EVALUATION OF NONINVASIVE PULSE TRANSIT TIME METHODOLOGIES FOR DIAGNOSIS OF HYPERTENSION

by

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ABSTRACT OF THE THESIS

EVALUATION OF NONINVASIVE PULSE TRANSIT TIME METHODOLOGIES FOR DIAGNOSIS OF HYPERTENSION

Thesis Director:

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Cardiovascular disease (CVD) is the leading cause of global mortality, with an increasing burden on the populations of low and middle income countries as identified by the World Health Organization. Rapid, noninvasive screening methods for CVD using low-cost technology would allow for better healthcare. Pulse Wave Velocity (PWV) as measured by noninvasive methods such as photoplethysmograph and pressure sensors has been validated as a method for screening for CVD. PWV correlates closely with arterial stiffness, which is a strong indicator of CVD and is calculated using artery length and Pulse Transit Time (PTT) using multiple simultaneous recordings at two superficial arterial sites. While PTT is generally agreed to correlate with CVD, there is still ambiguity concerning the best way to analyze the arterial pulse contour to ascertain patient health. Proper pulse wave analysis could prove to be useful diagnosis of arterial stiffness in patients with hypertension. This analysis studied the efficacy of comparing the foot-to-foot (PTT_f) and peak-to-peak (PTT_p) delays as a means of differentiating between healthy control patients and hypertensive patients. Wave reflection is thought to affect the PTT_p while leaving the PTT_f unaffected, so that a comparison should reveal a ratio close to one in healthy patients but a ratio deviated from one in hypertensive

patients. The results of this analysis reveal that increased arterial stiffness is consistently associated with reduced PTT_f and improved upon anti-hypertensive drug treatment. However the results did not show a statistically significant difference in comparing some of the control and test groups using the ratio of PTT_f and PTT_p. These results should be further pursued and validated with more detailed analysis, rigid and consistent parameters, and better accounting for wave reflection.

Table of Contents

List of Tables

List of Illustrations

Chapter 1: Introduction

Cardiovascular Disease

Cardiovascular disease (CVD) is the leading cause of death in the United States [1]. It is estimated there are over 62 million Americans with CVD making the prevalence of CVD above 20 percent in the general population [2]. In 2011, the CVD death rate in the US was 229.6 per 100,000 including congenital CVD [3]. CVD is known to increase the risk of stroke, myocardial infarction, heart failure, and renal failure as shown by the results of many clinical trials [4].

Need for rapid, noninvasive assessment

Rapid, noninvasive, and cheap assessment methods for cardiovascular health allow for better treatment of CVD. A cheap, rapid assessment technique would especially help health care efforts in low and middle income countries, where the World Health Organization has identified increased rates of death due to CVD. The 2014 WHO Global Status Report noted 82% of premature deaths are in low and middle income countries where cardiovascular disease causes the largest percentage of deaths due to non-communicable disease [5]. In both low and high income countries, invasive, intra-arterial catheterization is considered the gold standard for accurate and reliable monitoring of blood pressure [6, 7]. However, even in high income countries there is growing concern with finding noninvasive replacements for the invasive catheterization that is the gold standard. Noninvasive methods have several advantages over invasive methods including reduction in procedure time, no risk of bleeding, or risk of infection [8].

Relationship of arterial stiffness and PWV with CVD

Clinical study has shown that assessment of pulse transit time (PTT) and the related measurement of pulse wave velocity (PWV) can show insights into a patient's cardiovascular status. PTT is defined as the time from when a pulse arrives at one location to the time when that same pulse arrives at a second recording site further from the heart. PWV is defined as the PTT divided by the length of the artery between the recording sites. Figure 1.1 illustrates this concept. PWV may also be defined by the Moens-Korteweg equation, where E is the elastic modulus of the artery, *h* is the wall thickness, *r* is the vessel radius, and ρ is the blood density.

$$PWV = \sqrt{\frac{E \cdot h}{2r\rho}}$$

Because arterial stiffness, E_{inc} above, is a known contributor to CVD and because high PWV correlates with arterial stiffness, assessment of PWV has been proposed as a possible assessment method for CVD [9-11]. High PWV is correlated with an increased risk of organ damage and has been used as a marker to assess damage to the vasculature [12]. For instance, a 2010 meta-analysis of 17 longitudinal studies found that an increase in PWV of one standard deviation correlated with a 47% increase in cardiovascular events, such as stroke and heart attack, a 47% increase in cardiovascular mortality, and a 42% increase in all-cause mortality [13]. Even adjusted for conventional risk factors like age, sex, cholesterol, diabetes, etc., PWV remained a predictor for coronary heart disease, stroke, and CVD events [14].

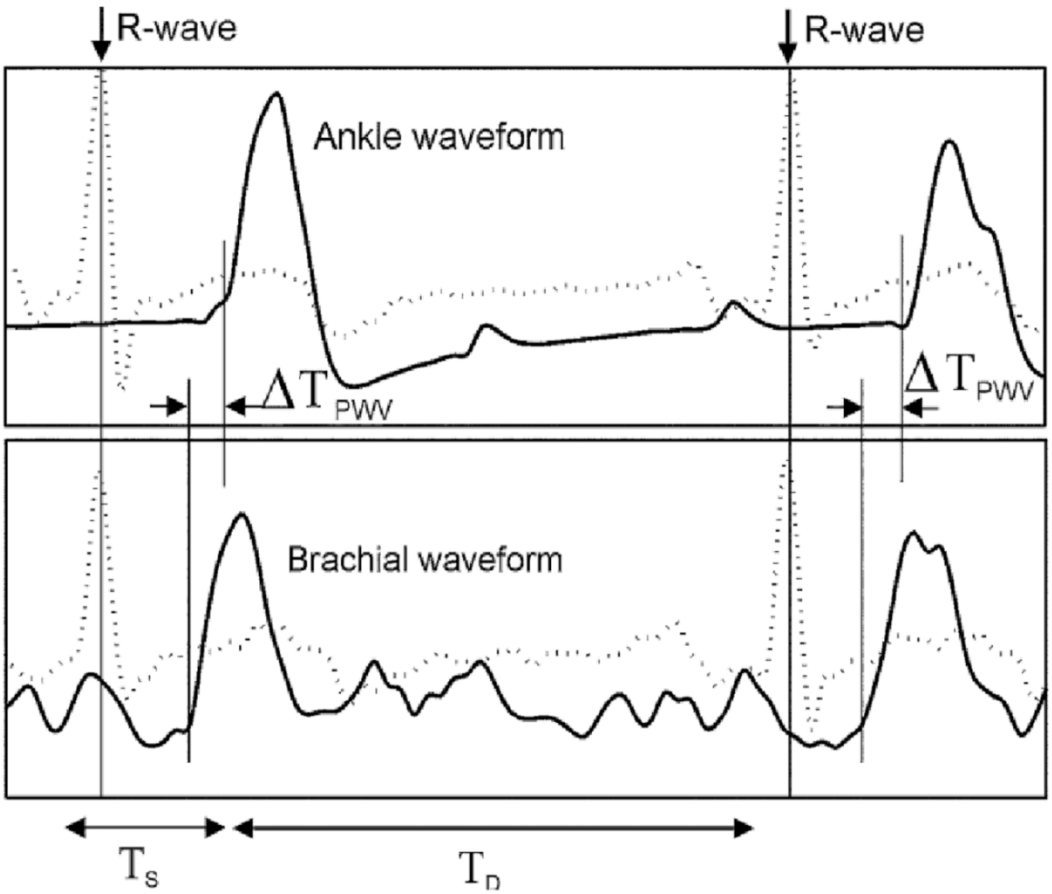

Figure 1.1 Illustration of PTT measurement

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Relationship between arterial stiffness, wave reflection, and PTT

High arterial stiffness is associated with wave reflection upstream, which can interfere with the arterial pulse wave [16, 17]. Because the degree of wave reflection increases with arterial stiffness, it follows that distortion of the arterial pulse contour should increase with arterial stiffness. The reflected wave increases central systolic blood pressure which in turn increases the load on the heart, contributing to increased CV risk [18, 19]. The augmentation index (AIx) has been one method to quantify the degree of reflected pressure contributing to systolic load on the heart [20]. AIx is defined as the ratio of the augmented pressure due to the reflected, backwards wave to the overall measured pulse pressure. Calculation of AIx requires analysis software to separate the forward and reverse waves from the measured pulse, so this study hopes to employ the same theory as AIx using only PTT for a more rapid assessment. Measurement of the arterial pulse contour at multiple locations of the artery should allow for this rapid assessment of the change in pulse contour due to arterial stiffness which would in turn indicate the status of the patient's cardiovascular health.

Description of PTT comparison

Change in arterial pulse contour has been noted as a distinguishing characteristic between younger, healthy patients and older patients with stiffer arteries. The premise of this study is that the change in pulse contour due to wave reflection can be approximated by comparing PTT measured from the foot of the wave (PTT_f) compared to PTT measured from the peak of the wave (PTT_p) and that these two PTT will differ in proportion to the wave reflection due to arterial stiffness. Figure 1.2 illustrates

measurement of PTT at the foot and peak of the pulse contour. Note that Prb stands for photoplethysograph (right brachial) and Pra stands for photoplethysmograph (right radial). This PTT comparison is based on the same premise as AIx, but differs in that the analysis does not require the separation of forward and reverse waves from the measured pulse. If the validation of PTT comparison shows an acceptable accuracy for CV health assessment, this method may prove more appropriate for the rapid assessment required in the low and middle income countries where the WHO has identified a growing amount of premature deaths due to CVD. In addition to simpler data analysis, this method requires peripheral recordings that can be taken noninvasively versus the central aortic pulse traditionally measured invasively for AIx. For the purpose of reference, the ratio of PTT (PTT_p/PTT_f) will be referred to as the pulse distortion index (PDI).

