We will then compare results from people who have a large response to those with a low response. If you choose to also participate in another study (IRB# STUDY00001782) we may compare your blood pressure responses to your TRPV1 genotype. The TRPV1 channel is in many of your cells and is made of many amino acids that form a certain shape. This channel is partially responsible for increasing blood pressure during challenges like exercise. Among different people there are naturally occurring changes in the instructions for making this channel- that is, differences in the gene for the protein. The knowledge gained from this study will be a valuable addition to understanding individual differences in blood pressure responses.

About 200 people will take part in this research study.

## **2. What will happen in this research study?**

### **Screening:**

Informed Consent: You will first read and if you chose, sign, the informed consent document (this document) before completing any other parts of the study. An investigator working will be available to answer any questions you have about the research.

Medical History and Contact Information Questionnaire: You will be asked to fill out a form about your medical history (i.e. major injuries, illnesses, etc.). You will also be asked to include contact information. You are free to skip any questions that you would prefer not to answer.

Screening Data: We will collect some initial screening data. Data collected for screening is explained below.

Urine Analysis: Pre-menopausal women will have a urine pregnancy test done prior the study visit.

Familiarization: During screening, you will be shown the lab area and given the opportunity to ask any questions about the study. You will have resting blood pressure and heart rate measured (details below). You will do an initial hand-squeezing exercise- protocol 1 (below). Finally, we will also expose you to the basics of the other protocols (protocols 2-4). We will not collect any data for protocols 2-4, we will just make sure you understand what is going to be done for each protocol. The results from the initial hand squeezing test will help determine if you are invited back for day two of testing.

Finally we would like to know if you would like to be included in another study (IRB# STUDY00001782) in which we collect some mouth cell on several cotton swabs. If you are interested we will show you the (separate) informed consent for that study as well. If you choose to be in both studies we may compare the data collected in this study (blood pressure and etc.) to your genotype measured in the other study.

### **Testing:**

Heart Rate: Electrodes (sticky patches) will be applied to the skin of your upper body to measure your heart's activity. We may shave 2-3 small areas (~1 inch) on your chest and abdomen (if necessary) for the patches.

Blood Pressure: Pressure will be measured continuously using a Finapres system and periodically with an upper arm cuff. If using an automated blood pressure measurement device, your finger will be placed in a cuff that inflates with air to monitor your blood pressure.

Leg Blood Flow: To measure the blood flow in your leg we will place a cuff on your thigh, just above your knee. We will also place a cuff on your ankle. We will inflate the cuff on your ankle to a high pressure and the cuff on your thigh to a lower pressure. Blood will enter your lower leg but not leave because of the cuffs. Using a monitor on your calf that tells us how much it has changed size, we can measure how much blood has entered your leg.

Muscle oxygen and/or H<sup>+</sup> level: A sticky plastic sensor will be placed over the muscles in your forearm. This sensor will emit light into your forearm muscles. This measures the amount of oxygen and hydrogen ions (H<sup>+</sup>, a byproduct of metabolism) in your muscle.

Pulse Wave Velocity: Pulse wave velocity is a non-invasive test that allows us to estimate the “stiffness” of your blood vessels. You will lay flat on a bed with a cuff placed around your femoral artery (a blood vessel in your thigh). A researcher then holds a small (pen-sized) sensor over your carotid artery (a blood vessel in your neck). To make a measurement, the cuff placed on your thigh will inflate to a pressure that temporarily prevents blood flow into your leg. The cuff will then deflate over 1-2 minutes. Sensors in the cuff and on your neck measure how fast each pulse of blood travels through your blood vessels. This measurement will be performed 3-4 times.

Nerve Activity: The nerve that we record from is located close to the surface of the skin. It is on the lower leg, just below the knee. To measure nervous system activity, we will first apply a mild external electrical stimulus to this area using a wand-like device. This allows us to find the approximate location of the nerve beneath the skin. After we find the general location of the nerve, a fine wire needle (called a microelectrode) will be inserted through the skin to record activity from the nerve. A second fine wire needle will be inserted about 3 cm away (termed the reference needle). We will measure nervous system activity throughout the experiment. We will measure nervous system activity directed to the muscle. You may be asked to perform Valsalva’s maneuver to check the placement of the electrode. This involves contracting muscles to expel air while not letting any air escape from your lungs.

Breaks: A minimum of 10 minutes will be taken between each protocol as a break before starting the next protocol.

Abstinence from Caffeine and Alcohol: We ask that you abstain from all alcohol, caffeine, energy drinks, large doses of vitamin B, and any over-the-counter substances that contain ephedrine or other stimulants for 12 hours prior to each study.

Exercise: We ask that you abstain from heavy exercise for 24 hours prior to each study. This includes activities like running or lifting weights.

Fasting: We ask that you arrive for each day having not eaten since dinner the night before. We will have a light snack for you if you want it when the study day is over.

Female subjects: You will only be tested during the early follicular phase of your menstrual cycle (days 2-6). We will coordinate scheduling with you based upon your history that you fill out in the screening form.



Randomization: The following protocols may be done in any order. They will be semi-randomized with similar tests being placed apart from each other. For example, tests involving hand/arm exercise will not be done back-to-back.

