LOCAL PULSE WAVE VELOCITY DETECTION OVER AN ARTERIAL SEGMENT USING PHOTOPLETHYSMOGRAPHY

by

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Abstract

The goal of this thesis is to determine the validity of using photoplethysmography (the detection of changes of blood volume using light) to measure pulse wave velocity as part of a continuous and non-disruptive blood pressure monitor. There has been a limited advancement over the years in technologies to monitor personal blood pressure, which have rendered at-home monitoring still relatively intrusive. The main method for at-home blood pressure monitoring is the use of an inflating cuff that obstructs the artery to detect pressure. This system suffers from inherit drawbacks, such as limitations on recording accuracy if insufficient time has passed between samples and the restrictive nature of the cuff which can induce pain on a user. An alternative device that can monitor continuously would thus benefit people who are sensitive or need 24-hour monitoring. Ideally this would be a system that can be worn without discomfort and does not interfere with the user in any way. The ideal device would also allow continuous blood pressure monitoring throughout the cardiac cycle, independent of the level of physical activity of the user. Furthermore, this type of device would allow athletes to measure blood pressure during activity.

To this end, a model is developed to describe blood pressure by measuring the arterial diameter on the radial artery and the pulse wave velocity (PWV) through it. Research suggests that these two metrics, along with the elasticity of an artery, can be used as a means to measure blood pressure non-invasively. This thesis focuses on the measurement of pulse wave velocity. The system design, including the hardware, is covered. The analysis techniques used to obtain raw signals, as well as the methods used to determine the PWV, will be discussed. The measurement location is described in detail. The results are shown to be comparable to values

found in literature. However, due to lack of comparable measurement techniques, no direct comparisons between methods could be performed.

Preface

This thesis was completed under the supervision of Dr. Kenneth Chau and was co-supervised by Dr. Thomas Johnson at the School of Engineering, University of British Columbia Okanagan.

The author was a primary researcher and was involved in all aspects and collaborated with Tyler Worthing. Tyler is the author of a related thesis covering the ultrasound part of the proposed system. Both of us worked in collaboration on these systems and divided the thesis publication according to specialization.

This project originated as an undergraduate capstone project at UBC Okanagan that was sponsored by Rick Slamka of Questek Research and Development and completed with another group member Ryunosuke Nakamatsu.

Ethics approval has been granted by the Clinical Research Ethics Board at the University of British Columbia.

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List of abbreviations

AC	-	Alternating Current
ADC	-	Analog to Digital Converter
BNC	-	Bayonet Neill-Concelman (connector)
BP	-	Blood Pressure
CVD	-	Cardiovascular Disease
DC	-	Direct Current
ECG	-	Electrocardiogram
HES	-	School of Health and Sciences
LED	-	Light-emitting Diode
MRI	-	Magnetic Resonance Imaging
PD	-	Photodetector
PPG	-	Photoplethysmography
PWV	-	Pulse Wave Velocity
SNR	-	Signal-to-noise Ratio
USB	-	University Serial Bus

Acknowledgements

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The deepest appreciation goes to my dear friend and colleague Tyler Worthing, with whom this road traveled has been a blast, and I hope much more traveling is to come.

Finally, I must thank my family and friends for their undying support. Especially my wife, Suzanne, who knows when encouraging words are needed and, more often, when the whip needs cracking. Thank you all.

Chapter 1

Introduction

The goal of this thesis is to develop a local Pulse Wave Velocity (PWV) measuring device as part of an effort to design a wearable, non-constricting, continuous, blood pressure (BP) monitoring system. Such a system would allow athletes to obtain blood pressure information in real time whilst active, as well as allow easier 24-hour monitoring of medical patients. This system would overcome the drawbacks of the most prominent automatic home measurement device, which is the oscillometric cuff. Some drawbacks of the cuff method include the requirement of five minutes rest before measurement, not talking or moving whilst measurements are being taken, waiting for a period of time before taking another measurement, and taking blood pressure measurements only on certain intervals per day to keep tracking over multiple days consistent.

Personal blood monitoring today is fraught with shortcomings, some of which have been stated in the previous paragraph. What this means is that it is very difficult to obtain BP whilst being active. Obtaining continuous data would necessitate a catheter, which includes an invasive procedure requiring a clinical setting. Thus, there is a hindrance for people to obtain blood pressure while they are exercising. Furthermore, there are many conditions and situations that require ambulatory blood pressure monitoring (24-hour monitoring), some of which include detection of white coat hypertension, hypertension research, prognostic use, masked hypertension and episodic dysfunction. The current method involves an oscillometric cuff

inflating every twenty minutes or, during the night time, every hour. This process is quite painful, with some patients reporting the cuff unbearable, and can cause sleep disturbance and bruising where the cuff is located. All these side effects would be negated with a wearable device. A "wearable" is a device that can be worn upon a person with different effects and outputs. Furthermore, a wearable device should be able to be worn with comfort and ease. Some examples of these types of devices are health monitors like Fitbit, cosmetic devices, such as light strings integrated into clothes, or even integrating transit cards into watches. With a low-cost wearable, blood pressure data would become more available for the average person, if the constraints of the current BP measuring systems were addressed. A comfortable wearable device could be worn for extended periods of time without fatiguing the user and would enable athletes to wear a BP measuring system while active. This would also allow people to monitor their BP over longer periods of time and approach their doctors with the information collected. Furthermore, it will add the possibility of tracking blood pressure during strenuous activity without the requirement of catheterization. A wearable device would also be a tremendous help for older people to detect any early signs of any cardiac events allowing them to time to react to prevent or minimize damage.

Our proposed design for a wearable, continuous blood pressure monitoring system consists of two parts: direct measurement of the diameter of the radial artery and the pulse wave velocity over the same arterial segment. The purpose of this thesis is to determine if PWV can be obtained locally over a segment of the radial artery.

1.1 Blood pressure

In this section, more in-depth information will be given to the reader about the importance of blood pressure, including the diseases impacted by BP, what BP says about the overall health of an individual, the cost of treatment for BP related diseases and a general overview on how to measure blood pressure currently.

1.1.1 Importance of blood pressure

Blood pressure is the internal pressure in the arteries of a human. Systolic pressure is the higher pressure that is present when the heart contracts and releases a pressure pulse. Diastolic pressure is the lower pressure which is the normalized resting pressure between heart beats. As the heart beats, a surge of pressure occurs called a pulse wave which travels through the arterial tree, taking the shape of the waveform shown in figure 1.1.

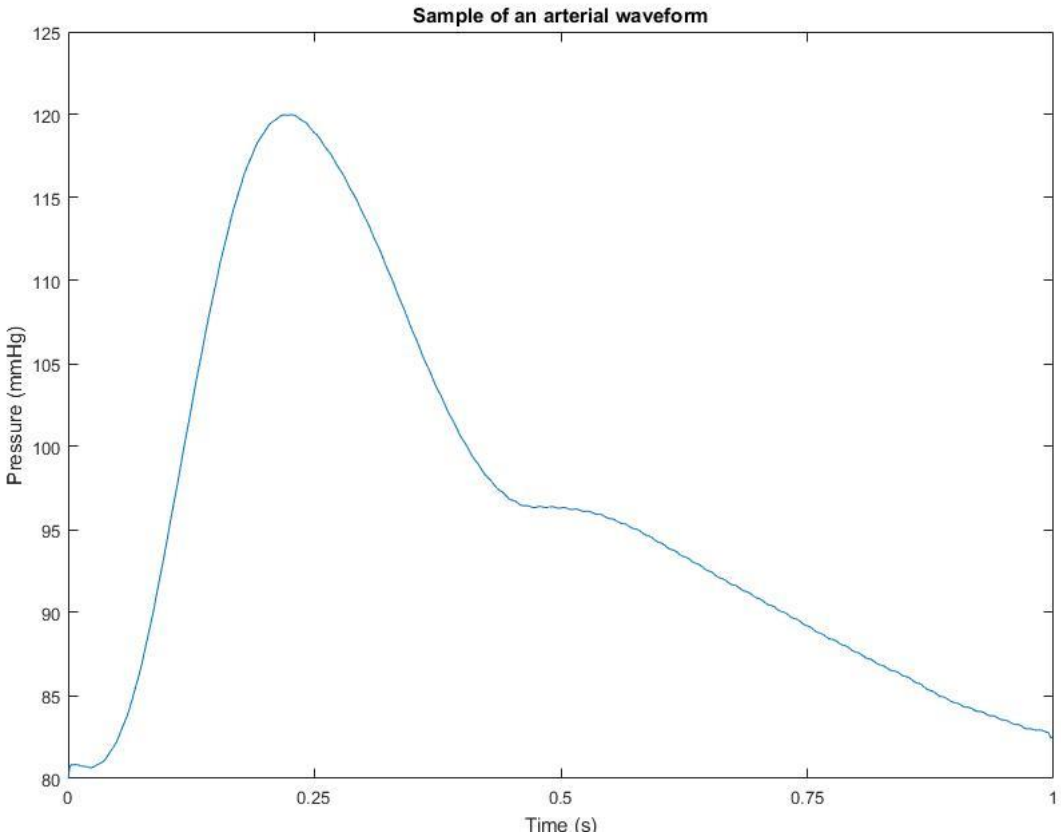


Figure 1.1 An example of an arterial pulse waveform.

The shape of the arterial waveform is different depending on which artery is measured, as expressed in figure 1.2, which shows 3 different types of arteries and how the pressure waveform is shaped when traveling through them. Blood pressure increases with age, due the stiffening of arterial walls, and loses some of its distinct wave shape. Blood pressure also changes with other factors, such as diet, weight, drug use, tobacco use and disease.

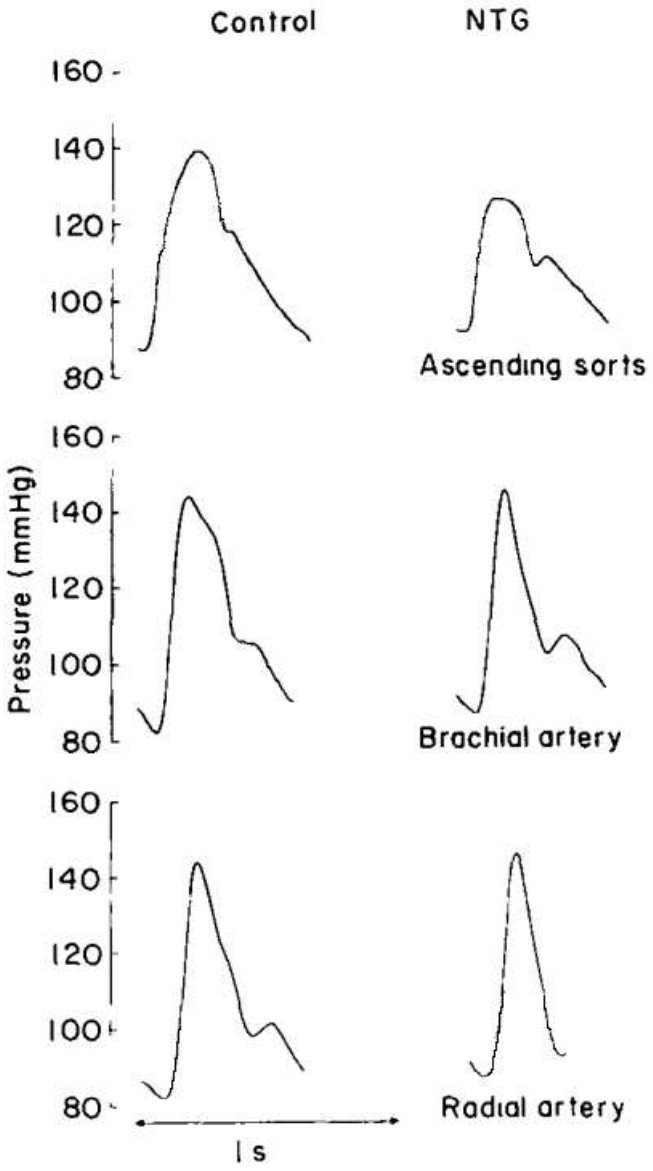


Figure 1.2 An overview of how the arterial pressure waveforms differ in 3 different arteries before and after sublingual administration of nitroglycerin which is a vasodilator. Vasodilators relaxes the blood vessels allowing more blood flow. Figure provided by [1].

Blood pressure is a good indication of a person's overall cardiovascular health, with hypertension (high blood pressure) being correlated to a higher risk of stroke, heart attack and other cardiovascular diseases [2]-[5]. As blood pressure increases, the risk of coronary heart disease directly increases as well [3], [4], [6], [7]. Hypertension is one of the leading causes of

death, with estimates of 7.1 million deaths worldwide [6]. In people between 40 to 70 years, an increase of 20 mmHg in systolic blood pressure and 10 mmHg diastolic doubles the risk of cardiovascular disease (CVD) [4]. Furthermore, in 2007/2008 around 23% of Canadian adults had diagnosed hypertension [3]. In America, 30% of individuals between ages 18-74 with hypertension were unaware they had hypertension [8]. Of individuals below the age of 65, 37.3% with a high normal blood pressure of 130-139 over 85-89 mmHg progressed to hypertension over 4 years [9]. A 5% weight gain was associated with approximately 20-30% increased odds of hypertension. The American Heart Association (AHA) has defined different ranges to fit within certain categories of blood pressure [10] which are listed in Table 1.1.