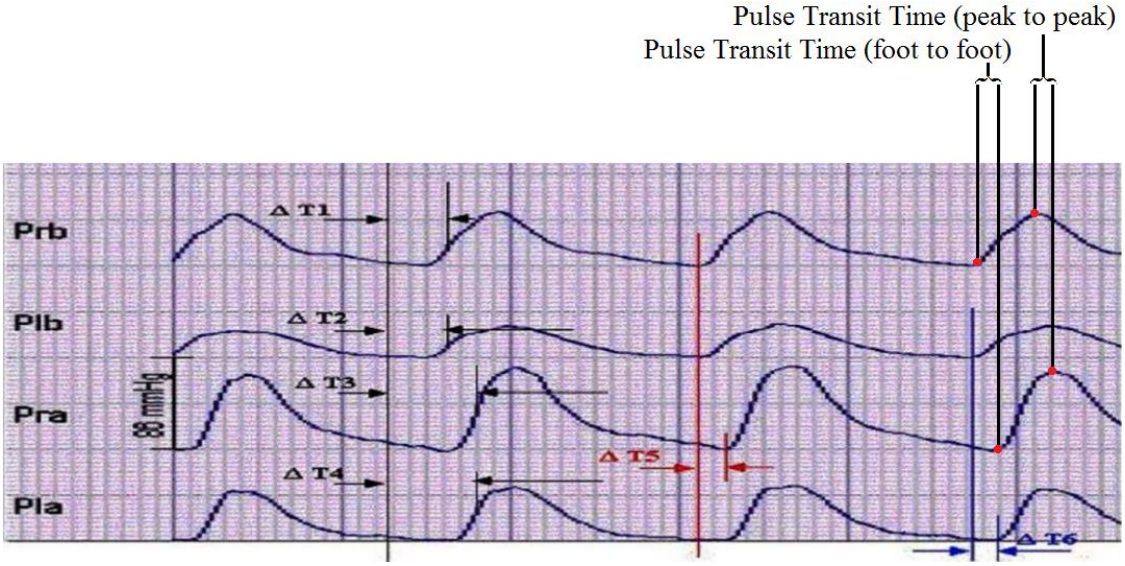

Figure 1.2 Illustration of the measurement of PTT_f and the measurement of PTT_p

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Expected results for normal and hypertensive groups

Normal patients with low arterial stiffness should have lower wave reflection and the reflected backflow wave should be less, causing less pulse contour distortion and resulting in a PDI close to one. The hypertensive patients should have higher arterial stiffness, more wave reflection, greater backflow and therefore greater pulse distortion resulting in a PDI not equal to one. For the hypertensive patient set PTT_f should be unaffected by the reflected wave and should be similar to the PTT_f for the normal set, but PTT_p should be distorted by the reflected wave and come earlier, resulting in a PDI less than one. Figure 1.3 illustrates how the reflected wave can alter blood pressure recordings and can change the pulse contour. P_m is the measured wave, P_f is the forward wave, and P_b is the backwards or reflected wave.

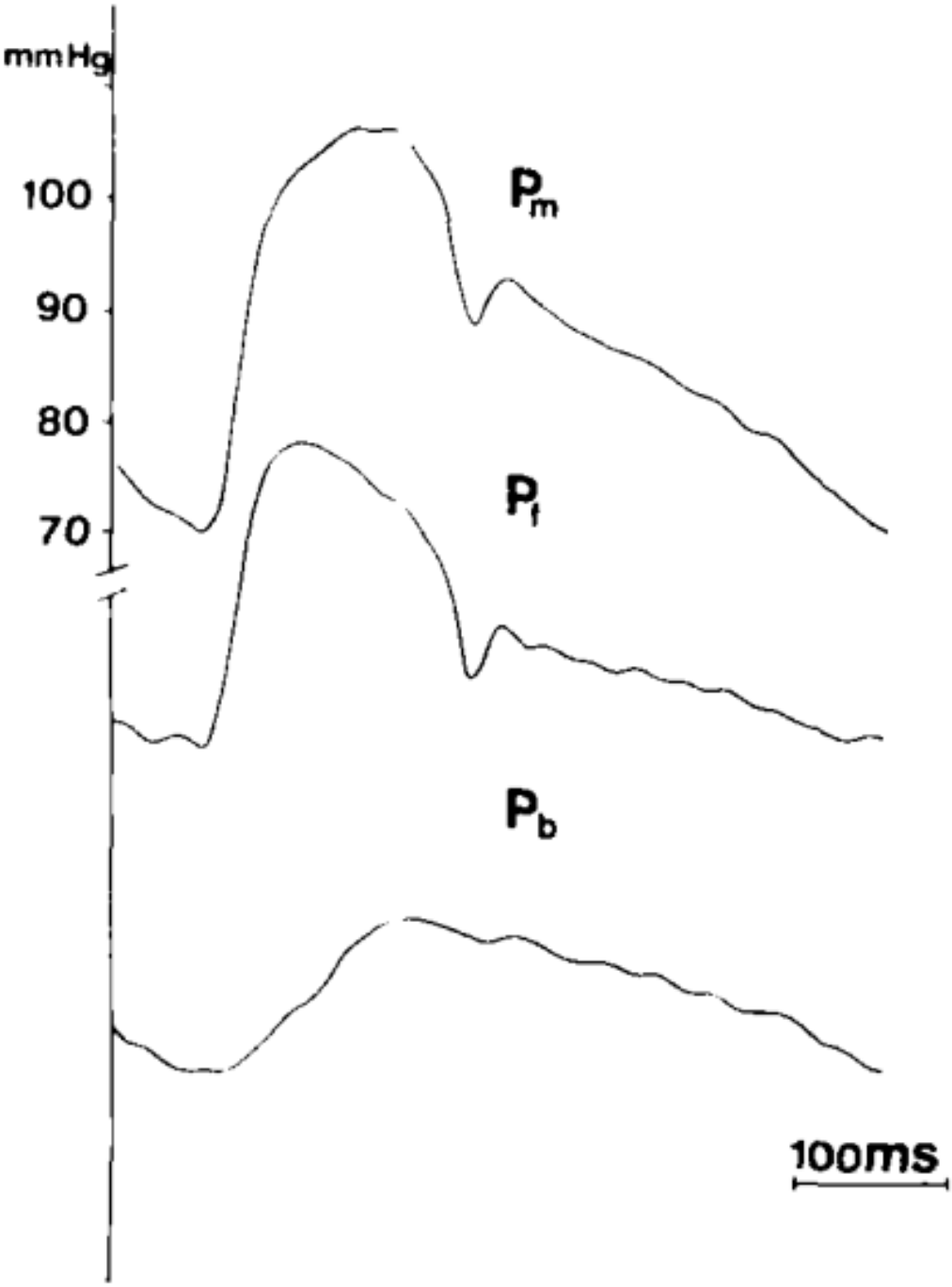

Figure 1.3 Illustration of measured, forward, and backward pressure waves

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Relationship of Hypertension and β-blockade on PTT analysis

Should the PDI be statistically different between the normal and hypertensive patient groups, this method of analysis may allow for a more accurate rapid assessment option of health care professionals. Additionally, this technique could be applied to hypertensive patients being treated with standard anti-hypertensive drug therapy. If there is a difference in PDI between the hypertensive group and a group of patients treated with anti-hypertensive pharmacological products, the method could be made to distinguish between the groups. This distinction could have utility in identifying when a patient is responding to anti-hypertensive drug therapy and when the patient is not responding to the treatment. For this study, β-adrenergic blocking agents were used for the anti-hypertensive drug treatment group. This group of patient data should result in a mean PDI close to one because arterial stiffness should be less than the stiffness of the untreated hypertensive group, resulting in less pulse contour distortion. Figure 1.4 includes typical recordings from healthy, untreated hypertensive, and treated hypertensive patients to provide a graphical illustration of the contrast in pulse contours.

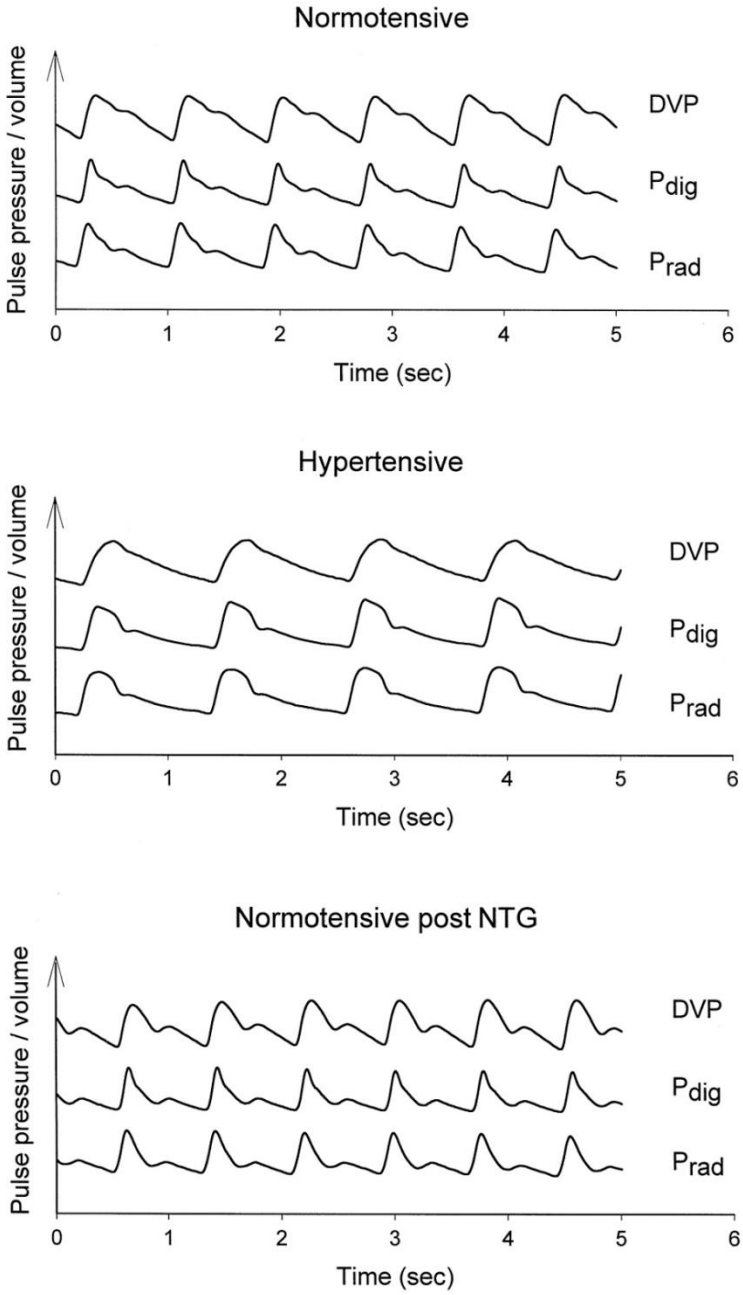

Figure 1.4 Graphical comparison of pulse contours for healthy, untreated hypertensive, and NTG treated hypertensive patients

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Relationship of diabetes on PTT analysis

Diabetes is another chronic disease affecting many Americans and is known to affect cardiovascular health. In 2010, approximately 25.8 million Americans had diabetes with a prevalence of nearly 8 percent in the general population [24]. While diabetes is often comorbid with CVD, it may have independent effects on PDI that warrant the inclusion of a set of diabetic patient data. Clinical studies have shown that PWV is greater in patients with diabetes than control subjects for any level of systolic blood pressure [25, 26]. A 2002 study of nearly 2,500 individuals yielded results supporting that type 2 diabetes accelerated vascular aging in a way that could be measured with PWV [25]. Similarly, another 2002 study found that PWV acted as an independent predictor of mortality in diabetes population samples [26]. Therefore, in addition to the groups mentioned above, a group of diabetic pulse recordings was included for study. It is hoped that PDI comparison will detect a significant, replicable difference allowing for the identification of diabetic versus healthy patient waveforms. The diabetic patient data should have a mean PDI similar to the mean PDI of the hypertensive group. Figure 1.5 is included to illustrate the difference in pulse contour between a typical healthy and diabetic pulse recording.