### **Protocols:**

#### **Protocol 1: Arm Compression after Continuous Squeezing Exercise.**

While lying on your back on a bed, we will measure your largest hand-grip force from your dominant hand using a device connected to a computer. We will also cover the upper part of your arm with a cuff connected to a compressor. We will monitor your blood pressure, heart rate, blood flow, pulse wave velocity, blood oxygenation, and nerve activity as outlined above- this will continue for the rest of the time. After at least three minutes of rest, you will begin to exercise at 30% of your maximum. This will be displayed on a computer for you. You will contract and hold at 30% for 3 minutes. With 5 seconds remaining before the end of 3 minutes of exercise, the cuff on your upper arm will be rapidly inflated to a high level- trapping all the current blood in your arm. You will stop exercise and relax and the cuff will remain inflated for 2 more minutes after which it will deflate. You will then remain stationary for 3 more minutes. Before, during, and after the exercise period, you will be asked to judge the difficulty of the exercise on a number scale. You will also be asked to rate pain on a number scale. Duration: approximately 30 minutes.

#### **Protocol 2: Arm Squeezing Test.**

The arm squeezing test will consist of you laying on your back on a bed for approximately 15 minutes while you are prepared for the test. We will monitor your blood pressure, heart rate, blood flow, pulse wave velocity, and nerve activity as outlined above- this will continue for the rest of the time. You will have a cuff placed on the upper part of the exercising arm. You will have a custom-built handgrip device fitted to your hand size and placed out to your side. Your maximum hand-grip will be recorded and your exercise goal will be set at 10-15% of your maximum. A blood flow measuring technician will use sound waves to measure the blood flow going into your lower arm. You will then begin to squeeze at 10-15% of your maximum at 30 squeezes per minute. The force you are creating will be displayed on a computer monitor for you to observe during exercise. During this exercise we will slowly pump up the arm cuff. Before, during, and after the exercise period, you will be asked to judge the difficulty of the exercise on a number scale. You will also be asked to rate pain on a number scale. The stopping point is based off of how hard you think you are working and the amount of blood flow measured by the sound waves. Once the stop point is reached (>90% of blood flow occluded or a rating of 19-20 on a 6-20 scale) or whenever you feel you want to stop, the cuff will be rapidly inflated to trap all blood in the arm. You will stop exercise and relax and the cuff will remain inflated for 2 more minutes after which it will deflate. You will then remain stationary for 3 more minutes. Duration: approximately 45 minutes.

### **Protocol 3: Lung Sensitivity Test.**

While lying on your back we will monitor your blood pressure, heart rate, blood flow, pulse wave velocity, and nerve activity as outlined above- this will continue for the rest of the time. To measure your breathing at rest, you will breathe in room (normal) air and breathe out into a tube. We will measure this air using a computer for a minimum of 3 minutes. To measure your breathing response to a change in air, you will start breathing in and out of a container of air that has oxygen and carbon dioxide. Carbon dioxide stimulates you to breathe more. As carbon dioxide builds-up we will measure your rate and depth of breathing. Your oxygen level will be higher than normal because of the higher level of oxygen in the air you will be breathing. After five minutes or after carbon dioxide builds to a certain amount, we will stop the test. You will begin breathing room air once again. Once breathing room air, we will ask you for your sensation during breathing in the tube. Duration: approximately 30 minutes.

### **Protocol 4: Water Temperature Test.**

While lying on your back we will monitor your blood pressure, heart rate, blood flow, pulse wave velocity, and nerve activity as outlined above- this will continue for the rest of the time. After at least three minutes of rest, we will lower your hand into water up to the wrist for three minutes. Using bubbles, the water will be kept moving around your hand. The temperature of the water will be hot (~47°C/~117°F), warm (~37°C/~98°F), and cold (~3°C/~37°F). Each temperature will be used for three minutes and the order applied will be random (other protocols may be done between temperatures). While your hand is in the water, we will ask you for your pain perception during each minute. After removal from the water, data will be recorded for a final three minutes and that will complete the test. Duration: approximately 60 minutes.

### **3. What are the risks and possible discomforts from being in this research study?**

There is a risk of loss of confidentiality if your information or your identity is obtained by someone other than the investigators, but precautions will be taken to prevent this from happening.

It is not possible to identify all potential risks of these research procedures, but the researchers have taken reasonable safeguards to minimize any known or potential risks.

- **Urine Sample (pregnancy test):** There are no known risks associated with the self-collection of one's urine.
- **ECG:** There is a minimal risk due to potential allergic reaction to adhesive on the ECG electrodes.
- **Blood pressure/Pulse Wave Velocity:** There is a risk of temporary discomfort at the sites where cuffs are inflated. The discomfort might be greater the longer the cuffs are inflated.

In addition, you may feel a numb, cooling, and/or tingling sensation in your hands/feet while the cuff is inflated. However, these feelings go away quickly after the cuff is deflated. During pulse wave velocity, you may also experience some temporary discomfort while the researcher holds a small sensor over an artery in your neck. However, this feeling will also go away quickly after the sensor is removed.