Table 1.1 The different categories of blood pressure conditions and the blood pressure range of each category. Created with data from [10].

Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Possible Condition
90	60	Hypotension
<120	<80	Normal blood pressure
120-139	80-89	Prehypertension
140-159	90-99	Hypertension stage 1
>160	>100	Hypertension stage 2
>180	>110	Hypertensive crisis

In America, the cost of treatment in 2010 for hypertension totalled $42.9 billion, with about $20.4 billion being prescription medication [11], and the annual expenditure for treatment averaged around $733 per adult. In a study [8], 22% of 292 patients with borderline hypertension

were found to have normal blood pressures during the day in what is called white coat hypertension. From 2005 to 2008, the number of cases of hypertension in Canada increased from 5.5 million to 6 million and is estimated to increase further [3].

Hypotension (low blood pressure) can be an indication of serious heart, endocrine or neurological disorders and can be life threatening [12]. Hypotension can cause dizziness, light-headedness, blurred vision, nausea and fainting. To recover from these episodes, one should sit or lie down to rest for a few minutes. If the episodes continue frequently a doctor should be consulted.

1.1.2 Ways to measure blood pressure

The most accurate way to measure blood pressure is to use an inline catheter in an artery. A catheter is often used when a patient's blood pressure needs to be monitored in greater detail, as it allows for continuous monitoring of the BP throughout each heartbeat over an extended period of time. The ability to monitor both systolic and diastolic pressure over each cardiac cycle is henceforth referred to as beat-to-beat BP. The inline catheter is also used when a subject needs to be monitored for a longer period of time, such as over a period of several days. These types of systems need to be zeroed before use on each patient and needs to be regularly calibrated by a mercury manometer [13]. Zeroing is performed by placing the transducer attached to the catheter heart level when the patient is supine, and then the system is opened to air and closed to the patient to adjust the 0 mmHg baseline [13]. An inline catheter is also an invasive technique, since it requires the sensor to be placed inline with an artery to measure pressure [13]. Furthermore, the invasive catheter not only displays both the systolic and diastolic values of BP, it also tracks the blood pressure waveform and can be used to detect other conditions through the trends and

shape of the blood pressure waveform. Some of these catheter systems also need accurate arterial waveforms to produce precise readings, due to the use of techniques such as pulse contour analysis [14]. Pulse contour analysis uses the shape of the arterial waveform to determine additional information relating to the cardiovascular system. The major weaknesses of these systems are that they need a clinical setting to operate, as well as specially trained technicians to place the catheter. They also need calibration and zeroing to be accurate. Complications and side effects can occur if something were to go wrong. It has been shown that catheter-based blood pressure measurement can result in 19% chance of temporal occlusion when probing the radial artery and 14% chance of haematoma [15]. There are also small chances of permanent ischaemic damage (0.09%), sepsis (0.13%), local infection (0.72%), and bleeding (0.53%) [15]. Due to the risks of infection and need for constant monitoring, this technique is usually only used in hospitals when either long-term monitoring is required or detailed BP information is needed.

Due to the invasive, and somewhat risky nature, of the catheter, there have been a few non-invasive methods to measure BP, such as the palpation method. This method uses an inflatable cuff that is placed on the arm and is pressurized until the arterial pulse is no longer felt further down the arm. The pressure is then slowly released out of the cuff, until the pulse can be felt again, and this is taken to be systolic pressure. The drawback of this system is that it cannot estimate diastolic pressure and mean arterial pressure. Furthermore, the system is dependent on the sensitivity of a user to feel the pulse, and thus can be inaccurate. Also, the systolic pressure is underestimated due to the transition time from the cuff to the point of arterial pulse investigation [13].

A way to improve the previous method is to use a Doppler probe to detect the systolic pressure. The Doppler effect is a shift in frequency of a wave reflected from a moving object. A

sound wave at a fixed frequency is generated over the artery and the reflections are monitored. When an arterial pulse is present, the frequency of the waves reflected from the artery will be altered. This removes the need for an operator to physically feel when an arterial pulse transpires. The disadvantages of this system are that diastolic pressure can not be detected, it needs an acoustic medium between the probe and skin to conduct the sound waves, and sensitivity to the placement of the probe, with signal clarity being lost if the probe is not directly placed over an artery [13].

Another method is the Auscultation method which also uses a pressure cuff placed on the arm to depress the brachial artery to the point where no blood can flow through. A trained technician then slowly releases the pressure of the cuff whilst listening with a stethoscope for what is called Korotkoff sounds, a collection of sounds that signify different things such as when the systolic blood pressure overcomes the pressure of the cuff. When the only sound distinguished is a faint murmur, the cuff has reached diastolic pressure [16]. These sounds can be picked up by microphones and amplified, thus increasing sensitivity. However, this method relies on the interpretation of the technician preforming the test to determine the systolic and diastolic pressures, which renders it only as accurate as the skill of the technician [13]. Furthermore, some ailments render the Korotkoff sounds difficult to ascertain, leading to misdiagnosis of blood pressure, if any can be obtained at all [13]. This method is also prone to errors due to user motion.

The oscillometric method is the blood pressure monitor that most people are familiar with, as it is often used at home and in pharmacies. It consists of a pressurized cuff placed on an extremity and inflated, and every time an arterial pulse arrives, oscillations occur in the pressure of the inflated cuff. These oscillations are recorded by the cuff. Maximum oscillations occur at

the mean arterial pressure, and decrease considerably above systolic pressure and diastolic pressure. In most commercial devices, the diastolic and systolic pressures are then algorithmically estimated from the mean arterial pressure. This method is easy to use and affordable, it is sensitive to motion artefacts, and the size of the inflatable cuff is of importance. If the cuff is too small, the pressure needed to occlude the artery is higher, thus skewing the pressure data to the higher end [13]. If the cuff is too large, the pressure measured will register too low. To accurately use these types of devices, the patient needs to be sitting at rest with their arm resting on a table and slightly bent, with the cuff being at the same height of the heart (since the pressure is going to be different along the arterial tree).

There are a few beat-to-beat blood pressure monitor systems as well, such as the plethysmographic method. The plethysmographic method uses a light emitting diode (LED) paired with a photodiode (PD) placed on opposite sides of a patient's finger, and an inflatable cuff around the same finger. The photodiode detects the amount of blood volume that passes between it and the LED, and inflates or deflates the pressure cuff around the finger in order to try to get the volume passing by to remain constant. The pressure in the cuff can then be measured as this process is ongoing, and that pressure reading will describe the arterial pulse waveform [13]. These types of machines can be uncomfortable for the user, due to the continuous inflating and deflating of the cuff. Also, the plethysmographic method can be erroneous if the patient has low blood flow to the peripheral arteries, such as in the case of hypothermia, or if the hand is elevated too high.

Another beat to beat monitoring system is arterial tonometry. This method requires a tonometer to be placed immediately over an artery that is adjacent to a bone. The tonometer is then pressed into the skin, as to deform the artery slightly. If this position is maintained, the

stress between the skin and tonometer surface is a good approximation of the intraluminal pressure [17]. There are several disadvantages with these types of systems, including the need for a specific measuring location, due to the need of a bone adjacent to the artery, as well as sensitivity to movement when measuring. Furthermore, it needs to be calibrated to track the actual values of blood pressure and not just the relative change from top to bottom.

1.2 Hemodynamics

This section covers some background information concerning the blood pressure system, including the vessel dynamics and the equations relating pulse wave velocity and blood vessel elasticity to blood pressure. Since there are many different types of vascular systems in the body that have widely different characteristics, this section will focus on the arterial tree as it relates to the goal of this thesis.

1.2.1 Arterial vessel properties

A major contributor of the behaviour to arterial blood flow is the structure and composition of the arterial walls. To begin, we disregard the complexities of the geometry and applied loads of the arterial system and focus on the basic principles. We can consider the artery to be a straight cylindrical segment [18]. The arterial system acts as the conduit through which blood is transported through the body, supplying oxygen to cells, picking up carbon dioxide, and distributing hormones [19]. The arterial system characteristics vary remarkably depending on where one focuses, with larger diameter vessels transporting oxygen rich blood around the body and smaller, low pressure vessels transporting blood from the heart to the lung [19].

All arteries consist of three major layers identified as the inner most layer, tunica intima, the middle layer, tunica media, and the outer layer, tunica adventitia. An illustration of these layers is depicted in figure 1.3. The intima layer mostly consists of a monolayer of endothelial cells on basal lamina. The endothelial cells are a lining on blood vessel walls, and form an interface between the circulating blood and the rest of the vessel components. The basal lamina

consists mostly of collagen and provides structural support for the arterial wall and acts as a surface for which endothelium to grow. Under these layers is the subendothelial layer. While the endothelial layer does not give a lot of strength to the artery, the subendothelial layer may do so [20].

The second arterial wall section is the tunica media. The tunica media consists of complex networks of smooth muscle cells, elastin and collagen fibres. Towards the outside of the layer, the elastin loses its organization. The media layer is separated from the other layers by the internal and external lamina. This combination of collagen and elastin gives the media layer the ability to resist high loads of stress [20].

The final layer in the arterial wall is the tunica adventitia. This layer consists of mostly collagen fibres in thick bundles, and is surrounded by connective tissue. The adventitia layer contributes the most to the strength and stability of the artery [20]. The structure of an arterial wall is depicted in figure 1.3, which show the individual layers and describes the composition of the layers.

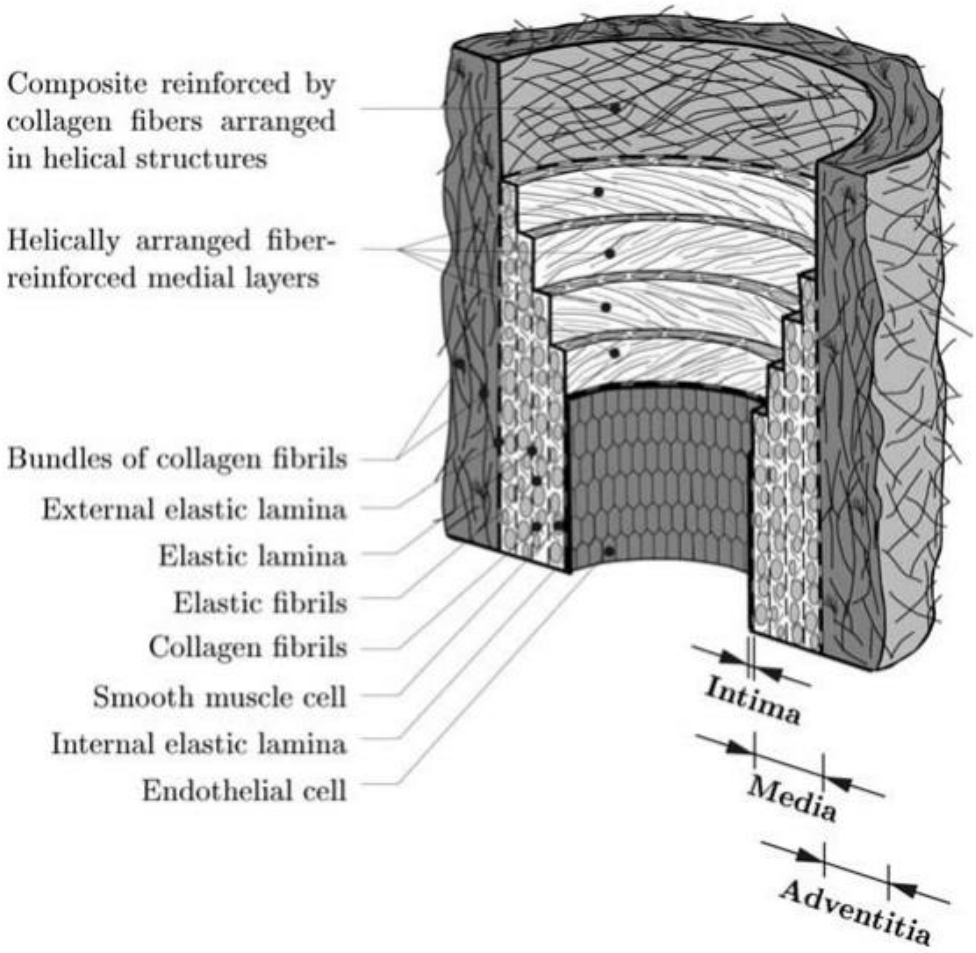


Figure 1.3 A cross section of an artery with labels for the layers and the constituents of the individual layers. Figure provided by [21].