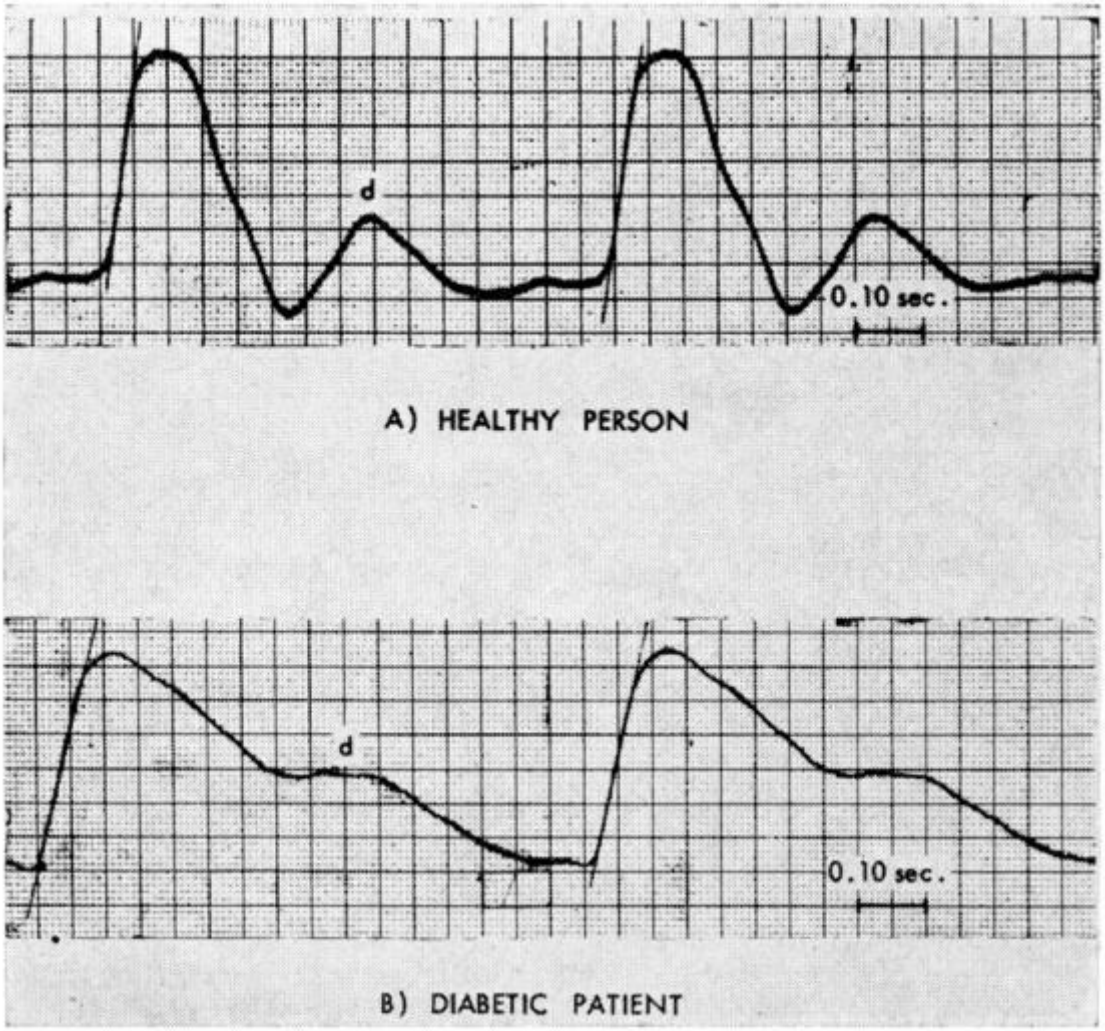

Figure 1.5 Graphical comparison of healthy and diabetic patient pulses [27]

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Chapter 2: Specific Aims

Introduction

Cardiovascular disease (CVD) remains the leading cause of death worldwide [1], with an increasing burden on low and middle income countries according to the World Health Organization [5]. Accurate, rapid assessment techniques would allow health care providers to better screen for and monitor CVD. Pulse Wave Velocity (PWV) can be measured noninvasively and has been shown to correlate with arterial stiffness, a strong indicator of CVD [9-11]. PWV is calculated based on Pulse Transit Time (PTT), which is calculated by taking two recordings of the arterial pulse and measuring the pulse arrival time between the two recordings sites. Wave reflection due to arterial stiffness has been shown to affect the pulse contour, and the measurement of PTT can quantify the degree of pulse wave distortion due to arterial stiffness [16, 17]. Comparing PTT of different parts of the wave as the wave travels from the heart may show a significant, replicable difference in pulse wave distortion between groups of patients. Hypertensive patients with stiffer arteries should display greater distortion of the pulse wave contour, while patients treated with anti-hypertensive vasodilators should display less distortion. Diabetic patients should also display more distortion than the control subjects. For this study, the comparison of PTT_p to PTT_f (PTT_p/PTT_f) will be referred to as the pulse distortion index (PDI).

Specific aim 1: Does the comparison of PDI allow for distinction between healthy patients and hypertensive, β-blocker treated, and diabetic patients

Objective: To determine if comparing PDI shows a significant and replicable degree of pulse contour distortion when comparing the difference in PDI between the control and the groups of interest. *Approach:* Compare PDI in multi-site, noninvasive arterial pulse recordings. Through data analysis, note if the difference in PDI is significant within and between groups to validate whether the method of comparing PDI can be used to qualify patient health. *Rationale:* Hypertensive, β-blocker treated, and diabetic patients have qualitatively different pulse wave contours when compared to control pulse contours. This difference in pulse contour may be great enough to be detected by the method of PDI comparison. If so, PDI could be a useful measure for screening and assessing patient cardiovascular health.

Specific aim 2: Does the comparison of PDI allow for distinction between hypertensive and β-blocker treated patients

Objective: To determine if comparing PTT_f and PTT_p shows a significant and replicable change in PDI when comparing hypertensive and β-blocker treated patient recordings. *Approach:* Compare PDI from multi-site, noninvasive arterial pulse recordings. Through data analysis, note if the difference in PDI is significant within and between groups to validate whether comparing PDI can be used to qualify patient health. *Rationale:* Blockade of β-adrenergic receptors is associated with vasodilation, which reduces PWV. The hypertensive patient group should have a different pulse contour when compared to the β-blocker treated group. This difference in pulse contour should be detected and quantified by the PDI.

Chapter 3: Methods

3.1 Recording Methods

Multiple noninvasive recording methods were used to obtain the data used in this study. Data taken with invasive recording methods were excluded because the aim of this study is to validate this method for rapid assessment. Invasive techniques take more time than noninvasive methods, defeating the purpose of a rapid assessment. The recording methods used to obtain the data used in this study are described below.

3.1.1 Photoplethysmography

Photoplethysmography (PPG) is a noninvasive method for recording the arterial pulse wave that measures blood volume change via the attenuation of light as detected by a nearby sensor. PPG experimental setup involves a light source and a photodetector. The light source is typically an LED emitting light in a narrow bandwidth at an infrared or near infrared frequency. These frequencies create the best signal based on the tissue refractive index and anisotropy factor. The photodetector is often a photodiode or photoresistor [28].

The arterial pulse attenuates the light transmitted by the LED as the light reaches the photodetector, creating a pulsatile recording corresponding to the arterial pulse wave. PPG as a method for arterial pulse recordings has already been validated [29].

Some advantages of PPG are the instrumentation is low-cost, noninvasive, and portable. Some disadvantages of PPG are a high susceptibility to motion artefact and the fact that the recording is not calibrated, making exact measurement of blood pressure

impossible. Instead of mm Hg, PPG recordings are scaled to arbitrary units (AU). Figure 3.1 Illustrates the experimental setup for taking multiple simultaneous PPG recordings for the purpose of finding PWV.

3.1.2 Piezoelectrotransducer (Ultrasound)

Another method for recording the arterial pulse wave is the use of piezoelectric transduction. An inflated balloon is applied to the patient at a site near the artery of interest and this balloon is agitated by an actuator. As the blood volume of the arterial pulse displaces the balloon, pressure in the balloon rises in sync with the arterial pulse. This displacement is detected by an ultrasound sensor that consists of piezoelectric. Figure 3.2 illustrates the use of Doppler ultrasound to find the pulse at the carotid artery.

3.1.3 Electrocardiogram

The electrocardiogram (ECG) is another method for noninvasive detection of the heartbeat. Although ECG recordings do not show the arterial pulse wave, they provide a reference point for the beginning of the heartbeat which can be then used for calculation of PTT. The ECG records the electric pulse of the heart with electric leads, which record the electric potential across the patient, allowing for the recording of the electric pulse that corresponds to the mechanical pulse of the heart [30]. The QRS complex is associated with left ventricular ejection and is treated as occurring simultaneously with mechanical systole at the heart in this study.