- **Muscle oxygen and/or H<sup>+</sup> level:** There are no known risks associated with use of the near-infrared device. However, it is possible that the adhesive on the sticky plastic sensor may irritate your skin.
- **Microneurography:** With regard to the laboratory assessment of nervous system activity, the use of the wand-like device may cause minor discomfort. There may also be mild discomfort when the fine wire needle is inserted through the skin; however, this needle is very small. Brief sensations of pins and needles and/or cramping are likely to be felt during the nerve search. This fine wire needle will be left in place for the duration of the experimental visit (approximately 4 hours). It is also possible that feelings of muscle weakness and/or pins and needles sensations can be felt after completion of the procedure. There is no specific treatment for these sensations, and in the small number of volunteers that have experienced them, they have disappeared spontaneously. It is generally thought that the risks of side effects are minimized when no more than 45 minutes is used to locate the nerve with the fine wire needle; therefore, in this study, this time limit will be strictly enforced. There is also a small risk of infection at the site where the fine wire needle is inserted.
- **Valsalva's Maneuver:** Some subjects experience very brief dizziness or lightheadedness during or immediately following forced exhalation (Valsalva maneuver). These symptoms, when present, are very short-lived and are a minimal risk when already laying down.
- **Medical Screening:** You may feel shy about giving health information. The staff collects the information in a private and professional manner. You may feel shy about being measured. You may request someone of the same sex to conduct the screening.
- **Latex:** Some gloves and medical materials are made of latex rubber. You will inform us if you are allergic to latex and decline to participate in the study.
- **Squeezing exercise and inflation of the pressure cuff on your arm:** Forearm tiredness and muscle "burning" may be present during the 3 minutes of hand squeezing exercise. These feeling should end quickly after the end of the test. You may feel a tightness and/or tingling feeling in your hands and upper arm when the arm cuff is inflated. These sensations are only temporary should last only for the 3 minutes of cuff inflation. Mild soreness in the muscles of the forearm/hand could develop sometime after the exercise test is completed (usually the day following). This soreness, if it occurs, usually goes away in about 2 days.

- **Hand in water test:** Putting your hand in the hot and cold water may be considered painful. The temperatures used in this study should cause no lasting damage or pain in the hand after 3 minutes in the water. Any pain associated with placing the hand in water should subside quickly once the hand is removed from the water.
- **Measurements of blood flow through an artery in your upper arm at rest and during exercise:** You may feel minor discomfort (pressure) when the research assistant is pressing the ultrasound sensor against your upper arm. This discomfort, if it occurs, is very mild and stops immediately after the measurement is completed (measurement takes about 15 minutes). There is a small risk that the ultrasound gel will irritate your skin. This irritation/redness, if it occurs, should go away soon after the study is completed. Forearm muscle tiredness is likely. This discomfort goes away quickly after the completion of the exercise. Mild soreness in the muscles of the forearm/hand could develop sometime after the exercise test is completed (usually the day following). This soreness, if it occurs, usually goes away in about 2 days. Finally, there is some risk of the appearance of small red dots on the skin (called petechia) due to the high blood pressure in the occluded arm during exercise. If present they may persist for a few days before going away. They should not be associated with any pain.
- **Lung Sensitivity Test:** During the test you may feel the sensation of “shortness of breath” or feel like it is generally “hard to breathe”. These feelings should subside immediately at the end of the test. The air mixture you are breathing starts high in oxygen and therefore, you will never be short of oxygen during the test. We will continually measure your oxygen and carbon dioxide status each breath during the test and we will end the test at the appropriate time. The build-up of carbon dioxide will stimulate you to breathe more rapidly and deeply. There is little risk of this test at the CO<sub>2</sub> levels we will use. About one in 10 people feel a little anxious and develop a slight headache when breathing carbon dioxide. If these feelings occur they should end within minutes after ending the test.
- **Leg Blood Flow:** During this test, blood flow will be stopped to your foot for up to 2 minutes (usually <1 min) at a time. This may lead to brief tingling in the area that should end quickly. The cuff around the upper leg and the stretch measurer around the calf should cause no discomfort. It is possible the tape used will irritate your skin or pull on limb hair.
- **Stopping the Test:** If you should feel that you cannot continue a test, you may stop the experiment at any time. It will be considered an uncompleted test.

#### 4. What are the possible benefits from being in this research study?

##### 4a. What are the possible benefits to you?

Benefits to you are a measurement of basic health parameters such as height, weight, and blood pressure.

##### 4b. What are the possible benefits to others?

Benefits to society in general relate to the further understanding of the way genes play a role in blood pressure control and how individuals have different blood pressure responses. Eventually, this could help with understanding heart-related diseases.

**5. What other options are available instead of being in this research study?**

You may decide not to participate in this research.

**6. How long will you take part in this research study?**

If you agree to take part, it will take you about 5 hours to complete this study. You will be asked to return to the site 2 times. The first visit is a screening (introductory) visit to determine your eligibility (~1 hour). The second visit is the study visit (~4 hours). For each visit, you must avoid all caffeine and alcohol for 12 hours prior to arrival. For each visit you must not do heavy exercise for 24 hours prior to arrival. Scheduling of these visits will depend on your availability.

**7. How will your privacy and confidentiality be protected if you decide to take part in this research study?**

Efforts will be made to limit the use and sharing of your personal research information to people who have a need to review this information.

- A list that matches your name with your code number (assigned by us) will be kept in a locked file or password protected file physically located in Noll lab or electronically located in the Pawelczyk section of the secure Noll lab computer server system. Only researchers listed on this document will have any access to your research records.
- Your research records (electronic and physical) will be labeled with your code number and will be kept in a separate locked file or password protected file physically located in Noll lab or electronically located in the Pawelczyk section of the secure Noll lab computer server system. Only researchers listed on this document will have access to your research records.

In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

We will do our best to keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people may find out about your participation in this research study. For example, the following people/groups may check and copy records about this research.

- The Office for Human Research Protections in the U. S. Department of Health and Human Services

- The Institutional Review Board (a committee that reviews and approves research studies) and
- The Office for Research Protections.

Some of these records could contain information that personally identifies you. Reasonable efforts will be made to keep the personal information in your research record private. However, absolute confidentiality cannot be guaranteed.

**8. What are the costs of taking part in this research study? What happens if you are injured as a result of taking part in this research study?**

In the unlikely event you become injured as a result of your participation in this study, medical care is available. It is the policy of this institution to provide neither financial compensation nor free medical treatment for research-related injury. By signing this document, you are not waiving any rights that you have against The Pennsylvania State University for injury resulting from negligence of the University or its investigators.