The distribution of elastin and collagen of these layers allows the arterial wall to stretch in the intima layer at increasing pressures, and the media layer to have elasticity for the increasing pressure. The adventitia layer will stretch until the collagen fibres are straightened and the artery will then act as a stiff tube. This prevents the artery from stretching to the point of bursting, whilst still allowing the arteries to store the energy of a traveling wave from the heart. The energy stored in the arterial wall is dissipated when the pressure pulse has passed.

Due to this combination of the elastin rich media layer and the more collagen saturated adventitia layer, the arterial wall has a non-uniform expansion when the internal pressure increases. This is an example of a viscoelastic material, which means that deformation of the artery will depend not only on the magnitude of the stress applied, but also the rate of application [5]. When stress is applied quickly, the deformation is dampened, when stress is applied slowly, the deformation is elastic. During the elastic phase, the artery behaves in accordance with Hooke's law, which means that the strain on the artery is proportional to the stress. However, the theory of elasticity that originates from Hooke's law makes two extra assumptions: 1) that the deformations of the material are infinitesimal and 2) that the structure is homogenous throughout [22]. In the case of an artery, this is not true due to the mixture of collagen and elastin in the arterial wall and the fact that the wall is easily extensible [5].

To visualize the distensibility of the arterial wall, we must consider the stress-strain relationship. Strain (ε) can be expressed as

$$\varepsilon = \frac{\Delta L}{L_0} = \frac{L - L_0}{L_0} \tag{1.1}$$

where L is the observed body of length and L_0 is the original length of the body. This equation expresses the strain as the change of dimension of the artery as a fraction of the original size. Stress (σ) can be calculated by

$$\sigma = \frac{F}{A} \tag{1.2}$$

where F is the force exerted by the stretched tissue and A is the area over which the force is exerted. Using these two equations we can express the "elastic modulus" of the arterial wall. The longitudinal modulus is known as the "Young's modulus" and is expressed as

$$E = \frac{\sigma}{\varepsilon} \tag{1.3}$$

where the stress, in this case, is the pressure in the system. This relationship only holds true when the stress-strain curve is linear, as can be seen in figure 1.4 [5], [23].

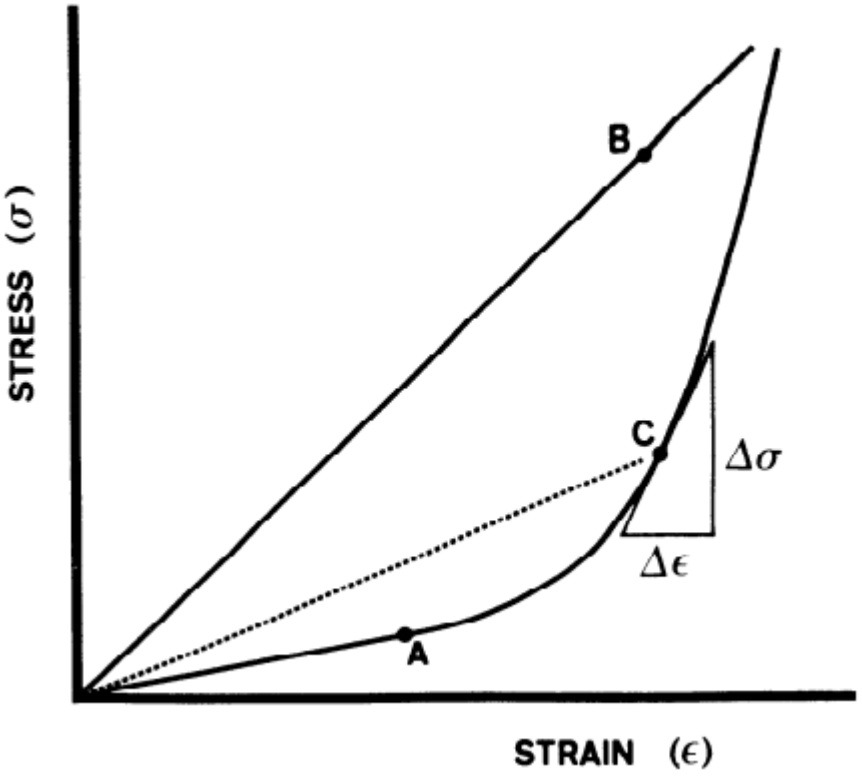


Figure 1.4 A typical stress strain curve of an artery, where A and B are the linear Young's moduli. At point C the slope of the curve is the incremental Young's modulus (Δσ/Δε) and non linear. The dotted line indicates a line with slope of σ/ε would intersect but no be on the plotted line. Figure obtained from [23].

To appropriately describe the stress strain curve of the arterial wall, we have to use the incremental Young's modulus, since the stress-strain curve of an arterial wall is not linear. The incremental Young's modulus is given by

$$E_{inc} = \frac{\Delta\sigma}{\Delta\varepsilon} \tag{1.4}$$

this relationship is best graphically described as an exponential curve, where the stress increases linearly with strain until the collagen fibres engage and the arterial wall becomes stiffer, thus resisting change in size [5], [23]. E_{inc} is also called arterial stiffness [5], since it describes the elasticity of the arterial walls. The arterial stiffness changes over time, affected by age, diet, exercise and drug use. The principal changes that happen over time occur in the intima and media layers, with the endothelial cells becoming irregular in size and shape, leading to a reduced function [24]. Furthermore, the artery stiffens, dilates, lengthens and the arterial walls thicken [25], with these effects hastened by hypertension.

The elasticity of the artery affects the propagation of the pressure wave that is ejected from the build-up of pressure in the heart. With increased stiffness of the arteries, the velocity of the pulse waves also increases [25]. This velocity can be expressed by the Moens-Korteweg equation,

$$PWV = \sqrt{\frac{E_{inc}h}{2r\rho}} \tag{1.5}$$

where h is the arterial wall thickness, r is the inner radius of the artery and ρ is the density of the arterial wall. In this expression, there are two implicit assumptions: 1) that the wall thickness (h) is small relative to the diameter of the artery and 2) that the tube is filled with an ideal, incompressible inviscid liquid [5]. We can modify equation 1.5 to take into account the viscous properties of the artery to give

$$PWV = \sqrt{\frac{E_{inc}h}{2r\rho(1-\gamma^2)}} \tag{1.6}$$

where γ is the Poisson ratio of the arterial wall, which is assumed to be 0.5 [5]. Thus, we can see that the elastic modulus of an artery has a large effect on the propagation of pulse waves in the arterial system. PWV can be used as an indication of the arterial stiffness of a person, with higher speeds suggesting a stiffer artery. The pressure inside the artery can also be linked to the elasticity of the arterial walls and the pulse wave velocity by the Bramwell-Hill equation

$$PWV = \sqrt{\frac{V\Delta P}{\rho \Delta V}} \tag{1.7}$$

where V is the volume of some arbitrary length of artery, ΔP is the change in pressure in the artery, ΔV is the volumetric change and ρ is the density of blood [5]. With the Moens-Korteweg and Bramwell-Hill equations, the change of blood pressure in an artery can be detected if the pulse wave velocity and change in blood volume is known. Since pulse wave velocity can be measured, as will be covered in a later section, and the arterial diameter can be measured with ultrasonics, the only missing link to estimating blood pressure with the Moens-Korteweg or Bramwell-Hill equations is the incremental Young's modulus. As stated above, E_{inc} varies from person to person, and also varies with age, sex and life style. So, to use the aforementioned equations to measure blood pressure continuously, either a substitution must occur to remove the need for E_{inc} or a model describing the Young's modulus must be used. Due to lack of experimentation and analysis of continuous blood pressure in a large population group, models for incremental Young's modulus is difficult to obtain, thus most methods to measure BP substitute E_{inc} with known relations.

One such substitution is using Laplace's theory for thin-walled tubes, which allows Young's modulus to be expressed as

$$E_{inc} = \frac{\Delta P\ D^2}{2\ h\ \Delta D} \tag{1.8}$$

where ΔP is the change in pressure and ΔD is the change in arterial diameter [26]. This relationship can then be inserted into the Moens-Korteweg equation to form

$$\Delta P = \frac{2\ PWV^2\ \rho\ \Delta r}{r} \tag{1.9}$$

where *r* is the radius of the artery. This equation describes the change in pressure as it relates to the change in radius of an artery and the speed of a pulse wave. If we were to integrate this over r, which is a function of time, we can form an expression for the instantaneous pressure at any given point of the cardiac cycle

$$P(t) - P_0 = 2\rho\ PWV^2\ \log\left(\frac{r(t)}{r_0}\right) \tag{1.10}$$

where *r(t)* is the instantaneous radius of the artery. P_0 and r_0 are the pressure and radius at diastolic pressure, respectively. With this relationship, the pressure change in the system can be traced if pulse wave velocity and the radius of the artery can be tracked. However, the major flaw of this tracking method is the need to take a calibration reading to determine artery radius and pressure at diastole, otherwise it cannot track blood pressure in real time [27]. Equation 1.10 also assumes a linear relationship between pressure and diameter of an artery to simplify the expression. This assumption will result in an underestimation of the pressure averaging of about 1.6 mmHg [28], which falls within the American Association of Advancement of Medical Instrumentations protocol for accuracy of test devices. In equation 1.10, the most sensitive term in respect to errors is the radius measurement, where a 10% error results in a tenth of the pressure calculated. The pulse wave velocity had a change of 9 mmHg with a 10% error.

As one can imagine, the need for a calibrated base line when using a system based on equation 1.10 would hinder the user friendliness of a wearable device. To be able to measure continuously and non-invasively, some insight into the elastic modulus would be required beforehand. To achieve this, a model of the incremental Young's modulus needs to be developed for different population groups, such as age, ethnicity, sex, height, lifestyle etc. E_{inc} can be expressed as

$$E_{inc} = E_0 e^{A*P} \tag{1.11}$$

with E_0 and A being constants describing the curve of the non-linear relationship of the stress-strain curve of the human artery [29]. Thus, if the constants for different population groups can be established, the incremental Young's modulus can be substituted in equation 1.11 to form

$$P = \frac{1}{A} \ln\left(\frac{PWV^2\, r\, \rho}{E_0\, h}\right) \tag{1.12}$$

This type of model depends greatly on the matching of the Young's modulus constants to maintain accuracy. With enough information, such a model could be established and allow any person to use a BP estimation system based on equation 1.12. For example, by entering their identifying information into a smart phone or similar device, the best match of elasticity can be selected. In equation 1.12, the pulse wave velocity is the more influential parameter, since the error would be squared.

To gain a database of these characteristics, data collection needs to be performed on many groups of people with the same type of incremental Young's modulus. With this database, models can be developed to assign the correct constants to encompass factors such as age, sex, ethnicity, height and weight. In principle, when the characteristic constants have been

determined, continuous and instantaneous blood pressure can be tracked non-intrusively, as long as pulse wave velocity can be determined and the arterial diameter measured non-invasively.

1.3 Pulse wave velocity

As demonstrated in the previous section, pulse wave velocity is of vital importance to the estimation of both arterial stiffness and conversely, the estimation of blood pressure through equation 1.10. In this section, different methods of obtaining pulse wave velocity will be discussed, as well as the analysis of the waveform obtained. Furthermore, in this section the changes that can be seen in the pulse wave velocity due to aging or ailments will be discussed. An overview of the diagnostic importance of pulse wave velocity will also be covered.

1.3.1 Measurement types of pulse wave velocity

There are several ways to measure, or estimate, pulse wave velocity, which all have different advantages and disadvantages. PWV measurement is either invasive or non-invasive. Non-invasive pulse wave velocity can be measured either locally or regionally. As the blood pulse generated from the contraction of the heart travels down the arterial tree, the changing structure of the vessels affects the velocity across the arterial tree. This will cause the PWV to change at different parts of the body, and depending on what vessel is measured. To obtain regional pulse wave velocity, two different arteries in different locations of the body are measured, which are usually carotid and femoral. These arteries are usually chosen for their ease of access to palpation on the surface. Since these types of measurements are taken with the measuring sites so far from each other, the pulse wave velocity obtained is going to be an average of the two local measurements [30]. Since these measurements are averages, some

characteristic information of the measurement sites will be lost, and thus the mechanical properties of an artery cannot be easily determined. Furthermore, when measuring the regional pulse wave velocity, the distance between the points of interest have to be measured externally to assess the distance between them, and this will introduce errors for arteries that have bends or curves [30]. When determining the distance between arterial measurement sites, the distance is approximated from the outside of the skin, which can introduce significant errors, depending on the technique used to obtain the distance. There is also a significant source of error if the patient has abdominal obesity, especially in men, and large bust size in women [31].