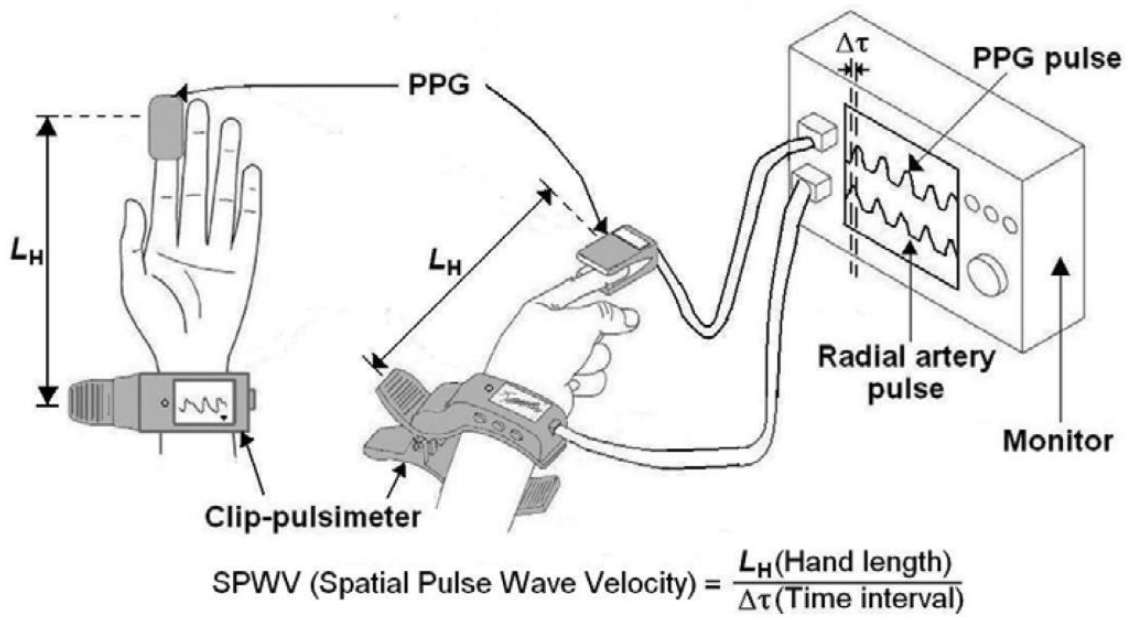

Figure 3.1 Illustration of PPG recording technique

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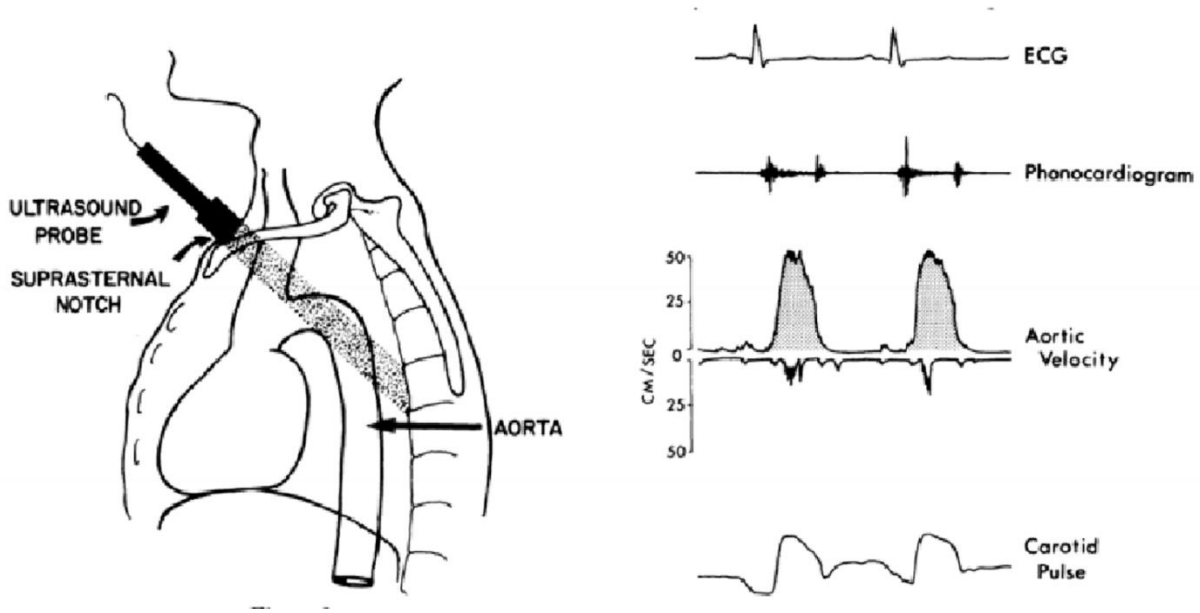

Figure 3.2 Illustration of ultrasound recording technique

The above figure was produced by combining Figures 1 and 2 from the original source.

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3.1.4 Oscillometry (Pressure Cuff)

Oscillometric blood pressure recording involves the use of an inflatable cuff that is displaced by the patient's artery during the arterial pulse. In a method similar to the one used for piezoelectric pulse wave recording, the pressure cuff displacement is recorded by a manometer. Traditionally, sphygmomanometers used the displacement of mercury to measure blood pressure, but the data used in this study was recorded using modern digital manometers. Instead of displacing liquid mercury, the pressure cuff displaces a mechanical pressure gauge. This displacement is then amplified and converted to a digital signal read by a computer [33].

Since the development of pressure cuff-mediated sphygmomanometry, new technology has been developed to detect the arterial pulse in applanation tonography. Instead of measuring the displacement of a large, inflated pressure cuff some new instruments are the size of a pen and can be easily placed on the patient's skin at the arterial site, reducing the setup time. For the purposes of identification in Tables 4.9 through 4.12, pressure cuff-mediated oscillometric recording will be labeled "pressure cuff" while recordings made with newer applanation tonography will be labeled "tonometry".

3.2 Data Collection

The data used in this study was gathered from a review of the literature. Once sources were identified, there were still a number of steps to measure the time points for the foot and peak of the leading and lagging wave and to calculate the PTT. The method of selecting sources and collecting PTT is described below.

3.2.1 Selection Criteria

As mentioned above, it was essential that all data be recorded using a noninvasive method. Many studies in the literature use intravenous catheterization to measure the pulse wave, but these waveforms could not be used for this analysis because the aim of the study was to validate the accuracy of noninvasively obtained pulse wave forms. Source data also had to include at least two recordings synced to the same time scale. Additionally, each source needed at least one site arterially downstream of another recording site, although not necessarily on the same artery. Some source recordings contained three or more recording sites that allowed for multiple PTT comparisons to be made from the same source recording.

3.2.2 Digitization Process

To convert an image of arterial pulse wave recordings into PTT_f and PTT_p, the image had to be digitized and the relevant time points manually measured. The process involved calibrating the axes to scale one second to the appropriate number of pixels. Figure 3.3 illustrates how the data digitization software is used to scale one second as indicated within the figure to the appropriate amount of pixels for accurate scaling. Then

the time of proximal foot, proximal peak, distal foot, and distal peak could be recorded. From these time points, PTTs were measured and PDI calculated. Figure 3.4 illustrates how the time points for the foot and peak of the wave are found and used to calculate PTT. Vertical distances were not relevant to time calculation, and so only the X values of the points were used in PTT calculation.

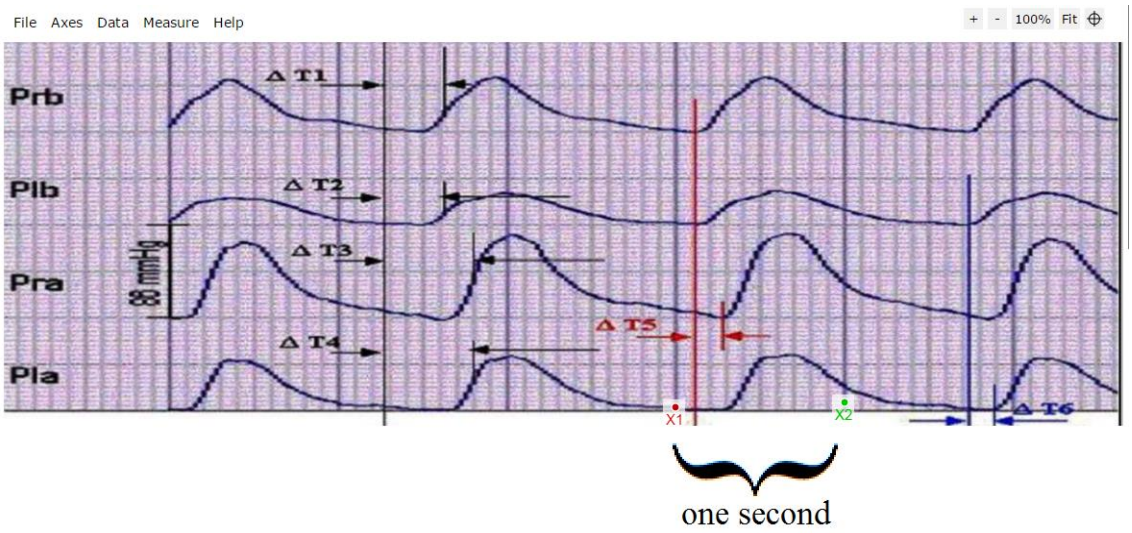

Figure 3.3 Illustration of time scale calibration

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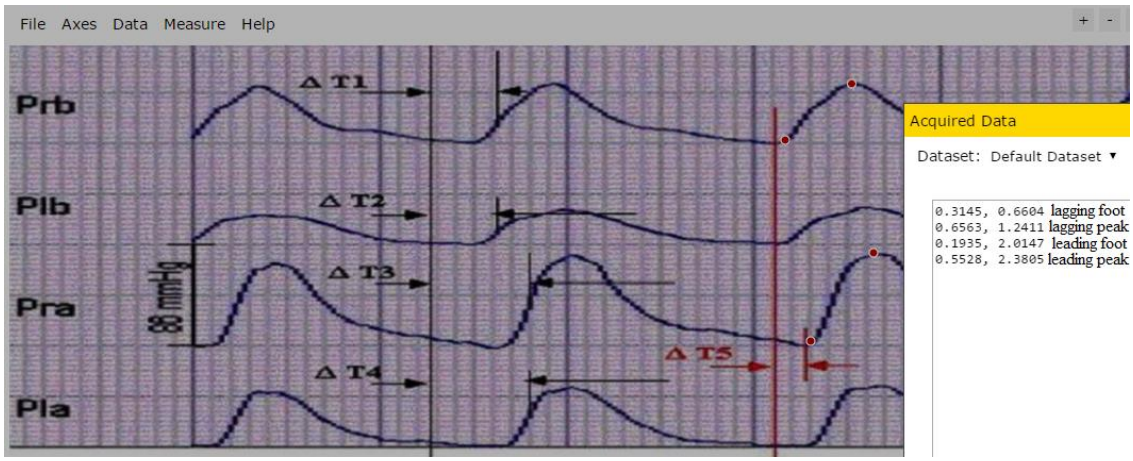