**Will you be paid or receive credit to take part in this research study?**

Compensation is based on time spent in the laboratory. The entire study will result in payment of \$80 for approximately 4-5 hours of time.

Screening: \$5

Placement of the microneurography needle: - \$15

Protocol 1: Arm Compression after Continuous Squeezing Exercise. -\$15

Protocol 2: Arm Squeezing Test. -\$15

Protocol 3: Lung Sensitivity Test. -\$15

Protocol 4: Water Temperature Test. -\$15

**10. What are your rights if you take part in this research study?**

Taking part in this research study is voluntary.

- You do not have to be in this research.
- If you choose to be in this research, you have the right to stop at any time.
- If you decide not to be in this research or if you decide to stop at a later date, there will be no penalty or loss of benefits to which you are entitled.

The person in charge of the research study or the sponsor can remove you from the research study without your approval. Possible reasons for removal include any medical issue or scenario where the researcher/ research-team is uncomfortable with you participating in the protocols described in this document.

During the course of the research you will be provided with any new information that may affect your health, welfare or your decision to continue participating in this research.

**11. If you have questions or concerns about this research study, whom should you call?**

Please call the head of the research study (principal investigator), James Pawelczyk at 814-865-3453 if you:

- Have questions, complaints or concerns about the research.
- Believe you may have been harmed by being in the research study.

You may also contact the Office for Research Protections at (814) 865-1775, [ORProtections@psu.edu](mailto:ORProtections@psu.edu) if you:

- Have questions regarding your rights as a person in a research study.
- Have concerns or general questions about the research.
- You may also call this number if you cannot reach the research team or wish to talk to someone else about any concerns related to the research.

## **INFORMED CONSENT TO TAKE PART IN RESEARCH**

**Signature of Person Obtaining Informed Consent**

Your signature below means that you have explained the research to the subject or subject representative and have answered any questions he/she has about the research.

Signature of person who explained this research	Date	Time	Printed Name
(Only approved investigators for this research may explain the research and obtain informed consent.)			

**Signature of Person Giving Informed Consent**

Before making the decision about being in this research you should have:

- Discussed this research study with an investigator,
- Read the information in this form, and
- Had the opportunity to ask any questions you may have.

Your signature below means that you have received this information, have asked the questions you currently have about the research and those questions have been answered. You will receive a copy of the signed and dated form to keep for future reference.

**Signature of Subject**

By signing this consent form, you indicate that you voluntarily choose to be in this research and agree to allow your information to be used and shared as described above.

\_\_\_\_\_ Signature  
of Subject Date Time Printed Name

**CONSENT FOR RESEARCH**  
The Pennsylvania State University

Title of Project: Genotyping a cohort for gene association studies.

Principal Investigator: James A. Pawelczyk

Address: 107 Noll Laboratory, Pennsylvania State University, University Park, PA 16802

Telephone Number: 814-865-3453

Subject's Printed Name: \_\_\_\_\_

**We are asking you to be in a research study. This form gives you information about the research.**

**Whether or not you take part is up to you. You can choose not to take part. You can agree to take part and later change your mind. Your decision will not be held against you.**

**Please ask questions about anything that is unclear to you and take your time to make your choice.**

**1. Why is this research study being done?**

We are asking you to be in this research because we would like to know about your genes related to blood pressure. We will determine what genes you have from a sample you give us and store that sample for future analysis. We will use this sample to find out if you qualify for our future studies.

The purpose of this study is to get a large group of people who all have their genotypes determined. We can then recruit from this large group for other studies. About 300 people will take part in this research study here on Penn State's campus and the surrounding area.

**2. What will happen in this research study?**

To participate in this study you must:

1. Read, understand, and then sign this informed consent document.
2. Be eligible by all inclusion and exclusion criteria described on the "screening data" and "medical history" documents.



3. Be willing to give a DNA sample by mouth swab and allow it to be stored indefinitely.
4. Be willing to be contacted for- and likely participate in- future studies by our lab.
5. Allow us share your de-identified data with other labs at Penn State.
6. Be willing to consider volunteering for several protocols designed to raise blood pressure; for example, a “cold pressor test” (where we put your hand in icy water for 3 minutes) and hand squeezing exercise tests. We would not do these in this initial study, but we would in the follow-up studies.
7. Be willing to volunteer for protocols with additional measurements; for example, a technique that measures nerve activity. To do this, we record signals from a nerve located close to the surface of the skin, on the lower leg, just below the knee. A fine wire needle (called a microelectrode) will be inserted through the skin to record activity from the nerve. A second fine wire needle will be inserted about 3 cm away (termed the reference needle). We would not do this in this initial study but we would in the follow-up studies.

We are using this study to create a group of people to recruit from for other studies. If you are not willing to be recruited for other studies, we will not include you in this protocol.

If you do meet the above requirements and sign this document, we will go on with the study as follows:

1. You will arrive in the morning without eating anything and without brushing your teeth yet that day.
2. You will lay in bed quietly for 15 minutes. We will then place a cuff on your upper arm and use it measure your blood pressure and heart rate. We will measure your blood pressure 3 times total with a least 1 minute between each measurement. This should take about 20 minutes.
3. You will then stand up and we will measure your height and weight.
4. While still standing we will measure your blood pressure and heart rate once more using the same cuff as explained above.
5. We will explain to you the technique to collect a DNA sample from the inside of your mouth. You will use multiple small swabs to repeatedly wipe the inside of your cheek and then lock your sample in a container. This should take 5-10 minutes.

Please note that this is not a complete analysis of your genetic makeup. We are only currently interested in genes related to blood pressure. However, we will store your sample and may use it to analyze for future genes of interest.