On the other hand, local pulse wave velocity measurements are taken over a small segment of the same artery, and can therefore be used to estimate the mechanical characteristics of the artery. However, the PWV in large elastic arteries sees a more pronounced effect due to aging compared to other arteries, such as the brachial and femoral [32]. Despite this limitation, local PWV is preferable since it describes the biomechanical features of a given artery.

One common way to measure regional pulse wave velocity is using a “PulsePen”, which consists of a tonometer and electrocardiogram (ECG), where the tonometer takes sequential readings above the femoral and carotid arteries, whilst the ECG is worn on the chest to detect any heartbeat. Every time the heart contracts, a pressure pulse is generated, which travels through the arterial tree. This pulse is detected with the tonometer situated over either the carotid or femoral artery. The time lapse between when the ECG detects a heartbeat to when the resulting pulse wave is detected by the tonometer is then recorded. The distance from the tonometer site to the sternal notch is then measured with a measuring tape [33], [34]. The pulse wave velocity is then calculated with the accompanying software. As discussed in the previous section, this method is a regional pulse wave velocity and will be dependent on the accuracy of

the external distance estimated. Furthermore, the operator needs special training to ensure that the tonometer reading is not affected by the pressure of the application, and to make sure the operator can accurately apply the tonometer over the arteries. Also, worth noting is the relatively hands on procedure, since two sites need to be monitored with the tonometer and in quick succession.

Another regional measurement system is the “Complior”, which uses two pressure transducers placed over two different arteries, such as the femoral-carotid, brachial-carotid etc. When the transducers have been placed on the arteries, the distance between them is measured on the surface of the body with a tape measure. Then the arteries are monitored for pressure waves, and the time difference between the activation of the first transducer to the second is measured. Once the time difference has been observed, the distance between the sensors is divided by the time between the detection of the pulses to obtain pulse wave velocity. Since this is also a regional measurement system, details relating to the specific arteries are lost, and the distance measurement can be wrong, due to the estimation of distance between arteries from the surface measurement [35].

The “SphygmoCor” also uses pressure sensors to determine pulse wave velocity and works much in the same way as the “PulsePen”, with an ECG being combined with a tonometer. Two arterial sites are selected, usually carotid-femoral, brachial-carotid etc. and the tonometer is moved between them and pulse wave velocity is calculated in a similar way to the “PulsePen”. As with the “PulsePen”, the accuracy is dependent on the distance measurement between the arterial sites, as well as the skill of the technician operating the device [30], [36].

These three systems are all examples of tonometer based devices operating on the Pulse Transit Time (PTT) principle, which is the time it takes for an arterial pulse to travel from one measurement site to another, or the time from the detection of a heart contraction from an ECG to the pulse detection from a pressure sensor.

Pulse wave velocity can also be measured using an "Arteriograph", which does not use tonometers, as opposed to the previously covered methods. This method uses an oscillometric cuff around the upper arm to measure the oscillations of the artery when inflated. The Arteriograph inflates to about 35 mmHg above systolic pressure, which is measured in conjunction to obtaining the PWV, and then pressure changes in the brachial artery are measured from the beginning of the first wave and beginning of the second reflected wave. Through this, the Arteriograph can detect the local pulse wave velocity [37]. This method does not require specialist training to operate with accuracy. However, the high pressure exerted by the cuff (35 mmHg over systolic pressure) can be uncomfortable, and PWV cannot be measured continuously.

One can also obtain PWV from imaging techniques, such as ultrasound. Using a high frame rate of data gathering from an ultrasound, the pulse wave velocity of an artery can be obtained visually. With a sufficient sized array on the ultrasound probe, the pulse wave going through a segment of artery can be observed. Since ultrasound devices are calibrated to read distance, the arterial wall distension can be observed as a pulse propagates. Through this information, a trained technician can see the distance an arterial pulse travels and how long it takes to travel said distance, and from that the pulse wave velocity can be determined [27]. The major drawbacks of this type of system are the high initial cost of ultrasound imaging systems,

and the lack of portability. Furthermore, an operator needs to be trained in its use to effectively obtain the required information.

Another imaging system that can be used to directly obtain pulse wave velocity is Magnetic Resonance Imaging (MRI). Using a technique similar to that of ultrasound, the MRI can image a segment of artery and observe as a pulse is transmitted through it, and see the distance a pulse has traveled and in what time frame, to gain the pulse wave velocity [38]. This system is very helpful when imaging patients of larger body habitus, since the resolution through depth is better than an ultrasound. However, MRI systems are expensive, and require special circumstances of operation, making them suitable almost exclusively in hospitals and medical clinics. Specialist training must also be undertaken to adequately operate an MRI.

The last non-invasive pulse wave velocity measuring system is photoplethysmography (PPG), which uses changes in observed light through the surface of the skin to detect when a pulse travels underneath. Using a photodiode with an LED positioned, usually next to the PD, light is emitted into the skin and the reflection is detected by the PD. As increasing blood volume goes by the measurement site, the light reflected decreases. By varying the angle and distance between the PD and LED, as well as the light wavelength emitted, different depth of penetration of measurement can be obtained [39]. This measurement system is comparatively inexpensive and easy to use. However, only peripherals can be measured with PPG, since it has only a limited depth of penetration.

Pulse wave velocity can be invasively measured using an arterial catheter. However, as stated in previous sections, this is a highly invasive procedure, that can have many negative side effects, and should be mostly only considered in medical procedures.

In all the methods covered, except the imaging techniques and the invasive technique, the data obtained from the tonometers and the photoplethysmography is a representation of the volumetric blood flow through the artery at any given time. These waveforms have distinct and characterized parts, and to obtain the pulse wave velocity from one waveform to another requires special techniques. Furthermore, these waveforms differ depending on the measurement site along the arterial tree. As can be seen in figure 1.5, there is a distinct swell when blood travels by the sensor, with a small bump half way through. This bump is called the dicrotic notch, which symbolizes the closure of the aortic valve.

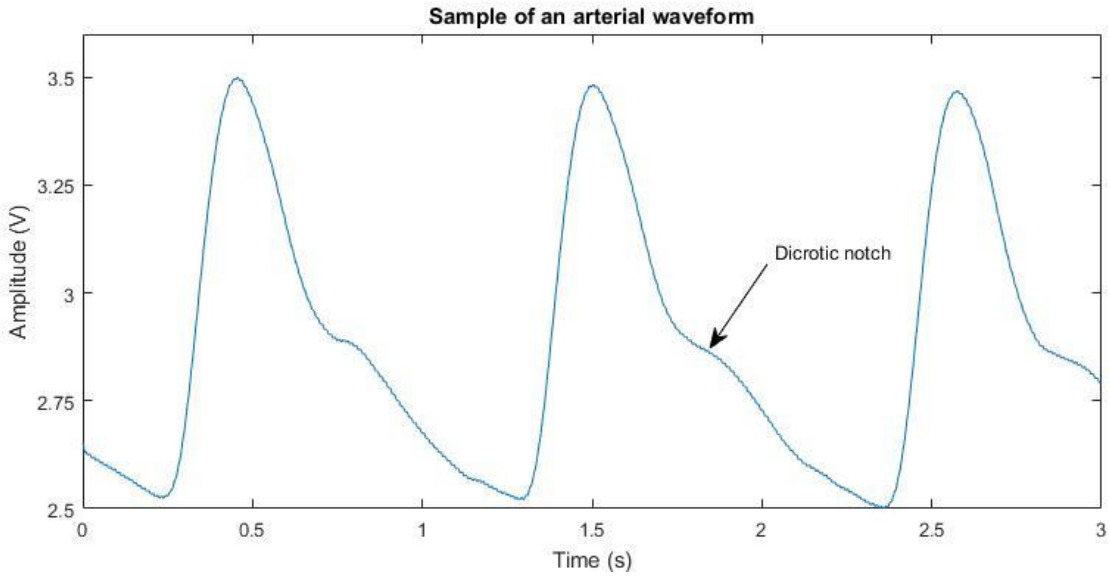


Figure 1.5 Arterial pulses formed from blood traveling by an optical sensor with an arrow indicating the dicrotic notch.

In older populations, this notch becomes less and less defined due to stiffening of arterial walls [40]. As the measuring site moves from the aorta, the wave changes shape as well, with the systole amplitude increasing and the diastole amplitude decreasing slightly, as the site moves towards the peripheries. However, the waveform is composed of both a forward traveling wave generated from the heart contraction as well as a reflected wave from the changing oncoming

arterial structure. This means that for systems where one wants to measure the pulse wave velocity from two different sites, the resulting tonometer information from each respective site is going to be different in both shape and amplitude to each other. This makes selecting a distinguishable point for comparison between the two signals difficult. In systems that combine a volumetric flow sensor (such as tonometer or PPG) with ECG, this problem is alleviated by the ability to use the ECG waveform to detect the contraction of the heart and then see the onset of the pulsatile flow under the flow sensor. In systems with only two flow sensors, the reflected wave and changing characteristics mean that if the sensors are on two different arteries the obtained waveform is going to be different in both amplitude and shape. The two features that remain comparable between the different measurement sites are the onset of the systole and the dicrotic notch. Therefore, most common pulse wave velocity estimations from pulsatile flow measurement use the time difference between either the onsets of the systole or dicrotic notch. However, the dicrotic notch is less distinct in older and stiffer arteries, thus it is more reliable to use the onset time difference [41].

As briefly mentioned above, with the increase of age, the arterial waveform alters due to the stiffening of arterial walls, as is shown in figure 1.6. With advancing age, the systolic rise is increased and the diastolic low is decreased, and the dicrotic notch starts to blend into the general shape of the rise and fall of the forward traveling wave and the reflected wave. This is due to the increased stiffness of the artery, and as stated before, this trend is not as drastic in the peripheral arteries as it is in the central ones. This further cements the notion to use the onset of the rise of the pulsatile motion as the measurement point for pulse wave velocity [41]. Due to increased arterial stiffness as an individual ages, the pulse wave velocity and the reflected wave component both increase [42]. The increase of pulse wave velocity is a good indicator of future cardio

vascular disease. A significant portion of individuals with higher PWV will, over time, develop CVD [43]-[45]. It has been shown [44] that individuals with higher PWV also developed more coronary heart disease than those with lower velocities.

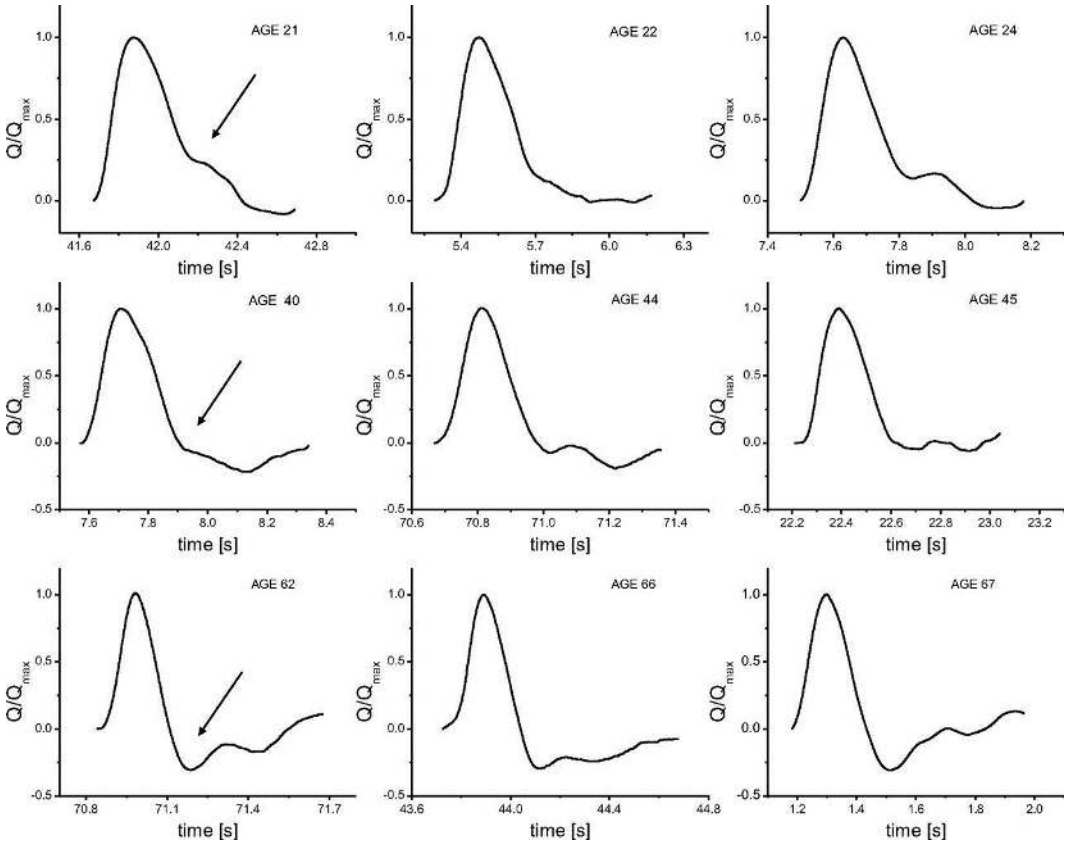


Figure 1.6 An overview of how the arterial waveform changes with age. Figure obtained from [41].