Figure 3.4 Illustration of PTT measurement and calculation

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Chapter 4: Results

It is the aim of this study to determine through pulse wave analysis whether the PTT_f is statistically different from PTT_p. Additionally, this study aims to determine whether there is a consistent, experimentally replicable difference in PTT that could be detected by noninvasive, multi-site pulse wave recording. A consistent difference in PTT_f compared to PTT_p could be used as a method for rapid assessment of a patient's cardiovascular health. With the aim of comparing PTT_f to PTT_p, this study has compared the ratio of PTT_f to PTT_p were PTT_p/PTT_f = PDI. Pulse wave velocity (PWV) was not used because when taking the ratio of PTT, the arterial length would be in both the numerator and the denominator of the equation. Therefore, comparing PTT should result in the same ratio as comparing PWV.

$$PWV = \frac{artery\ length}{PTT}$$

Therefore, ratio of PWV is:

$$\frac{PWV_f}{PWV_p} = \frac{\frac{L}{PTT_f}}{\frac{L}{PTT_p}} = \frac{PTT_p}{PTT_f}$$

Additionally, comparing PWV is difficult when using pre-existing pulse wave recordings from the literature because individual patient artery lengths are rarely published, meaning calculation of PWV from these data would require the use of average artery lengths of the general population. Absolute difference in PTT, i.e. PTT_p - PTT_f, was also considered as a measure of comparison, but was rejected because the absolute difference between PTT might scale with distance from the aorta. Figures 4.1 through 4.3 illustrate representative examples of PTT and PDI calculation for normal, untreated, and treated hypertensive test groups. Refer to Figures 3.3 and 3.4 for similar methodology in calculation of PTT and PDI in the diabetic group.

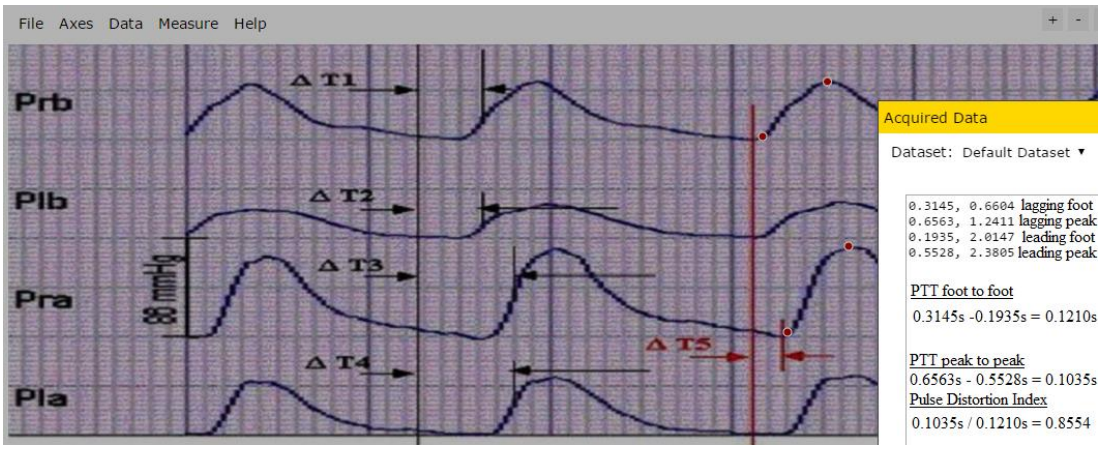

Figure 4.1 Example of PTT and PDI calculation for a normal patient's recording

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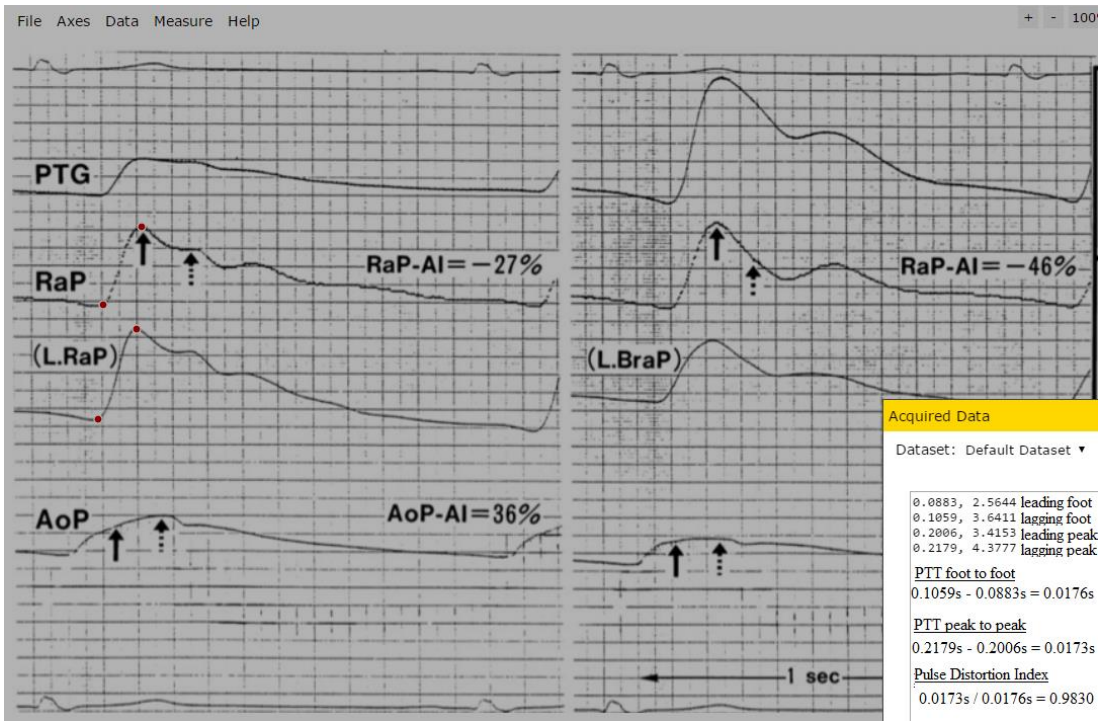

Figure 4.2 Example of PTT and PDI measurement for an untreated hypertensive patient's recording

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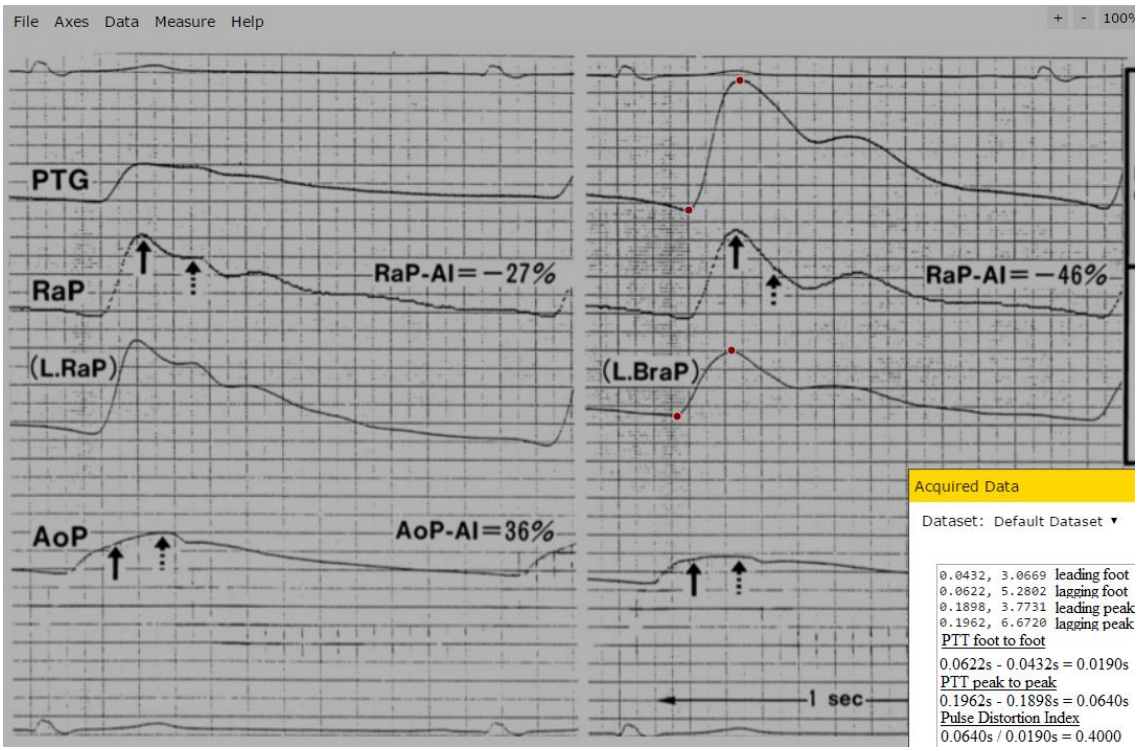

Figure 4.3 Example of PTT and PDI measurement for a treated hypertensive patient's recording

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Tables 4.1 through 4.4 show the time points used for PTT calculation. Tables 4.5 through 4.8 show PTT_f, PTT_p, and PDI. Tables 4.9 through 4.12 show the proximal and distal recording sites and the proximal and distal recording methods. Table 4.13 is a summary of the data in Tables 4.5 through 4.8. Figure 4.4 contains a bar graph that shows the mean PDI values from table 4.13 for the test groups. It is important to note that some of the samples in these groups were taken from the same recording. In these cases, the samples would involve different anatomical recording locations that were recorded, i.e. if a given sample included 3 or more simultaneous recordings then multiple comparisons of PTT could be made.

Table 4.14 is a summary of a single factor analysis of variance (ANOVA) test which assesses the statistical likelihood that one of the groups is statistically significantly different from the other groups. The traditional threshold for the p-value is 0.05, and that threshold is used for this study. The F value is another indicator of statistical significance, with greater F values indicating greater likelihood of a statistically significant result. The F critical value is a third measure provided by the ANOVA test, and is compared to the F value. F values greater than the F critical value denote statistical significance.