Your total time in lab should be 45-60 minutes.

### **3. What are the risks and possible discomforts from being in this research study?**

There is a risk of loss of confidentiality if your information or your identity is obtained by someone other than the investigators, but precautions will be taken to prevent this from happening.

The medical risks in this study are minimal.

- **Blood pressure:** The inflated arm cuff may cause temporary tingling, numbness, and cool or cold feeling in your arm.
- **Mouth Swab:** A mouth swab has no greater risk above normal daily living.

### **4. What are the possible benefits from being in this research study?**

#### **4a. What are the possible benefits to you?**

Benefits to you are a measurement of basic health parameters such as height, weight, and blood pressure.

#### **4b. What are the possible benefits to others?**

Benefits to society in general relate to the further understanding of the way genes play a role in blood pressure control. Eventually, this could help with understanding heart-related diseases.

### **5. What other options are available instead of being in this research study?**

You may decide not to participate in this research.

### **6. How long will you take part in this research study?**

If you agree to take part, it will take you about 45-60 minutes to complete this research study. You will not be asked to return to the research site for this study. You may be asked to return for follow-up studies.

### **7. How will your privacy and confidentiality be protected if you decide to take part in this research study?**

We will limit the use and sharing of your personal research information to people who have a need to review this information.

- A list that matches your name with your code number will be kept in a paper file and/or password protected computer file. The paper file will be kept in a locked filing cabinet in a locked room in Noll Lab. Electronically, the file will be secured in a section of a protected computer server located at Penn State.
- Your research records (electronic and physical) will be labeled with your code number only, and will be kept in a separate locked paper file in Noll Lab. It will be stored electronically in a secure server.
- Your research samples (DNA) will be labeled with your code, the name of our lab, and the date. They will be stored in a secure facility here on campus.

In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

We will keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people may find out about your participation in this research study. For example, the following people/groups may check and copy records about this research.

- The Office for Human Research Protections in the U. S. Department of Health and Human Services
- The Institutional Review Board (a committee that reviews and approves research studies) and
- The Office for Research Protections.

Some of these records could contain information that personally identifies you. Reasonable efforts will be made to keep the personal information in your research record private. However, absolute confidentiality cannot be guaranteed.

## **8. What happens if you are injured as a result of taking part in this research study?**

In the unlikely event you become injured as a result of your participation in this study, medical care is available. It is the policy of this institution to provide neither financial compensation nor free medical treatment for research-related injury. By signing this document, you are not waiving any rights that you have against The Pennsylvania State University for injury resulting from negligence of the University or its investigators.

## **9. Will you be paid or receive credit to take part in this research study?**

Payment in the form of \$3 cash will be given upon completion of the study.

**10. Who is paying for this research study?**

The primary investigator, Dr. Pawelczyk, is paying with research incentive funds.

**11. What are your rights if you take part in this research study?**

Taking part in this research study is voluntary.

- You do not have to be in this research.
- If you choose to be in this research, you have the right to stop at any time.
- If you decide not to be in this research or if you decide to stop at a later date, there will be no penalty or loss of benefits to which you are entitled.

The person in charge of the research study or the sponsor can remove you from the research study without your approval. Possible reasons for removal include any medical issue or scenario where the researcher/ research-team is uncomfortable with you participating in the protocols described in this document.

**12. If you have questions or concerns about this research study, whom should you call?**

Please call the head of the research study (principal investigator), James Pawelczyk at 814-865-3453 if you:

- Have questions, complaints or concerns about the research.
- Believe you may have been harmed by being in the research study.

You may also contact the Office for Research Protections at (814) 865-1775, ORProtections@psu.edu if you:

- Have questions regarding your rights as a person in a research study.
- Have concerns or general questions about the research.
- You may also call this number if you cannot reach the research team or wish to talk to someone else about any concerns related to the research.

## **INFORMED CONSENT TO TAKE PART IN RESEARCH**

### **Signature of Person Obtaining Informed Consent**

Your signature below means that you have explained the research to the subject or subject representative and have answered any questions he/she has about the research.

\_\_\_\_\_  
Signature of person who explained this research    Date \_\_\_\_\_ Time \_\_\_\_\_ Printed Name \_\_\_\_\_  
(Only approved investigators for this research may explain the research and obtain informed consent.)

### **Signature of Person Giving Informed Consent**

Before making the decision about being in this research you should have:

- Discussed this research study with an investigator,
- Read the information in this form, and
- Had the opportunity to ask any questions you may have.

Your signature below means that you have received this information, have asked the questions you currently have about the research and those questions have been answered. You will receive a copy of the signed and dated form to keep for future reference.

### **Signature of Subject**

By signing this consent form, you indicate that you voluntarily choose to be in this research and agree to allow your information to be used and shared as described above.

\_\_\_\_\_  
Signature of Subject                      Date \_\_\_\_\_ Time \_\_\_\_\_ Printed Name \_\_\_\_\_

### **Optional part(s) of the study**

In addition to the main part of the research study, there is another part of the research. You can be in the main part of the research without agreeing to be in this optional part.

#### Optional Sharing of Genetic Information with Personally Identifiable Information

In the main part of this study, we are collecting DNA samples from you. From this DNA we will get genetic information. If you agree, the Pawelczyk Lab may share your genetic information with partner labs with personally identifying information. For this sharing to happen the partner lab must first have an IRB approved protocol specifically including the sharing of information from this study.

These labs may be interested in recruiting you for their studies. If the partner lab expresses interest in recruiting you based on your genotype- our lab would then contact you and ask for permission. If you are interested we will share your contact information with the other lab. If you are NOT interested we will NOT share your contact information.