1.3.2 Photoplethysmography

As discussed in the previous section, there are multiple ways of measuring the pulse wave velocity, which each having different advantages and shortcomings. However, due to the end purpose of the project, being able to measure PWV in motion and with ease of use, the method that was decided best suited to meet these requirements was PPG. The PPG method will be discussed more in depth in this section.

The main principle of operation of photoplethysmography is the use of light to illuminate the biological tissues, including bone, skin, and blood. Since blood absorbs light as it travels by, a pulse wave passing under the sensor leads to greater light absorption detectable by the photodiode. Thus, PPG is an indirect measure of volumetric changes in the arteries. There are two constituents to the PPG waveform, the DC (direct current) offset and the AC (alternating current) component. The DC is formed from reflections off the tissues around the arterial measurement site, including the skin, bone, muscles and fatty tissues, and as the name suggests, this does not change with the pulsatile motion of the blood. This sets the base line of the PPG signal, which is dependent on the structure that is being measured and the average blood flow through the system. The DC component does slowly vary with time due to the respiration of the subject. The AC portion of the wave is the absorbed light due to the volumetric change in blood flow under the light and sensor. This change is the result of pressure wave that is generated during systole and then the diastole when it has passed. The frequency of occurrence of this AC component depends on the heart rate of the person measured, and the waveform depends on the subject's vascular health and age. This AC component is superimposed on the DC component that is set by the system, which, as discussed, can drift due to respiration [46].

PPG monitoring can be done by transmissive or reflective measurements, which depend on where the photodiode is placed. In transmissive mode, the LED and photodiode sit opposite each other, on either side of the measurement site. This system is best suited for placement where light can easily and readily transmit, such as a finger, nose, earlobe etc., since the light penetration depth is a substantial limiting factor. Furthermore, depending on the placement chosen, bones can be a major problem, since they do not transmit light. The placement restrictions of the transmissive systems render it more suitable for clinical use, since placement

on an ear or nose is greatly affected by ambient temperature, and the finger placement infers an obstacle for normal tasks that would involve the hands. For reflective mode, the PD sits next to the LED and detects changes in light from the reflected light that is scattered from the deep tissues of the measurement site, especially bones. Reflective sensing alleviates the sensor placement restriction of transmissive sensing. This measurement type is more sensitive to motion, but the inclusion of an accelerometer can negate this shortcoming [47]. With varying wavelengths of light, as well as the angle between the photodiode and the LED source, different depths can be monitored.

PPG monitoring is also sensitive to the pressure of which the sensor is applied to the skin. When the sensor pressure increases, the AC waveform amplitude decreases and deforms. When the sensor pressure is insufficient, the AC amplitude is low, the signal to noise ratio goes down, and loose sensor placement can cause the sensor to move on the skin during activity. Thus, it is important to ensure that the PPG is adhered well enough as to not lose contact with the skin, but not so tight as to obscure the waveforms obtained or apply pressure to the measured artery.

Furthermore, the choice in wavelength of light plays an important role in PPGs, with different wavelength being absorbed at different rates from different tissues. The depth that can be measured depends heavily on the colour of the LED. From 400 nm to 1000 nm wavelength, the depth of penetration increases steadily from around 0.5 mm to around 2.5 mm [48]. This means that as wavelength increases, the signal is going to be increasingly affected by deeper tissues. The two most common PPG light sources are infrared (higher wavelength, with deeper penetration) and green (lower wavelength, with shallow penetration). Furthermore, the wavelength of the light not only affects the penetration of the signal, but also specific wavelengths have other interactions with tissues as well. The green wavelengths on the spectrum

have a higher absorption in oxyhaemoglobin and deoxyhaemoglobin, resulting in a larger signal swing when a blood pulse travels by, giving a better SNR. Studies have shown that green light is less prone to signal errors from motion induced artefacts, and shows better volumetric blood tracking over a larger temperature range than that of red light [48]-[51].

Since photoplethysmography uses only LEDs with accompanying PDs to measure PWV, the sensors can be designed to fit into a small package. Furthermore, the relatively low power draw of LEDs renders this detection scheme the most suitable for wearables.

1.3.3 Measurement locations

With both reflective and transmissive PPG sensors, there are several locations on the body where good signals can be obtained. As mentioned previously, a common application is on the finger for devices such as the photoplethysmographic blood pressure monitor. Other positioning includes the forehead, wrist, earlobe, brachia, and ear cartilage. The main problem with a finger probe as part of an everyday monitor is the hindrance to daily activity that would require finger dexterity, as discussed previously. Another area explored for PPG monitoring is the ear and earlobe. For an earlobe sensor, a clip with the sensor is attached, and PPG is obtained through transmissive operation. This clip can, when worn for a long time, be painful. The other ear monitoring system is using reflective PPG in the ear canal. This system obtained PPG signals fairly well compared to those of finger monitoring [52]. However, the waveform was not as clearly defined in shape as that of the fingers, and ear buds would have to be worn continuously for PPG detection, which could limit hearing. Both of these systems have integrated accelerometers to detect motion induced artefacts in the signal to adaptively cancel out the noise. The earlobe sensor would require, due to the thin media measured, to have ambient noise

cancelation to not be affected by changing outside light sources. Other methods include monitoring of the wrist-located radial and ulnar arteries using an array of LEDs and PD located in a wristband, akin to that of a watch [53]. Around the sensors, conductive rubber can be placed to reduce outside noise. Brachial PPG monitors have also been discussed in literature [54], which use ECG combined with a reflective PPG on the brachial artery to detect pulse wave velocity in the human arm.

The system discussed in this thesis uses the radial artery as a measurement site, since it sits close to the surface of the skin, around 2 mm deep [55]. Furthermore, a wrist mounted device should offer little discomfort to wearers. With a measurement of the radial artery, there are transfer functions to relate the BP to aortic or brachial pressure [56] which are more common for diagnostic and informative purposes.

Chapter 2

Method

In this chapter we will discuss the methods that we have undergone to obtain pulse wave velocity locally over an arterial segment. The following sections will also discuss the hardware that we used, the raw signals obtained, where we chose to measure the PWV, measurement procedure as well as the analysis we performed on the data and finally the results of our test runs.

2.1 Hardware

As stated in the previous chapter, the method to obtain pulse wave velocity in this manner uses a LED with a wavelength that is absorbed in blood, paired with a photodiode to detect oncoming pulsatile motion. In our case, we chose to use a reflective mode PPG to increase freedom in measurement site placement, since the transmissive mode is limited to a narrow set of measurement sites as previously discussed. For the LED, a green wavelength was chosen since we are measuring arteries that are close to the surface of the skin. A longer wavelength would cause a lot of deep tissue interference, especially when in motion. Furthermore, green light PPG is more resistant than red and infrared to motion artefacts, which benefits us, since we aim to be able to use it as part of an activity tracker. To be able to increase measurement precision, we chose to procure a commercially available bio monitor [57], which uses surface mount LEDs and a photodiode, with a controlled distance between them to optimize signal quality. The sensor chosen is the OSRAM SFH 7050, which is a sensor package containing three emitters of different wavelengths (Green-530 nm, Red-660 nm and Infrared-940 nm), to add the possibility

of measuring blood oxygenation in the future. This sensor has a very small form factor of 4.7 x 2.5 x 0.9 mm^3, which will allow it to be versatile when integrated into wearable technology.

We used a breakout board from an evaluation kit for the AFE4404 from Texas Instruments (TI), which had the SFH 7050 connected to a series of pins [58] that we could interface the LEDs and PD to our own driving circuit. With this breakout board, we soldered on resistors of appropriate values for a 5 V input signal, since the evaluation board was controlling the LEDs with programmable current output. We chose the 5 V operating voltage so we could power the device from a USB port. The PD output was then connected to a transimpedance amplifier to transform the current driven signal to a voltage signal, which in turn was put through a bandpass filter with gain stages. The filters were used to remove the 60 Hz noise and the harmonics that are caused by it, and also remove any DC component of the signal. The circuit design is illustrated in figure 2.1.

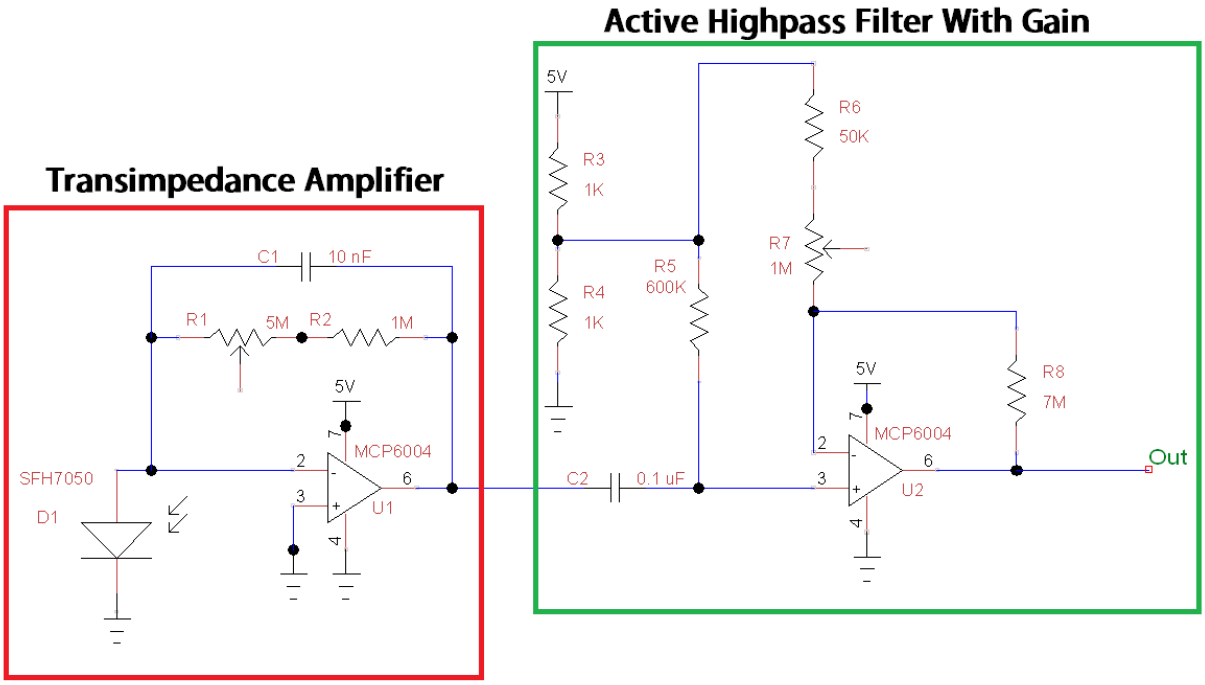


Figure 2.1 The circuit diagram of the detector which includes the transimpedance amplifier in the red box and the active high pass filter with accompanying gain

Even with these filtering components, a slight shift can be seen in the signal from the drifting DC offset as caused by the respiratory action of the lungs. These signals are then amplified to get a good signal swing on the output. When we designed the system, we included individual gain controls on the output and transimpedance amplifiers to ensure that we did not rail our operational amplifiers. Furthermore, a potentiometer was put on the LED driving circuit to control the intensity of light as to ensure that the PD will not saturate if too much light is reflected from the sampled tissue. Since the filtering and powering circuit is controlled from a box that is placed away from the subject, there is a lengthy cable that has the power supply to the LED and the signal cable from the PD. Since these cables can pick up noise from the environment, they were covered in a metal shielding connected to ground to ensure the signal remains true to the source, as is shown in figure 2.2. To facilitate easier use, a USB cord was

interfaced to the control box to power the system. We put each sensor circuit on separate boards, powered by individual power banks. This was done because powering the USB from a computer port added interference. Similarly, when the two sensor processing circuits were on a single chip amplifier, a timing drift error was introduced.