Table 4.1: Normal Patient Data Pulse Time Points

Number	Prox. foot (s)	Dist. foot (s)	Prox. peak (s)	Dist. Peak (s)
N1	0.1518	0.5278	0.3454	0.7428
N2	0.5670	0.8866	0.7990	1.1134
N3	0.4150	0.5549	0.5106	0.7026
N4	0.4468	0.4681	0.6312	0.6596
N5	0.4686	0.5781	0.5905	0.7154
N6	0.1243	0.3880	0.1662	0.4374
N7	0.1058	0.3856	0.1552	0.4355
N8	0.5298	0.7381	0.6607	0.9048
N9	0.5536	0.6845	0.7321	0.8750
N10	0.2083	0.5298	0.2857	0.6607
N11	0.2083	0.5536	0.2857	0.7321
N12	0.1261	0.1796	0.2032	0.2584
N13	-0.0484	0.1796	0.0036	0.2584
N14	0.2485	0.4076	0.4279	0.5458
N15	0.2719	0.6594	0.3094	0.7563
N16	0.6707	0.9582	0.7087	1.0592
N17	0.6707	0.9711	0.7087	1.0858
N18	0.6539	1.0385	0.7180	1.1026
N19	0.1863	0.2009	0.2858	0.3035
N20	0.4101	0.4573	0.4459	0.4932
N21	0.3484	0.4101	0.3720	0.4459
N22	0.1544	0.3873	0.1878	0.5054
N23	0.3971	1.0180	0.4517	1.1395
N24	0.3864	0.7340	0.4128	0.8796
N25	0.4915	0.8303	0.5335	0.9622

Table 4.2: Hypertensive Patient Data Pulse Time Points

Number	**Prox. foot (s)**	**Dist. foot (s)**	**Prox Peak (s)**	**Dist. Peak (s)**
H1	0.1014	0.1032	0.1077	0.1095
H2	0.1112	0.3062	0.1562	0.3341
H3	0.1112	0.3915	0.1562	0.4206
H4	0.1112	0.5441	0.1562	0.6091
H5	0.2862	0.4496	0.3201	0.4941
H6	0.1392	0.2454	0.1970	0.3174
H7	0.0391	0.1392	0.0770	0.1970
H8	0.0888	0.1031	0.1889	0.2060
H9	0.0157	0.2004	0.0397	0.3214
H10	0.4618	0.5895	0.4846	0.6549
H11	0.0110	0.0566	0.1975	0.2329
H12	-0.0014	0.0602	0.1306	0.2364
H13	-0.1430	0.0566	-0.1132	0.2329
H14	-0.1430	0.0602	-0.1132	0.2364
H15	0.0400	0.1314	0.0627	0.1886
H16	0.1009	0.3437	0.1307	0.4387

Table 4.3: β-Blocker Treated Patient Data Pulse Time Points

Number	Prox. foot (s)	Dist. foot (s)	Prox. peak (s)	Dist. Peak (s)
B1	0.2924	0.3366	0.4164	0.4606
B2	-0.0057	0.2102	0.0292	0.3054
B3	-0.0989	0.0960	-0.0659	0.1966
B4	-0.0989	0.1357	-0.0659	0.2387
B5	0.3372	0.6336	0.3829	0.7863
B6	0.0003	0.2624	0.0295	0.3625
B7	0.4470	0.7106	0.5582	0.8937
B8	0.3508	0.5179	0.4294	0.6395
B9	0.1155	0.3051	0.1481	0.3872

Table 4.4: Diabetic Patient Data Pulse Time Points

Number	**Prox. foot (s)**	**Dist. foot (s)**	**Prox. peak (s)**	**Dist. Peak (s)**
D1	0.7031	0.7500	0.7831	0.8281
D2	0.7031	0.8750	0.7831	0.9375
D3	0.7031	1.1563	0.7831	1.2656
D4	0.8613	0.9570	1.0500	1.1333
D5	0.8613	1.3869	1.0500	1.6112
D6	0.8613	2.5672	1.0500	2.7429
D7	0.2392	0.3447	0.3156	0.4481
D8	0.2392	0.5028	0.3156	0.6048
D9	0.5616	0.7397	0.6164	0.8356
D10	0.5616	0.9863	0.6164	1.0548
D11	0.2828	0.5454	0.3249	0.6260
D12	0.2828	0.7719	0.3249	0.8439
D13	0.4093	0.4446	0.4974	0.5376
D14	0.5160	0.8609	0.5695	0.9409
D15	0.5160	1.1920	0.5695	1.3062
D16	0.5145	0.8116	0.6156	0.9331

Table 4.5: Normal Patient Data PTT and PDI

Number	**PTT_f (s)**	**PTT_p (s)**	**PDI**
N1	0.3760	0.3974	1.0569
N2	0.3196	0.3144	0.9837
N3	0.1399	0.1920	1.3724
N4	0.0213	0.0284	1.3333
N5	0.1095	0.1249	1.1406
N6	0.2637	0.2712	1.0284
N7	0.2798	0.2803	1.0018
N8	0.2083	0.2441	1.1719
N9	0.1309	0.1429	1.0917
N10	0.3215	0.3750	1.1664
N11	0.3453	0.4464	1.2928
N12	0.0535	0.0552	1.0318
N13	0.2280	0.2548	1.1175
N14	0.1591	0.1179	0.7410
N15	0.3875	0.4469	1.1533
N16	0.2875	0.3505	1.2191
N17	0.3004	0.3771	1.2553
N18	0.3846	0.3846	1.0000
N19	0.0146	0.0177	1.2123
N20	0.0472	0.0473	1.0021
N21	0.0617	0.0739	1.1977
N22	0.2329	0.3176	1.3637
N23	0.6209	0.6878	1.1077
N24	0.3476	0.4668	1.3429
N25	0.3388	0.4287	1.2653

Table 4.6: Hypertensive Patient Data PTT and PDI

Number	**PTT_f (s)**	**PTT_p (s)**	**PDI**
H1	0.0018	0.0018	1.0000
H2	0.1950	0.1779	0.9123
H3	0.2803	0.2644	0.9433
H4	0.4329	0.4529	1.0462
H5	0.1634	0.1740	1.0649
H6	0.1062	0.1204	1.1337
H7	0.1001	0.1200	1.1988
H8	0.0143	0.0171	1.1958
H9	0.1847	0.2817	1.5252
H10	0.1277	0.1703	1.3336
H11	0.0456	0.0354	0.7763
H12	0.0616	0.1058	1.7175
H13	0.1996	0.3461	1.7340
H14	0.2032	0.3496	1.7205
H15	0.0914	0.1259	1.3775
H16	0.2428	0.3080	1.2685

Table 4.7: β-Blocker Patient Data PTT and PDI

Number	**PTT_f (s)**	**PTT_p (s)**	**PDI**
B1	0.0442	0.0442	1.0000
B2	0.2159	0.2762	1.2793
B3	0.1949	0.2625	1.3470
B4	0.2346	0.3046	1.2984
B5	0.2964	0.4034	1.3610
B6	0.2621	0.3330	1.2705
B7	0.2636	0.3355	1.2728
B8	0.1671	0.2101	1.2573
B9	0.1896	0.2391	1.2611

Table 4.8: Diabetic Patient Data PTT and PDI

Number	**PTT_f (s)**	**PTT_p (s)**	**PDI**
D1	0.0469	0.0450	0.9595
D2	0.1719	0.1544	0.8982
D3	0.4532	0.4825	1.0647
D4	0.0957	0.0833	0.8704
D5	0.5256	0.5612	1.0677
D6	1.7059	1.6929	0.9924
D7	0.1055	0.1325	1.2559
D8	0.2636	0.2892	1.0971
D9	0.1781	0.2192	1.2308
D10	0.4247	0.4384	1.0323
D11	0.2626	0.3011	1.1466
D12	0.4891	0.5190	1.0611
D13	0.0353	0.0402	1.1388
D14	0.3449	0.3714	1.0768
D15	0.6760	0.7367	1.0898
D16	0.2971	0.3175	1.0687

Table 4.9: Normal Patient Recording Sites and Recording Methods

Number	Proximal Site	Distal Site	Proximal Method	Distal Method
N1	radial artery	digital artery	PPG	PPG
N2	carotid artery	brachial artery	Piezoelectric	Piezoelectric
N3	apical artery	radial artery	Piezoelectric	Piezoelectric
N4	brachial artery	radial artery	Piezoelectric	Piezoelectric
N5	radial artery	anterior tibial artery	Piezoelectric	Piezoelectric
N6	digital artery	dorsalis pedis artery (toe)	PPG	PPG
N7	digital artery	dorsalis pedis artery (toe)	PPG	PPG
N8	brachial artery	radial artery	PPG	PPG
N9	brachial artery	radial artery	PPG	PPG
N10	heart (ECG)	radial artery	ECG	PPG
N11	heart (ECG)	radial artery	ECG	PPG
N12	brachial artery	anterior tibial artery	Ultrasound	Ultrasound
N13	heart (ECG)	anterior tibial artery	ECG	Ultrasound
N14	digital artery	dorsalis pedis artery (toe)	PPG	PPG
N15	heart (ECG)	dorsalis pedis artery (toe)	ECG	PPG
N16	heart (ECG)	brachial artery	ECG	PPG
N17	heart (ECG)	brachial artery	ECG	PPG
N18	digital artery	dorsalis pedis artery (toe)	PPG	PPG
N19	radial artery	digital artery	PPG	PPG
N20	digital artery	dorsalis pedis artery (toe)	PPG	PPG
N21	heart (ECG)	digital artery	ECG	PPG
N22	heart (ECG)	digital artery	ECG	PPG
N23	heart (ECG)	digital artery	ECG	PPG
N24	heart (ECG)	dorsalis pedis artery (toe)	ECG	PPG
N25	heart (ECG)	dorsalis pedis artery (toe)	ECG	PPG

Table 4.10: Hypertensive Patient Recording Sites and Recording Methods

Number	Proximal Site	Distal Site	Proximal Method	Distal Method
H1	radial artery	digital artery	PPG	PPG
H2	femoral artery	posterior tibial artery (calf)	PPG	PPG
H3	femoral artery	anterior tibial artery	PPG	PPG
H4	femoral artery	dorsalis pedis artery (toe)	PPG	PPG
H5	femoral artery	posterior tibial artery (calf)	PPG	PPG
H6	digital artery	dorsalis pedis artery (toe)	PPG	PPG
H7	heart (ECG)	digital artery	ECG	PPG
H8	radial artery	digital artery	PPG	PPG
H9	heart (ECG)	digital artery	ECG	PPG
H10	heart (ECG)	digital artery	ECG	PPG
H11	brachial artery	anterior tibial artery	Pressure cuff	Pressure cuff
H12	brachial artery	anterior tibial artery	Pressure cuff	Pressure cuff
H13	heart (ECG)	anterior tibial artery	ECG	Pressure cuff
H14	heart (ECG)	anterior tibial artery	ECG	Pressure cuff
H15	heart (ECG)	carotid artery	ECG	tonometer
H16	heart (ECG)	femoral artery	ECG	tonometer