#### Optional study details:

- It is unlikely that these studies will have a direct benefit to you.
- Neither your doctor nor you will receive results of these future research tests, nor will the results be put in your health record.
- Sometimes tissue is used for genetic research about diseases that are passed on in families. Even if your sample(s) is used for this kind of research, the results will not be put in your health record.
- It is possible that your cells might be used to develop products or tests that could be patented and licensed. There are no plans to provide financial compensation to you should this occur. If you have any questions, you should contact a member of the research team.

Therefore, with your permission given below, we will share your information and sample[s] with our partner labs. We may also contact you for future studies on behalf of our partner labs.

1. Your information and sample[s] may be shared with other investigators/groups with identifying information.

\_\_\_\_\_ Yes    \_\_\_\_\_ No

2. We may contact you for recruitment on behalf of our partner labs.

\_\_\_\_\_ Yes    \_\_\_\_\_ No

**Signature of Person Obtaining Informed Consent**

Your signature below means that you have explained the optional part(s) of the research to the subject or subject representative and have answered any questions he/she has about the research.

\_\_\_\_\_  
Signature of person who explained this research    Date    Time    Printed Name

**Signature of Person Giving Informed Consent****Signature of Subject**

By signing below, you indicate that you have read the information written above and have indicated your choices for the optional part(s) of the research study.

\_\_\_\_\_  
Signature of Subject    \_\_\_\_\_    Date    Time    Printed Name

## BIBLIOGRAPHY

- 1) “American Heart Association statistical report tracks global figures for first time.”  
*News.heart.org*. American Heart Association, Inc., 17 December 2014.  
<https://news.heart.org/american-heart-association-statistical-report-tracks-global-figures-first-time/>. Accessed 26 June 2018.
- 2) Beevers, Gareth, Gregory Y H Lip, and Eoin O’Brien. “The Pathophysiology of Hypertension.”  
*BMJ: British Medical Journal* 322, no. 7291 (April 14, 2001): 912–16.
- 3) Berne, R. M" & Levy, M. N. Cardiovascular physiology, Saint Louis: Mosby, 1977.
- 4) Beulen, Bart W. A. M. M., Nathalie Bijmens, Gregory G. Koutsouridis, Peter J. Brands, Marcel C. M. Rutten, and Frans N. van de Vosse. “Toward Noninvasive Blood Pressure Assessment in Arteries by Using Ultrasound.” *Ultrasound in Medicine and Biology* 37, no. 5 (May 1, 2011): 788–97. <https://doi.org/10.1016/j.ultrasmedbio.2011.01.020>.
- 5) “Blood Pressure Measured with Ultrasound Scanner.” ScienceDaily. Accessed November 3, 2018.  
<https://www.sciencedaily.com/releases/2011/06/110614095651.htm>.
- 6) Booth, J. “A Short History of Blood Pressure Measurement.” *Proceedings of the Royal Society of Medicine* vol. 70, no. 11 (November 1977): 793–99.
- 7) Campbell NR, Chockalingam A, Fodor JG, McKay DW. Accurate, reproducible measurement of blood pressure. *CMAJ*. 1990 Jul 1;143(1):19-24. Review. PubMed PMID: 2192791; PubMed Central PMCID: PMC1452062.
- 8) Chiu, Y.C., et al. “Determination of pulse wave velocities with computerized algorithms.”  
*American Heart Journal*, vol 121, issue 5, pp 1460-1470, May 1991.  
<https://www.sciencedirect.com/science/article/pii/0002870391901539>. Accessed 1 July 2018.



- 9) Ding, X. and Y. Zhang. "Photoplethysmogram intensity ratio: A potential indicator for improving the accuracy of PTT-based cuffless blood pressure estimation." *IEEE Xplore*, 5 November 2015. <https://ieeexplore.ieee.org/document/7318383/>. Accessed 3 July 2018.
- 10) Ding, X., et al. "Pulse Transit Time Based Continuous Cuffless Blood Pressure Estimation: A New Extension and A Comprehensive Evaluation." *Scientific Reports*, Article Number: 11554, 14 September 2017. <https://www.nature.com/articles/s41598-017-11507-3>. Accessed 29 June 2018.
- 11) "Estimating Blood Pressure Using the Pulse Transit Time of the Two Measuring from Pressure Pulse and PPG." ResearchGate. Accessed November 3, 2018. <http://dx.doi.org/10.5369/JSST.2008.17.2.087>.
- 12) "Factors That Influence Blood Pressure – Vital Sign Measurement Across the Lifespan – 1st Canadian Edition." Accessed November 3, 2018. <https://opentextbc.ca/vitalsign/chapter/factors-that-influence-blood-pressure/>.
- 13) Gao, M., N.B. Oliver and R. Mukkamala. "Comparison of noninvasive pulse transit time estimates as markers of blood pressure using invasive pulse transit time measurements as a reference." *Physiological Reports*, 4.10 (2016): e12768. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4886159/>. Accessed 2 July 2018.
- 14) Garvin, Nathan M. *Association of Variability in Cardiovascular Responsiveness to Reflex Activation of the Autonomic Nervous System with Genetics of Peripheral Sensory Receptors*. Doctoral Dissertation. The Pennsylvania State University, 2017. Web. Accessed 26 June 2018.
- 15) Gholamhosseini, H., et al. "Smartphone-based Continuous Blood Pressure Measurement Using Pulse Transit Time." *Studies in Health Technology and Informatics*, vol. 224, 2016. <https://www.ncbi.nlm.nih.gov/pubmed/27225558>. Accessed 26 June 2018.