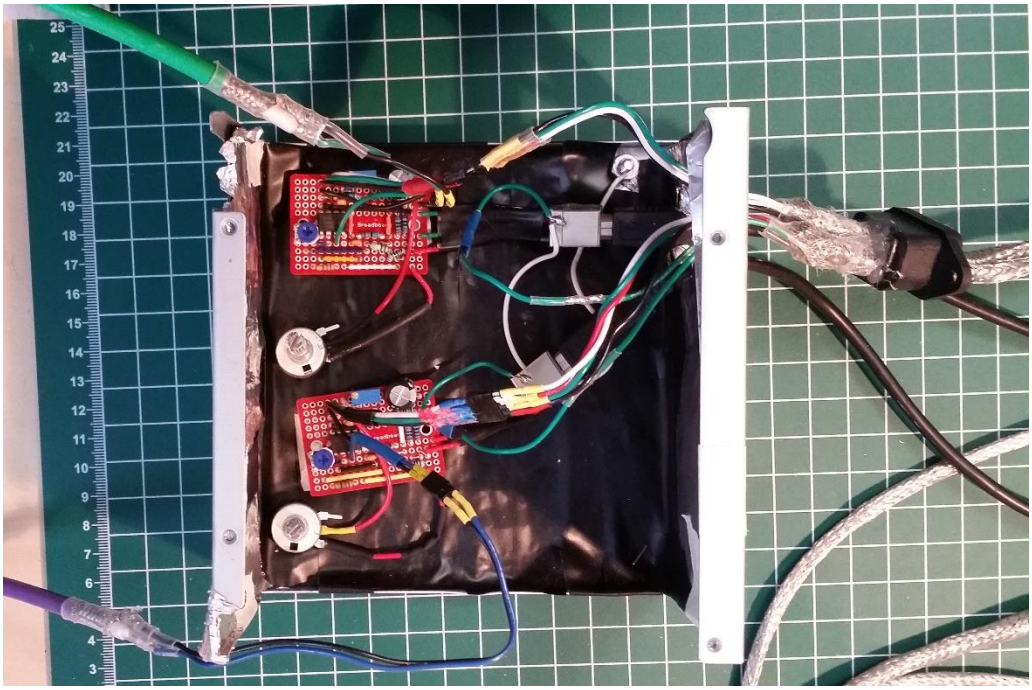


Figure 2.2 The PPG detector circuitry, where on the right is the shielded cables leading to the PPG sensors and on the left, the output cables to connect to a ADC.

The sensor boards were covered with vinyl tape for two reasons: 1) to ensure that there is no difference in height between the breakout board and the sensor head, and 2) to ensure that there are less reflective surfaces on the board, limiting extra reflections from light to skin to board back to skin. The height difference between board and sensor would make placement more difficult, since there would have to be enough force on the sensor to ensure there is no gap between the skin and the sensor head, which would lead to loss of signal power, but not so much pressure as to obscure the arterial waveform as described previously. These boards were then

fitted into a custom designed holder with straps so they could be placed around the forearm and wrist, which is shown in figure 2.3.

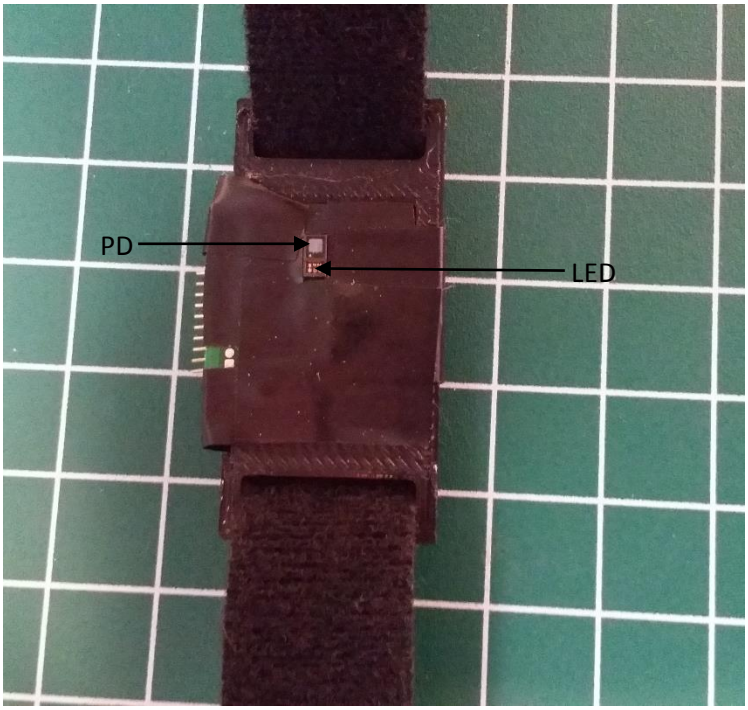


Figure 2.3 The PPG sensor armband with the vinyl cover. The arrows indicate the PD and LED.

To access the data, we attached two output cables that terminate in BNC connectors. Furthermore, there are headers in the main box assembly which provide access to the signal output. The BNC connectors were added for a quicker interface with both oscilloscopes and certain data acquisition modules.

To record the data, we use two analog-to-digital channels on a National Instruments USB-6210 [59] (henceforth referred to as NiDaq), which reads the voltage output from our device, at a sample rate of 10 KHz to ensure data quality for post processing and development of analysis techniques. The NiDaq is then interfaced into Matlab, where we store the data and perform our signal processing on it to determine the pulse wave velocity from the two channels.

The algorithms used for the signal processing are of our own design and will be covered in a later section.

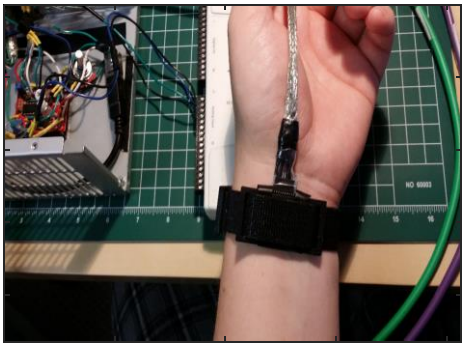
In summary, the hardware set up that we used to determine pulse wave velocity consists of two 530 nm green LEDs with accompanying PDs on separate breakout boards. With these, we can determine pulse transit time between them. The only filtering needed is a band pass, to discard anything higher than 5 Hz, since it's outside the realm of heart rate for humans, and no signal components are present in frequencies higher than that. The lower cut-off of the band pass is at DC to prevent an offset and to equalize signal swing, preventing saturation in the op amp.

2.2 Measurement location

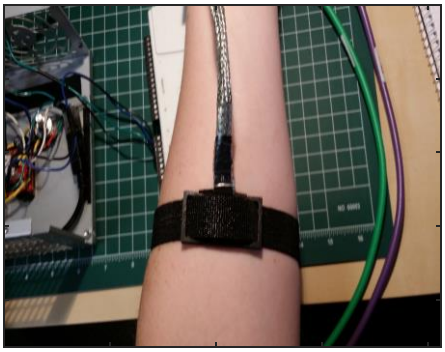
As discussed in the previous chapter, pulse wave velocity, and consequently blood pressure, taken from the radial artery can be related back to brachial or aortic blood pressure through the use of known transfer functions. Monitors can be worn near the radial artery with little discomfort or obstruction of movement to the person wearing them. Since the radial artery passes along the full length of the forearm, there are several positions where a sensor can be placed. Furthermore, the radial artery is very close to the surface of the skin, rendering it ideal to be measured with PPG. We placed the first sensor on the right arm, just above the thumb, where we could feel pulsatile motion, as seen in figure 2.4a. The second sensor was placed further up along the arm, along the radial artery, as high up as we could go without losing signal integrity in the deeper muscle tissues. We want to maximize the distance between the sensors in order to reduce the need for faster frame rates of data capture. This ensures that the waveform is captured correctly and with sufficient number of data points so that the velocity information is not lost. Given that the relationship is distance over time, as the distance between the two sensors

increases, the travel time increases as well. This means that less of a capture rate is required than if the sensors were close together. With a shorter distance between the sensors, the data capture rate would have to increase to compensate. For the test runs that will be described in this thesis, the second sensor was placed approximately two thirds up between the wrist to the elbow, as is depicted in figure 2.4b. The sensor boards are strapped to the wrist and arm via long strands of Velcro™ allowing adjustable length, to accommodate a variety of arm and wrist sizes. These straps also ensure that the pressure of the sensors applied is not so high that it causes the PWV waveform to be malformed, while still maintaining high enough pressure to hold the sensors stationary while testing is performed. The probe heads are not connected by any superstructure, since this can cause abnormal twisting of the arm and thus render the data unusable. At the moment of data recording, the distance between the two sensors needs to be measured to obtain the distance the pulse travels to estimate PWV. For this purpose, we used a tape measure. While positioning the sensors, the probes were connected to an oscilloscope to check signal clarity, and if the output, was railed the light intensity was altered to gain maximum signal swing and waveform clarity. With intensity adjusted, the gain stages were also altered to ensure maximum signal swing and amplitude.

a) Wrist mounted PPG sensor



b) PPG sensor mounted on upper arm



c) Both PPGs mounted on arm

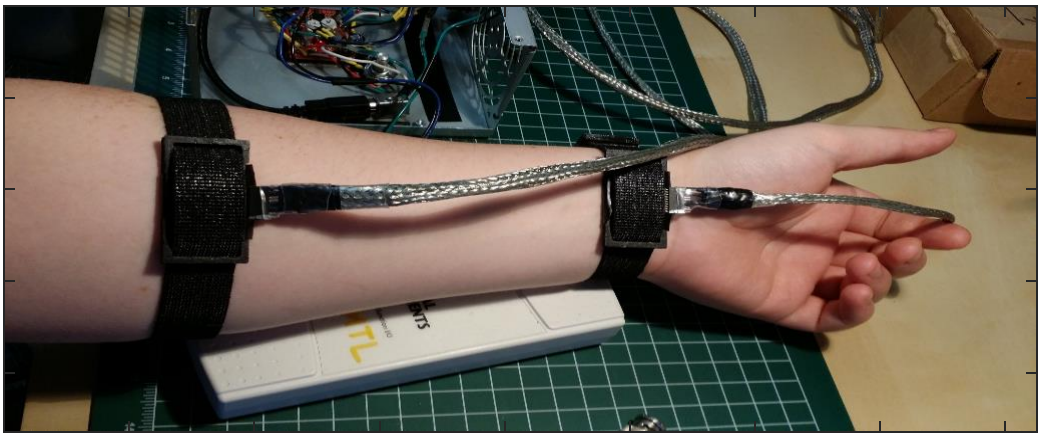


Figure 2.4 Shown is a) the PPG sensor closest to the hand, b) the second sensor that is located higher up the arm and c) the complete set up where the distance between the sensors has been measured and the PPGs connected to the circuit.

2.3 Procedure

To start the data run, we have the test subject sit at rest for a period of time before we ask them to locate their radial artery on the right arm, just above the thumb. They do so by feeling for pulsatile motion between the radius and the tendon of the wrist, and this is where the radial artery is located. The first sensor head is then placed on this spot, making sure that the SFH sits directly on top of the artery. The wrist strap of the sensor head is then tightened, ensuring that the strap is not so tight as to interfere with the signal, yet not so loose that it will move. The signal is

inspected on the oscilloscope to ensure that the output is not railed and the signal waveform is clear in shape and amplitude. After the first sensor has been placed, the second is attached further up the arm in line with the previous sensor, whilst being monitored again to ensure signal clarity and amplitude. If the output is found to be lacking, the intensity of the LED is first altered, and then the gain of the individual gain stages are set. Again, the tightness of the sensor band is adjusted to a satisfactory level to achieve an acceptable signal quality. After the second sensor has been situated, the distance between the two sensor heads are measured using a measuring tape, and this distance is recorded.

Once these steps have been performed, the NiDaq is activated and sensor readings are taken and stored in Matlab. For our testing purposes, we run data collection for 30 seconds per run, which amounts to about 25-35 pulses, depending on the heart rate of the user. The user is then disconnected from the device, and depending on the level of noise present in the signal, it is filtered to remove any unwanted components. Due to blood absorbing the light from the sensor heads, we invert the data after filtering. This will make an increase of blood volume traveling by the sensor visually correspond to an increase in signal voltage. Then this inversed data is graphed and inspected.

During the inspection, a few waveforms are observed to ensure that the timing of the pulses did not drift, and that the feet of the pulse waves are distinguishable. Before running any further detection schemes, a quick manual check of pulse wave velocity is performed by taking the time difference between the onset of the systole of the waveform obtained from one sensor to the onset of the same systole on the second sensor. The distance measured between the two sensors is then divided by this time to get an estimate of the PWV. Further analysis is then performed using several detection schemes, to compare different methods of pulse wave

detection. The results obtained are then compared to other data runs, as well as compared to average pulse wave velocity of the age group of the subject, as obtained from literature.

2.4 Signals obtained

In the following section, the initial signals obtained from a data gathering session will be shown, as well as the individual parts of which will be discussed. The filtering used to clean up the signals will also be discussed. The raw signal obtained from a single sensor through the NiDaq can be seen in figure 2.5.