Table 4.11: β-Blocker Treated Patient Recording Sites and Recording Methods

Number	**Proximal Site**	**Distal Site**	**Proximal Method**	**Distal Method**
B1	radial artery	digital artery	PPG	PPG
B2	heart (ECG)	digital artery	ECG	PPG
B3	heart (ECG)	brachial artery	ECG	PPG
B4	heart (ECG)	radial artery	ECG	PPG
B5	heart (ECG)	radial artery	ECG	PPG
B6	heart (ECG)	digital artery	ECG	PPG
B7	heart (ECG)	digital artery	ECG	PPG
B8	heart (ECG)	popliteal artery (knee)	ECG	PPG
B9	heart (ECG)	popliteal artery (knee)	ECG	PPG

Table 4.12: Diabetic Patient Recording Sites and Recording Methods

Number	Proximal Site	Distal Site	Proximal Method	Distal Method
D1	femoral artery	posterior tibial artery (calf)	pressure cuff	pressure cuff
D2	femoral artery	anterior tibial artery	pressure cuff	pressure cuff
D3	femoral artery	dorsalis pedis artery (toe)	pressure cuff	pressure cuff
D4	femoral artery	posterior tibial artery (calf)	pressure cuff	pressure cuff
D5	femoral artery	anterior tibial artery	pressure cuff	pressure cuff
D6	femoral artery	dorsalis pedis artery (toe)	pressure cuff	pressure cuff
D7	femoral artery	popliteal artery (knee)	pressure cuff	pressure cuff
D8	femoral artery	anterior tibial artery	pressure cuff	pressure cuff
D9	femoral artery	popliteal artery (knee)	pressure cuff	pressure cuff
D10	femoral artery	dorsalis pedis artery (mid-foot)	pressure cuff	pressure cuff
D11	femoral artery	popliteal artery (knee)	pressure cuff	pressure cuff
D12	femoral artery	anterior tibial artery	pressure cuff	pressure cuff
D13	femoral artery	popliteal artery (knee)	pressure cuff	pressure cuff
D14	proximal femoral artery	distal femoral artery	pressure cuff	pressure cuff
D15	proximal femoral artery	posterior tibial artery (calf)	pressure cuff	pressure cuff
D16	proximal femoral artery	distal femoral artery	pressure cuff	pressure cuff

Table 4.13: Summary of PDI

Groups	***n***	***mean***	***variance***
Normal	25	1.1460	0.0220
Hypertensive	16	1.2468	0.0909
Beta	9	1.2608	0.0109
Diabetes	16	1.0616	0.0110

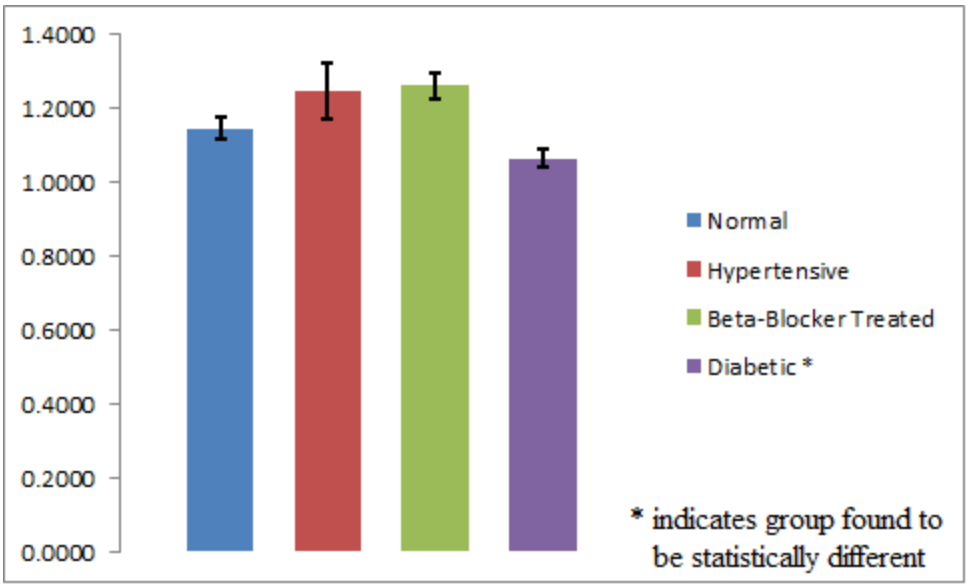

Figure 4.4 Mean PDI Bar Graph with error bars

Table 4.14: Summary of Single Factor ANOVA test for all four groups

Source of Variation	***Sum of Squares***	***Mean square***	***F***	***P-value***	***F critical***
Between Groups	0.3695	0.123173	3.5647	0.0191	2.7530
Within Groups	2.1423	0.034554			
Total	2.5119				

The first ANOVA test described above showed a high statistical likelihood that one of the data groups was different from the others. To further determine how the groups of data differ and to better validate the use of PDI, four more ANOVA tests compared pairs of the data groups. These tests were made to determine the utility of PDI in differentiating between patients with the conditions of the data groups. Test 1 compared the normal patient data with the hypertensive patient, Test 2 compared the normal patient data with the β-blocking agent treated patient, Test 3 compared normal patient data with diabetic patient, and Test 4 compared hypertensive patient data with β-blocking agent treated patient data to determine if PDI could differentiate between those groups of patients. Table 4.15 shows the results of Tests 1 through 4.

Table 4.15: Summary of Paired Group Tests 1 through 4

Test	**F**	***F critical***	***P***
1	2.0434	4.0913	0.1608
2	4.5429	4.1491	0.0408
3	3.9155	4.0913	0.0549
4	0.0181	4.2793	0.8943

Chapter 5: Discussion

Introduction

This study compares PTT_f and PTT_p to investigate whether there is a reproducible difference between these pulse transit times that would serve as in indicator of arterial stiffness. This indicator, defined as PDI, could serve as a rapid assessment used to classify a patient's cardiovascular health. If this novel method of pulse wave analysis is valid, the PDI will be different for healthy patients versus patients with the conditions tested, i.e. hypertension, β-blockade, and diabetes.

Discussion of mean and variance for PDI assessment of groups

Mean PDI values are displayed in Table 4.13. PDI for the normal group was less than PDI for the hypertensive and β-blocker treated group but greater than the diabetic group. Expected results would have shown PDI close to one for the normal and β-blocker treated group but PDI less than one for the hypertensive and diabetic patient groups because greater wave reflection in these groups would distort the time of systole, making PTT_p shorter than PTT_f. It is possible that wave reflection caused delayed pulse arrival time, which would result in $PTT_p > PTT_f$ and explain the increase in PDI between the normal and hypertensive groups. If this was the case, it does not explain why the diabetic group mean PDI was so much less than the mean PDI for the other three groups, nor would it explain why the β-treated PDI was close to but slightly greater than the hypertensive mean PDI.

ANOVA tests between groups

The first statistical test applied to the results was an ANOVA test to determine if any of the four groups was statistically different. The results of this test are in Table 4.14. The p-value shown in Table 4.14 is .0191, below the 0.05 threshold that indicates a strong likelihood of one of the groups being different. The F value shown in Table 4.14 is 3.5647. A large F value is another indicator the result is significantly different while an F value close to 1 indicates a lack of statistical significance. One more metric of statistical analysis is the F critical value, which is compared to the F value. If the F critical value is less than the F value, this result can also indicate statistical significance of the results. As shown in Table 4.14, the F critical value is 2.7530 and less than the F value.

Results of first set of ANOVA tests

This first test supports the hypothesis that there is a significant difference in the change in PTT between the groups. The p-value is below the threshold of 0.05 and the F critical value is less than the F value. However, the F value is close to one, indicating there is still a significant amount of variance within groups compared to the amount of variance between groups. It is likely that there were a number of sources of variance that contributed to the variance within groups, and therefore future study of PDI should eliminate these possible sources of variance.

To better understand the results, four more ANOVA tests were applied to make comparisons between the groups. The comparisons made were between the normal group and each of the three conditions, as well as a comparison of the hypertension group

to the β-blocker treated group. This made a total of four additional tests. The first three tests serve to fulfil Specific Aim 1 from Chapter 2, while the fourth test serves to fulfil Specific Aim 2. The other comparisons, e.g. diabetic to β-blocker, were not considered essential. For future reference, Test 1 was the comparison of normal patient data to hypertensive patient data, Test 2 was the comparison of normal patient data to β-blocker treated patient data, Test 3 was the comparison of normal patient data and diabetic patient data, and Test 4 was the comparison of hypertensive patient data and β-blocker treated patient data.

The results of these tests are included in Table 4.15. Tests 1, 3, and 4 had p-values greater than 0.05 and F values below the F critical value, although Test 3 was close to the threshold. These results show no significant difference between groups. Test 2 had a p-value below the threshold of 0.05 and an F value above the F critical value. These results show a difference between the normal and β-blocker treated group. Comparing the results of Test 2 with the data in Table 4.13, Test 2 compared the two groups with the largest difference in mean PTT ratio, which is likely the reason for the results.

Discussion of results for first set of ANOVA tests

Based on studies of the effect of β-blockers, an expected result might see the mean PDI of the β-blocker group between the normal and hypertensive group. That is, the normal group might have a PDI close to one corresponding to a PTT_p very close to PTT_f while the hypertensive patient group should have a PDI not close to one corresponding to greater wave distortion. In the hypothetical expected case, the β-

blocking agents would dilate the arteries, creating less wave reflection and therefore moving the mean PDI closer to the normal patients' PDI. The results of this analysis show the opposite, with the mean PDI of the β-blocker treated group greater than both the normal and hypertensive patient groups.

To compound with these counter-intuitive results, the diabetic patient data set yielded the lowest mean PTT ratio of all four groups. It was anticipated that the diabetic patient group would closely correspond with the hypertensive patient data group. Many of the data from their respective sources revealed the many of the diabetic patients were hypertensive in addition to being diabetic. Given the results of this analysis, more study is needed to validate PDI as a measure for assessing cardiovascular health.

Suggestions for improving future study

There are a number of ways that future studies involving pulse wave analysis of the arterial pulse could retrieve more reliable data. It is likely that much of the variance in PTT recordings is caused by the sourcing of the dataset. Rather than obtaining new recordings purely for the assessment of this method, this study used recordings from previously published studies in the literature. It was hoped that a difference in PDI between groups would be significant enough that validation of the PDI could be performed using previously published data. This study was therefore performed with the intent of identifying a stark difference in PDI that would be found in pre-existing pulse recordings regardless of experimental parameters. However, a further validation of this novel method should standardize experimental parameters to better assess the accuracy and utility of comparing PDI between groups of varying cardiovascular health.