- 16) “Heart Disease Facts.” *Cdc.gov*. Centers for Disease Control and Prevention, 28 November 2017.  
<https://www.cdc.gov/heartdisease/facts.htm>. Accessed 26 June 2018.
- 17) “How It Works.” *Heartisans.com*. Heartisans, 2017, <https://www.heartisans.com/pages/how-it-works>. Accessed 27 June 2018.
- 18) “Invasive blood pressure.” *Memscap.com*. Memscap, 2012.  
<http://www.memscap.com/applications-and-market-segments/medical-and-biomedical/invasive-blood-pressure>. Accessed 26 June 2018.
- 19) Kao, Y.H., et al. “A new cuffless optical sensor for blood pressure measuring with self-adaptive signal processing.” *2016 IEEE Sensors*, 9 January 2017.  
<https://ieeexplore.ieee.org/document/7808775/>. Accessed 29 June 2018.
- 20) Kemmotsu, O., Ueda, M., Otsuka, H., Yamamura, T., Winter, D. C. & Eckerle, J. S. 1991 Arterial tonometry for noninvasive, continuous blood-pressure monitoring during anesthesia.  
*Anesthesiology* 75 (2), 333–340.
- 21) Lokharan, M., et al. “Measurement of Pulse Transit Time (PTT) Using Photoplethysmography.”  
*The 16<sup>th</sup> International Conference on Biomedical Engineering*, pp 130-134, 30 June 2017.  
[https://link.springer.com/chapter/10.1007/978-981-10-4220-1\\_24](https://link.springer.com/chapter/10.1007/978-981-10-4220-1_24). Accessed 25 June 2018.
- 22) Markets, Research and. “Global Blood Pressure Monitoring Devices Market 2018-2022 - Key Vendors Are A&D, GE Healthcare, Koninklijke Philips, Omron Healthcare, SunTech Medical & Welch Allyn.” Accessed November 3, 2018. <https://www.prnewswire.com/global-blood-pressure-monitoring-devices-market-2018-2022---key-vendors-are-ad-ge-healthcare-koninklijke-philips-omron-healthcare-suntech-medical--welch-allyn-300656496>.
- 23) MacGregor, G.A. and F.J. He. “Importance of controlling blood pressure.” *Climacteric*, vol. 8, 8 October 2005.

<https://www.tandfonline.com/doi/abs/10.1080/13697130500330325?journalCode=icmt20>.

Accessed 27 June 2018.

- 24) Mukkamala, Ramakrishna, Jin-Oh Hahn, Omer T. Inan, Lalit K. Mestha, Chang-Sei Kim, Hakan Töreyn, and Survi Kyal. "Towards Ubiquitous Blood Pressure Monitoring via Pulse Transit Time: Theory and Practice." *IEEE Transactions on Bio-Medical Engineering* 62, no. 8 (August 2015): 1879–1901. <https://doi.org/10.1109/TBME.2015.2441951>.
- 25) Newlin, David B., and Robert W. Levenson. "Pre-Ejection Period: Measuring Beta-Adrenergic Influences Upon the Heart." *Psychophysiology* 16, no. 6 (November 1979): 546–52. <https://doi.org/10.1111/j.1469-8986.1979.tb01519.x>.
- 26) Payne R.A., et al. "Pulse transit time measured from the ECG: an unreliable marker of beat-to-beat blood pressure. *J Appl Physiol* (1985), pp 136-141, January 2006. <https://www.ncbi.nlm.nih.gov/pubmed?cmd=historysearch&querykey=5>. Accessed 2 July 2018.
- 27) Penaz, J. 1973 Photoelectric measurement of blood pressure, volume and flow in the finger. In Digest 10th International Conference on Medical and Biological Engineering, p. 104. Dresden.
- 28) "Pulse Wave Velocity (PWV)." Accessed November 3, 2018. [https://www.datasci.com/solutions/cardiovascular/pulse-wave-velocity-\(pwv\)](https://www.datasci.com/solutions/cardiovascular/pulse-wave-velocity-(pwv)).
- 29) Rodriguez-Iturbe, Bernardo, Hector Pons, and Richard J. Johnson. "Role of the Immune System in Hypertension." *Physiological Reviews* 97, no. 3 (July 1, 2017): 1127–64. <https://doi.org/10.1152/physrev.00031.2016>.
- 30) "Scanadu to Shut down Support for Its Scout Device per FDA Regulation and Customers Are Mad." *TechCrunch* (blog). Accessed November 11, 2018. <http://social.techcrunch.com/2016/12/13/fda-orders-scanadu-to-shut-down-support-for-its-scout-device-and-customers-are-mad/>.

- 31) Schoot, Tessa S, Mariska Weenk, Tom H van de Belt, Lucien J LPG Engelen, Harry van Goor, and Sebastian JH Bredie. "A New Cuffless Device for Measuring Blood Pressure: A Real-Life Validation Study." *Journal of Medical Internet Research* 18, no. 5 (May 5, 2016).  
<https://doi.org/10.2196/jmir.5414>.
- 32) Sharwood-Smith, G., J. Bruce and G. Drummond. "Assessment of pulse transit time to indicate cardiovascular changes during obstetric spinal anaesthesia." *British Journal of Anaesthesia*, vol 96, issue 1, pp 100-105, 1 January 2006. <https://academic.oup.com/bja/article/96/1/100/254042>. Accessed 1 July 2018.
- 33) Silke B, McAuley D. Accuracy and precision of blood pressure determination with the Finapres: an overview using re-sampling statistics. *Journal of human hypertension*. 1998;12:403–409. [[PubMed](#)]
- 34) Smith, Robin P, Jérôme Argod, Jean-Louis Pépin, and Patrick A Lévy. "Pulse Transit Time: An Appraisal of Potential Clinical Applications." *Thorax* 54, no. 5 (May 1, 1999): 452.  
<https://doi.org/10.1136/thx.54.5.452>.
- 35) Stickford, Abigail S. L., Yoshiyuki Okada, Stuart A. Best, Rosemary S. Parker, Benjamin D. Levine, and Qi Fu. "Sympathetic Neural and Cardiovascular Responses during Static Handgrip Exercise in Women with a History of Hypertensive Pregnancy." *Clinical Autonomic Research: Official Journal of the Clinical Autonomic Research Society* 26, no. 6 (2016): 395–405.  
<https://doi.org/10.1007/s10286-016-0372-8>.
- 36) Throll, U., K. Forstner and M. Anlauf. "Measuring blood pressure: pitfalls and recommendations." *Nephrology Dialysis Transplantation*, vol 19, issue 4, 1 April 2004.  
<https://academic.oup.com/ndt/article/19/4/766/1810372>. Accessed 27 June 2018.