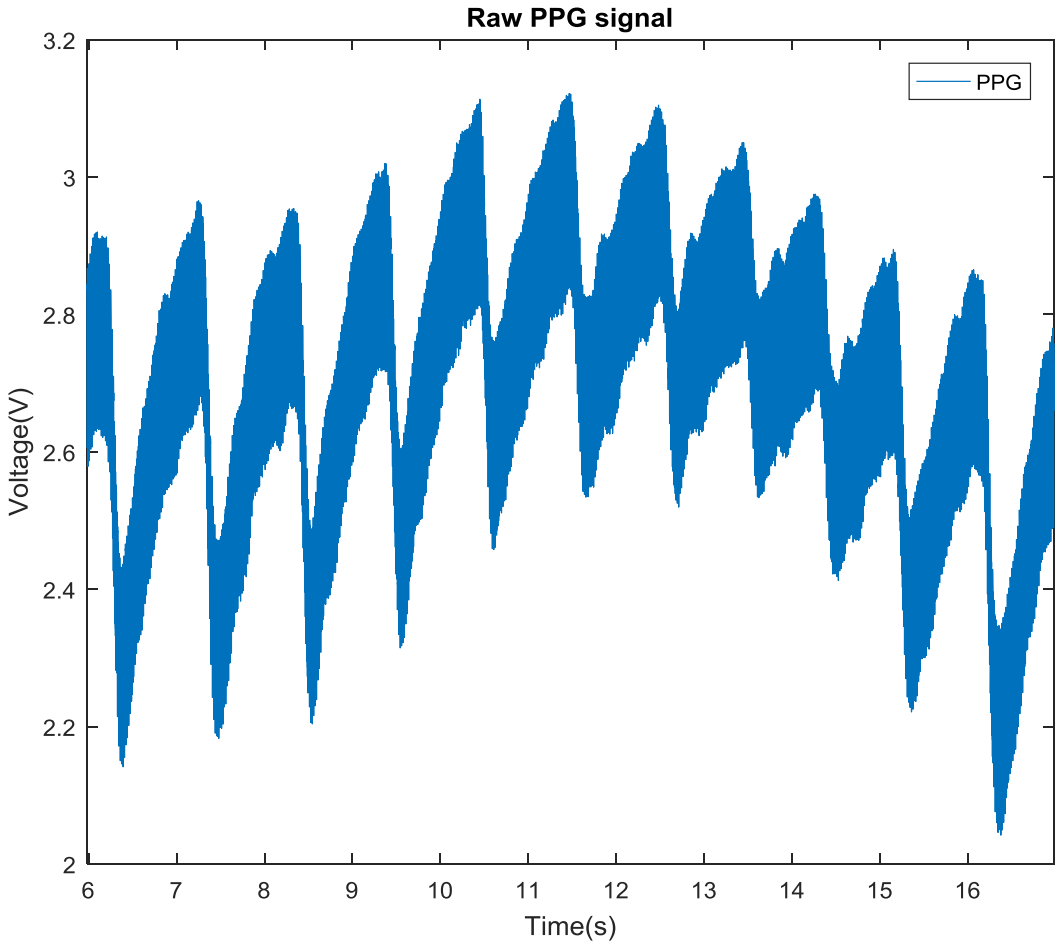


Figure 2.5 A typical signal obtained from a singular PPG sensor, before any post processing has been done to it. Note the sharp decrease in amplitude corresponds to a wave traveling by.

This is before the data has been inversed, and depicts the absorption of light into the blood as it passes the under the sensor. Note the shift in amplitude over time; this is due to respiration (as covered in the previous chapter). As can be observed, there is noise present in the waveform that is obscuring the dicrotic notch. Using a low pass filter with cut-off frequency of 51 Hz, we removed the noise component, and rendered the signal to be more recognizable, as well as convenient to work with, as observed in figure 2.6.

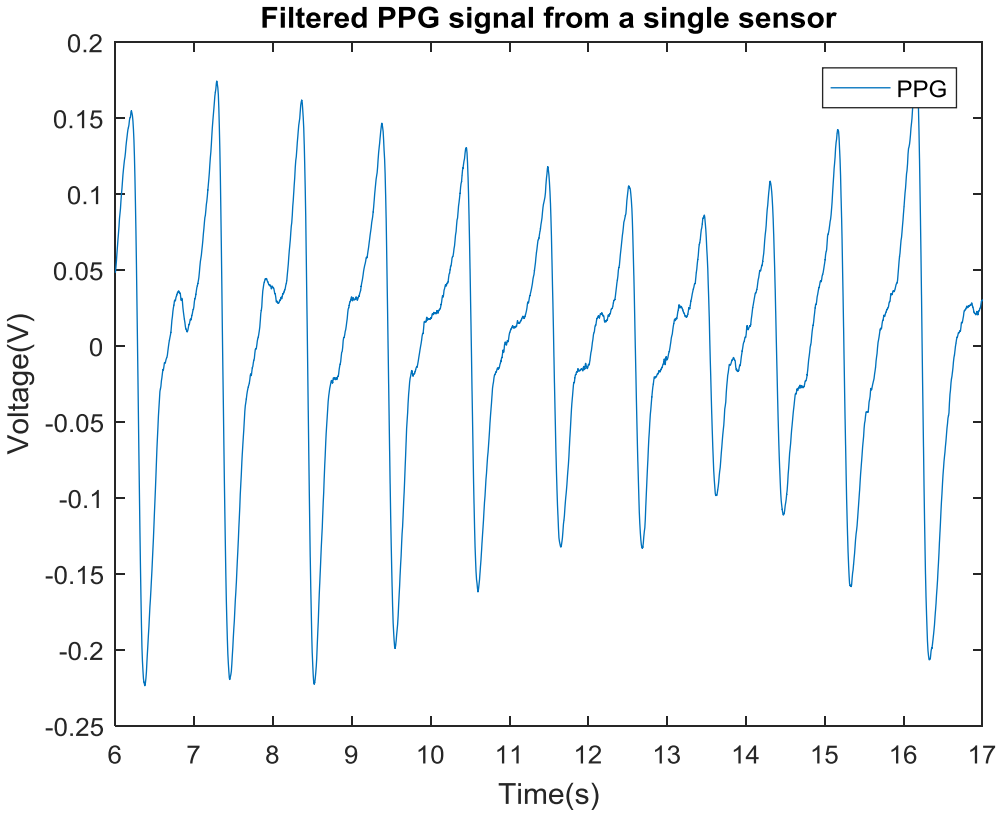


Figure 2.6 The inverted arterial waveform that becomes evident after filtering. To ease processing, the wave has been centered around zero volts.

Here we see the waveform more clearly and it has the characteristic shape of volumetric blood flow, as was demonstrated in chapter 1. However, since it is the change in absorption of the reflected light, meaning that when more blood is present, the sensor sees a decrease in

reflected light, i.e. the amplitude goes down. Thus, the next steps are to invert the data so that a rising wave corresponds to an increase of blood volume detected. In figure 2.7, we can see this inversed waveform and that we now have achieved the characteristic shape of the volumetric flow, no longer obscured by the noise.

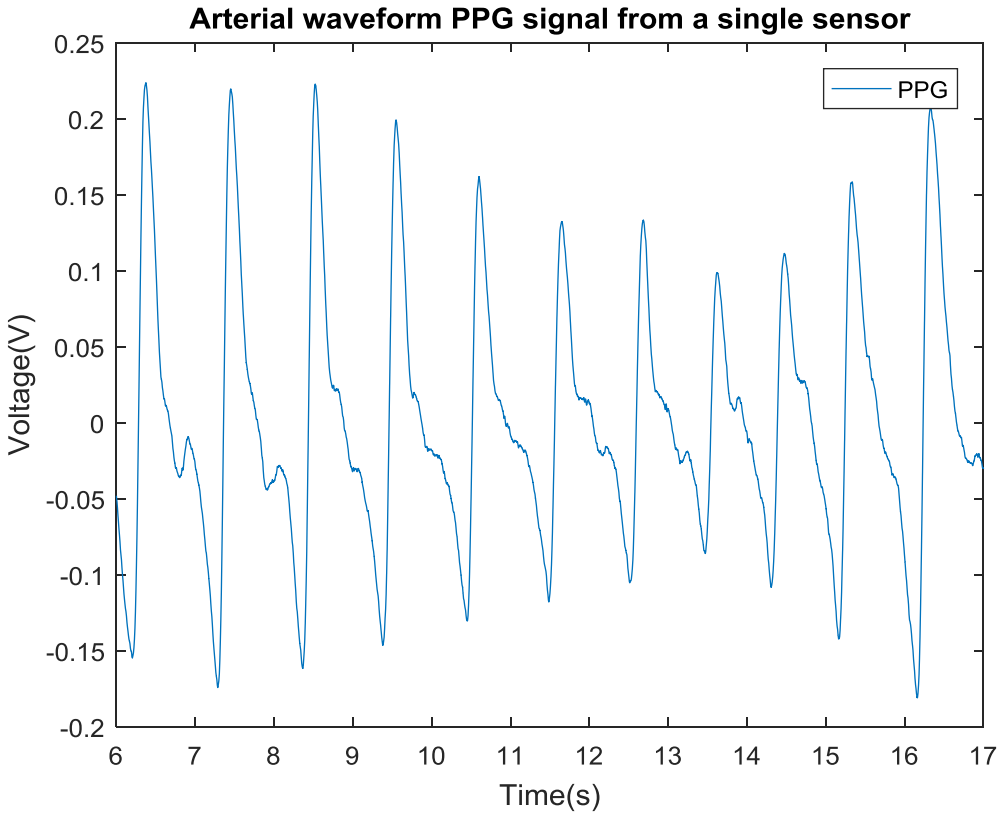


Figure 2.7 Once inverted and filtered, the arterial waveform becomes distinct, with both dicrotic notch and onset time clearly visible.

The same procedure is then performed on the data from the second sensor. As we can see in figure 2.8a and 2.8b, the amplitude of this signal is slightly lower as a result of the increased tissue volume between the artery and the skin, since the sensor sits higher up on the arm. These two waveforms are then plotted together, as can be seen in figure 2.8c, where we can see the time difference between the onset of the two waves.

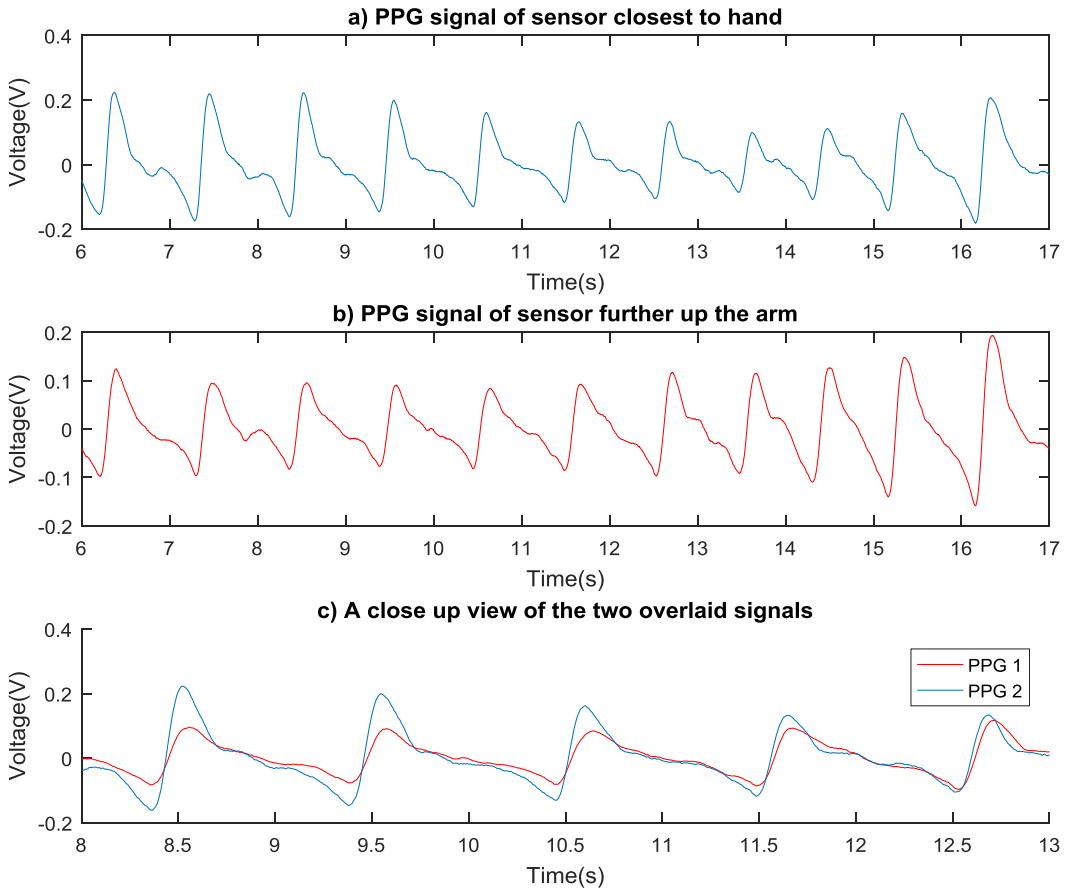


Figure 2.8 The PPG signals of a) the lowest PPG sensor that is located on the wrist, b) the PPG that is located on the forearm and c) the two signals together with the sensors 19 cm apart.