Suggestion: blood pressure classification

Within the hypertensive patient data set, no distinction was made between mild and severe hypertension. Instead, all recordings in this data set were taken from patients labeled within their respective studies as “hypertensive”, regardless of blood pressure. Because hypertension is a gradient rather than binary, it is possible that the PDI for a patient is correlated to blood pressure and therefore further analysis may find a correlative model linking PDI to severity of hypertension. It is relevant to note in Table 4.13 that the variance in PDI for the hypertensive group was far greater than the variance in PDI for the other three groups. In future study, rather than classifying patients as either healthy or hypertensive each recording could be correlated to its respective blood pressure. Therefore, future pulse wave analysis of hypertensive recordings should record blood pressure for every patient to investigate this possible correlation. Independent blood pressure recording would be especially necessary for a test using photoplethysmography because PPG technology does not scale to blood pressure.

Suggestion: diabetes isolation/normalization

One possible source of variation within the diabetic patient group was the lack of consistent health between the patients from which the recordings were taken. These patients did have diabetes in common between them, but other key indicators of cardiovascular health between these patients were inconsistent. Not all the publications containing the diabetic patient recordings used for this data set included other key indicators of health such as blood pressure, heart rate, age, etc. Diabetes may play a role

in distortion of the pulse wave, but it is possible these other factors outweigh the effects of diabetes and resulted in variation within the diabetic patient data set. Further study should take steps to normalize other factors to isolate the affect the role of diabetes in PDI that previous studies suggest may be present based on the relationship between diabetes and PWV [25, 26].

Suggestion: concerns regarding peripheral recordings in β-blockade antihypertensive treatment

Many studies in the literature suggest that pulse recordings taken from the periphery do not accurately reflect central arterial blood pressure and peripheral recordings underestimate the effect of β-adrenergic blocking agents on the central arteries [35-38]. The rationale for this study states that identifying a theoretical difference in PTT would allow for rapid assessment of the patients cardiovascular health. However, these studies suggest that peripheral site recordings of patients treated with β-blocking agents do not accurately portray pressure in the central aorta. Therefore, it is possible that a difference in PTT found at periphery sites of patients treated with β-blocking agents does not accurately diagnose a patient's cardiovascular condition.

Suggestion: recording site concerns

As noted in Tables 4.9 through 4.12, the proximal and distal recording sites were not consistent across or within data sets. The relative distance between recordings sites as well as the distance from the aorta may have affected the extent of wave reflection,

causing variation of PTT ratio within the data. The arterial pulse contour changes as it moves from the aorta.

Suggestion: concerns regarding recording methods

Like the recording sites, recording methods were not uniform for the data used in this analysis. As seen in Tables 4.9 through 4.12, the pulse wave recordings used for this study were obtained using several different recording methods. Although all these methods were noninvasive, it is still possible that the use of different recording methods in obtaining pulse wave recordings caused some variation within the results. Of particular concern was the use of the electrocardiograph as a recording method to obtain both a foot and a peak.

Suggestion: concerns regarding ECG

Because the ECG measures electric potential the time point for PTT_f calculation was measured at the starts of the QRS complex at the beginning of the electric pulse. This time point was used to approximate the start of mechanical systole in the heart, although there is likely some delay between electrical and mechanical systole. Similarly, the peak of the QRS complex was used as the time point for PTT_p to approximate peak mechanical systole although there is likely some delay.

Tests to isolate effect of ECG

To measure the impact the approximation between the electrical and mechanical pulse had on the dataset, an ANOVA test was applied between the two sets of data taken from the normal set. The first group contained all normal data found without using ECG as a recording method and the second group contained all normal data found using ECG for the proximal recording method. This test was applied to measure the effect of the use of ECG as a recording method on the measurement of PDI.

Test results

The results of this test are found in Table 5.1. This test found a statistically significant difference between the two groups, suggesting the use of ECG as a recording method strongly impacted the calculated PTT. The p-value was 0.0137, the F value 7.1179, and the F critical 4.293. These results support that the use of ECG had a greater impact on PTT ratio than hypertension, β-blockade, or diabetes.

Further analysis

To validate these results with a larger data set, the test was repeated using all data from the hypertensive and normal data sets. That is, the first group had all data that did not use ECG as a recording method from both the normal and hypertensive data groups and the second group had all data from the normal and hypertensive groups taken using ECG as a recording method. The β-blocker treated group contains all but one source that did use ECG while none of the diabetic data sources used ECG so these two groups were excluded. The results of this test are found in Table 5.2. This comparative test using non-

ECG versus ECG-only data groups showed an even stronger difference. The test resulted in a p-value of 0.0006, an F value of 14.0129, and an F critical of 4.0913. This second test supported that use of ECG had a greater impact than any other factor tested.

Discussion of results of tests

Based on these last two statistical tests, two more comparisons were made to try to distinguish PDI between the groups of normal, hypertensive, β-blocker treated, and diabetic patient. These tests compared all data collected without ECG and all data collected with ECG. The first test did not include the β-blocker treated group because all but B1 were found using ECG. The second test excluded the diabetic group because none of those data were found using ECG. These results of these two tests are shown in Tables 5.3 and 5.4 respectively. To reiterate, these tests were to control for ECG.

The test comparing all data found without ECG found no difference between any of the groups. The test had a p-value of 0.5525, an F value of 0.6019, and an F critical of 3.2257. The test comparing all data found with ECG found that at least one of the groups was different with a p-value of 0.0042, an F value of 7.0167, and an F critical of 3.4221. The normal data set had 11 samples, the hypertensive 7, and the β-blocker treated group 8. Given the small sample size and potential complications regarding the use of ECG, these results are not likely meaningful. Despite reservations regarding sample size, 3 final tests were made between normal and hypertensive patient data, normal and β-blocker treated patient data, and hypertensive and β-blocker treated patient data. The results of these final three ANOVA tests are in Table 5.5 and show only a statistically significant difference between the normal and hypertensive patient data groups.

Table 5.1: Comparison of ECG and non-ECG Samples within the Normal Set

Source of Variation	***Sum of Squares***	***Mean Square***	***F***	***P-value***	***F crit***
Between Groups	0.1246	0.1246	7.1179	0.0137	4.2793
Within Groups	0.4025	0.0175			
Total	0.5270				

Table 5.2: Comparison of ECG and non-ECG Samples within the Combined Normal and Hypertensive Set

Source of Variation	***Sum of Squares***	***Mean Square***	***F***	***P-value***	***F crit***
Between Groups	0.5258	0.5258	14.0129	0.0006	4.0913
Within Groups	1.4634	0.0375			
Total	1.9892				

Table 5.3: Comparison between Groups excluding all ECG Recorded Data

Source of Variation	***Sum of Squares***	***Mean Square***	***F***	***P-value***	***F crit***
Between Groups	0.0356	0.0178	0.6019	0.5525	3.2257
Within Groups	1.2112	0.0295			
Total	1.2468				

Table 5.4: Comparison between Groups using only Samples with ECG

Source of Variation	***Sum of Squares***	***Mean Square***	***F***	***P-value***	***F crit***
Between Groups	0.2198	0.1099	7.0167	0.0042	3.4221
Within Groups	0.3602	0.0157			
Total	0.5799				

Table 5.5 Results of ANOVA tests between groups of the ECG-only set

	F	***P-value***	***F crit***
Normal and Hypertensive	9.9681	0.0061	4.4940
Normal and β-Blockade	4.2330	0.0603	4.6672
Hypertensive and β-Blockade	4.2128	0.0558	4.4513

Additional concerns regarding the dataset

In addition to the concerns raised above, a number of additional factors confounded the results of this analysis by causing some studies to be excluded. Many recordings of pulse waves published in the literature do not contain a clear time scale. Therefore, to preserve the accuracy of the data many recordings that would have been added to the data set, allowing for more robust results, were excluded from analysis. Better marked time scales on several studies would have allowed for a larger dataset and therefore more robust results. Several studies were excluded from analysis because the resolution of the published images was too low. Low resolution images did not allow for precise measurement of the key time points for the analysis, i.e. the foot and peak of the pulse wave. These studies were also discarded, further reducing the size of the data set.

Desynchronization caused many studies to be excluded from this analysis, even more than time scales or resolution. These excluded studies shifted the simultaneously recorded waves so that they no longer have a common start time. The different recordings were desynced to better compare the changing shape of the pulse wave at different sites. However, this desynchronization makes calculation of PTT impossible.

Conclusions on dataset limitations

Given the concerns raised above regarding variance in the dataset, it is recommended further pulse wave analysis use uniform recording sites and the same recording method to eliminate possible sources of variance. Additionally, it is recommended that future study record each patient's blood pressure to allow for correlation between difference in PTT and blood pressure.

Final thoughts

Use of PDI might serve as a validated method for rapid, noninvasive cardiovascular health assessment. Many rigorous studies have already shown a correlation between PWV and cardiovascular health, including the use of PWV to predict cardiovascular events such as stroke or myocardial infarction. The augmentation index has also been shown to predict CVD. Initial statistical analysis of the results in this study supported that the PDI of one of the groups is significantly different. However, further examination showed that the results failed to successfully accomplish the Specific Aims of this study and therefore further research is needed to validate PDI as a means for rapid assessment of CV health.

Appendix: Source Data

Table Appendix-1.1: Sources for Normal Data

Data Sample	Source
1	31
2	39
3	39
4	39
5	39
6	40
7	40
8	21
9	21
10	21
11	21
12	15
13	15
14	15
15	15
16	41
17	41
18	42
19	23
20	43
21	43
22	44
23	45
24	46
25	46

Data Sample	Source
1	43
2	47
3	47
4	47
5	47
6	46
7	46
8	34
9	34
10	48
11	49
12	49
13	49
14	49
15	50
16	50

Table Appendix-1.2: Sources for Hypertensive Data

Data Sample	Source
1	43
2	51
3	34
4	34
5	33
6	51
7	52
8	53
9	53

Table Appendix 1.3: Sources for β-blocker Data

Data Sample	Source
1	54
2	54
3	54
4	54
5	54
6	54
7	55
8	55
9	55
10	55
11	55
12	55
13	55
14	56
15	56
16	56

Table Appendix 1.4: Sources for Diabetic Data

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