- 37) Vistisen et al., “Variations in the Pre-Ejection Period Induced by Deep Breathing Do Not Predict the Hemodynamic Response to Early Haemorrhage in Healthy Volunteers.”
- 38) Wang, Ruiping, et al. “Cuff-Free Blood Pressure Estimation Using Pulse Transit Time and Heart Rate.” *International conference on signal processing proceedings. International Conference on Signal Processing* 2014 (2014): 115–118. *PMC*.  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4512231/>. Accessed 27 June 2018.
- 39) Wibmer, T., K. Doering, C. Kropf-Sanchen, S. Rüdiger, I. Blanta, K. M. Stoiber, W. Rottbauer, and C. Schumann. “Pulse Transit Time and Blood Pressure during Cardiopulmonary Exercise Tests.” *Physiological Research* 63, no. 3 (2014): 287–96.
- 40) “Wiggers Diagram Tutorial.” Accessed November 3, 2018.  
<https://airfreshener.club/quotes/wiggers-diagram-tutorial.html>.
- 41) Wirch, Jennifer L., Larry A. Wolfe, Tracey L. Weissgerber, and Gregory A. L. Davies. “Cold Pressor Test Protocol to Evaluate Cardiac Autonomic Function.” *Applied Physiology, Nutrition, and Metabolism = Physiologie Appliquee, Nutrition Et Metabolisme* 31, no. 3 (June 2006): 235–43. <https://doi.org/10.1139/h05-018>.
- 42) Wesseling, K. H., Dewit, B., Vanderhoeven, G. M. A., Vangoudoever, J. & Settels, J. J. 1995  
Physiocal: Calibrating finger vascular physiology for Finapres. *Homeost. Health Disease* 36 (2-3), 67–82.
- 43) “WHO | The Top 10 Causes of Death.” WHO. Accessed November 3, 2018.  
<https://doi.org/entity/mediacentre/factsheets/fs310/en/index.html>.
- 44) “World Health Day 2013 – A Short History of Sphygmomanometers and Blood Pressure Measurement – Museum of Health Care Blog.” Accessed November 3, 2018.

<https://museumofhealthcare.wordpress.com/2013/04/07/world-health-day-2013-a-short-history-of-sphygmomanometers-and-blood-pressure-measurement/>.

- 45) Zhang, G., et al. "Pulse arrival time is not an adequate surrogate for pulse transit time as a marker of blood pressure." *J Appl Physiol* (1985), pp 1681-1686, 29 September 2011.

<https://www.physiology.org/doi/pdf/10.1152/japplphysiol.00980.2011>. Accessed 30 June 2018.

---

## Academic Vita of Amanda Sklarsky

amandasklarsky@gmail.com

---

### Education:

Master of Business Administration, Penn State University, Anticipated Spring 2020  
Bachelor of Science Degree in Science (BS/MBA Program), Penn State University, Fall 2018  
Honors in Kinesiology

Thesis Title: Evaluation of Blood Pressure Estimation Using Pulse Transit Time During Changes in Physiological Status

Thesis Supervisor: James A. Pawelczyk

### Work Experience:

Customer Success Intern at Touchtown, Inc. (Oakmont, PA)

May-August 2018

- Improved customer retention rate by creating insightful Customer Health Score
- Conducted extensive competitor research for internal use

Supervisor: Mike Rethage

Network Strategy Analytics Co-Op at Johnson & Johnson (Skillman, NJ)

July 2017-January 2018

- Increased efficiency of medical device data analysis 200% by leading cross-functional team in designing monthly protocol
- Obtained expert-level recognition in data analysis tool, Alteryx, which was subsequently used to save analysts an average of 40 hours per week

Supervisor: Brian Tremel

### Awards and Honors:

Smeal College of Business MBA Scholarship (2018)

Phi Beta Kappa Grant Recipient (2018)

Lean Yellow Belt Certification (2017)

Phi Eta Sigma National Honors Society (2016)

Phi Gamma Nu Professional Business Fraternity (2016)

President's Freshman Award (2016)

Balog Science Scholarship (2015)

Schreyer Honors College Scholarship (2015-2018)

Gateway High School Valedictorian (2015)

18<sup>th</sup> Congressional District of PA Leaders of Tomorrow Award (2015)

United States Army Reserve National Scholar/Athlete Award (2015)

Bobby Bao Memorial Scholarship (2015)

### Community Service:

Penn State Dance Marathon: Rules & Regulations Committee; Family Relations Specialist

Brad Kaminsky Foundation

Autism Speaks Foundation

### International Education:

"Exploring the Healthcare System in Costa Rica" through Penn State University (May 2019)