It is evident from this side by side comparison of the two waveforms that the general shape differs from one to the other, due to the different measurement sites and the back reflected wave that occurs from the changing arterial properties around said site.

2.5 Analysis

Several solutions were considered and developed to automatically detect the pulse wave velocity from the signals obtained in the data runs using our device, and in this section several of those will be covered.

The arterial waveform changes at different measurement sites given that the backwards traveling wave depends on the properties of the local arterial site. Due to this change in waveform shape, trying to cross-correlate the two waveforms to see where the time difference is expressed will render inaccurate estimates. To combat this source of error, several different estimation techniques have been tested in this work.

The defining point of the waveform is the systolic rise, which corresponds to the sharp increase of blood volume from a heart constriction. After this sharp increase, the backwards traveling wave causes interferences and alters the shape of the traveling pulse. Since we know that the feature we are looking for is the sharpest increase in amplitude per beat, we can identify the region of interest by taking the first derivative of the PPG signal and looking for the spikes that occur from the highest rate of change. If we then perform peak detection on the derivative waveforms of both the first and second PPG, the onset times from the two can be measured to estimate PWV. Alternatively, we can use the obtained time positions to isolate the entire onset time. By selecting a pre-set number of samples before and after the points of interest, gained from the derivative waveform, the rise times of each pulse wave can be separated and then cross-correlated. Using cross-correlation on the rise times separately will make the processing more resistant to signals that have been obscured, due to non-optimized gain stages and improper LED intensity settings. When the signal is distorted, due to the aforementioned reasons, the signal gets

clipped. This means only the upper parts can be seen, thus the foot of the pulse onset is not accurately expressed. This will induce errors in the method using only the first derivative.

We determine global PWV from the average determined from 30-second sample sets to validate the measurement scheme. This is made possible since all data runs have occurred with the test subjects at rest before, as well as after, the PPG recording. In future testing, we hope to use this set-up to measure PWV as it increases from exercise, which will require PWV measurements over smaller sampling intervals.

2.6 Results

As stated in the previous section, only averaged PWV is used due to a lack of a comparable, beat-to-beat, pulse wave velocity detection system. We assess the accuracy of our PWV measurement by comparison to literature values for subjects in the age range 25-30, which is 11.14 m/s.

We use three ways to detect PWV. The first method uses the timing of the foot of each wave, and determine the time difference between the pulses at the first and second sensors. The second method uses the derivatives of the two signals to compute the time difference between the pulses at the two sensors. The third method uses the rise time of each pulse and cross-correlation to detect the time difference between pulses.

The first method requires manual detection and is therefore time consuming. It requires user input to identify points of interest in the waveform, and renders the process of getting an average over 30 seconds tedious. As shown in figure 2.9, the foot of both arterial waves are identified and a data marker is placed to read the time difference. Since the distance the wave has

to travel is known, PWV can be detected for a heart beat. Using the derivative method, the selection of onset time is made easier, due to tracking the maximum rate of change of the arterial wave, as seen in figure 2.10. This means that a simple peak detection function can detect the reference points, allowing for greater automation of PWV estimation. For cross-correlation, either the full waveforms can be correlated to detect the time difference or, using the first derivative peak detection, each heart beat can be singled out and individually cross-correlated.

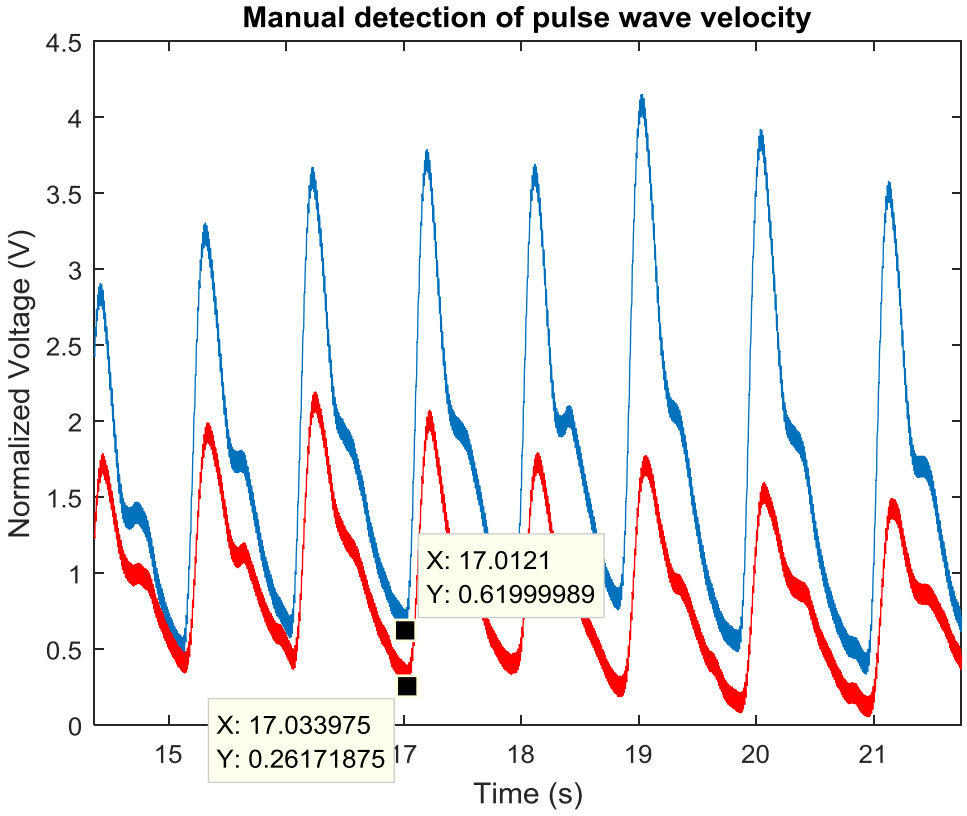


Figure 2.9 Two PPG signals with manually estimated onset times.

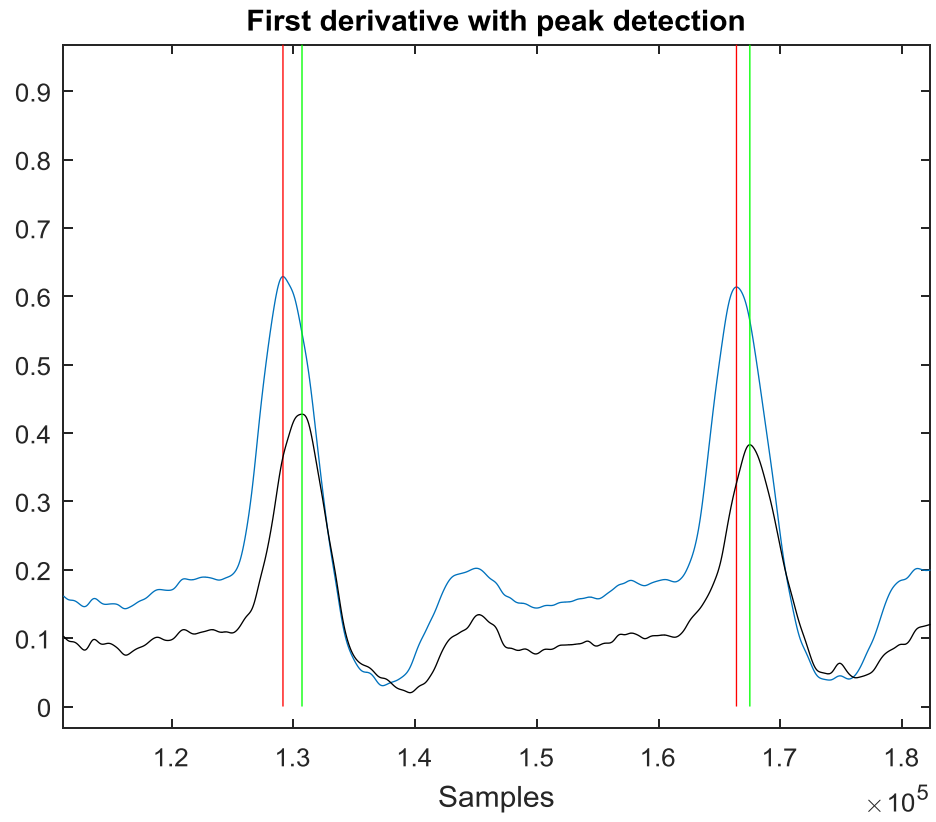


Figure 2.10 First derivative signal of PPG with peak detection to find the point of maximum rate of change.

2.7 Sample Run

Using the analysis techniques discussed in the previous session, a 60 second data run was evaluated and the PWV estimated and compared to typical values from literature. This 60 second data set was obtained from a 27 year old male, with no previous clinical history of cardiovascular disease, or high blood pressure. The subject is athletically built and not overweight.

Using the first method discussed in section 2.6, manual detection, applied to the sample set that is shown in figure 2.11, we get the PWV data shown in table 2.1. Doing the analysis manually takes a longer time, but it allows for greater flexibility in signal quality since a human user can use their judgement on where to measure the foot of the waveform. Using this analysis

method gives us an average PWV of 9.29 m/s and a median value of 9.19 m/s. However, we can still see some outliers in the data, with the maximum value being 28.79 m/s and the minimum being 4.69 m/s.

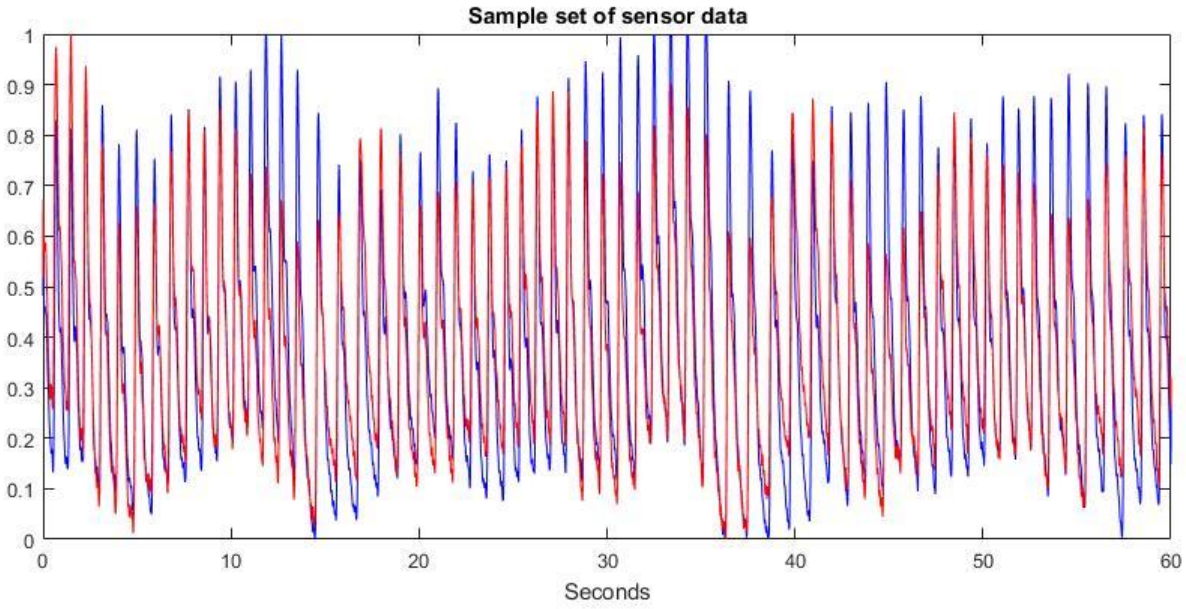


Figure 2.11 The 60 second sample set used to evaluate the 3 analysis techniques.

Table 2.1 The PWV data obtained using manual calculation.

Beat number	PWV(m/s):
1	10.74
2	4.70
3	9.44
4	4.74
5	5.15
6	5.72
7	12.71
8	8.31
9	9.20
10	6.38
11	11.21
12	5.57
13	5.59
14	9.24
15	8.62
16	9.16
17	28.80
18	7.36
19	7.12
20	6.83
21	6.80
22	12.44
23	9.91
24	8.55
25	10.88
26	9.75
27	11.61
28	11.63
29	9.31
30	9.27
31	11.74
32	12.26
33	6.09

Using the second analysis technique on this particular set of data was less successful. The automated detection of maximum rate of change from the first derivate is sensitive to the signal clarity obtained in the data run. As we can see in figure 2.12, there were some false and missed

triggers leading to erroneous PWV estimation on most beats. Furthermore, we can see there is no clear consensus reached with the derivative method. To salvage useable information from this method, we remove any erroneous peaks and substitute them for the average of the preceding and following values. The result is demonstrated in figure 2.13. This processing the average PWV is 7.74 m/s with a minimum value of 3.86 m/s and a maximum of 12.56 m/s.

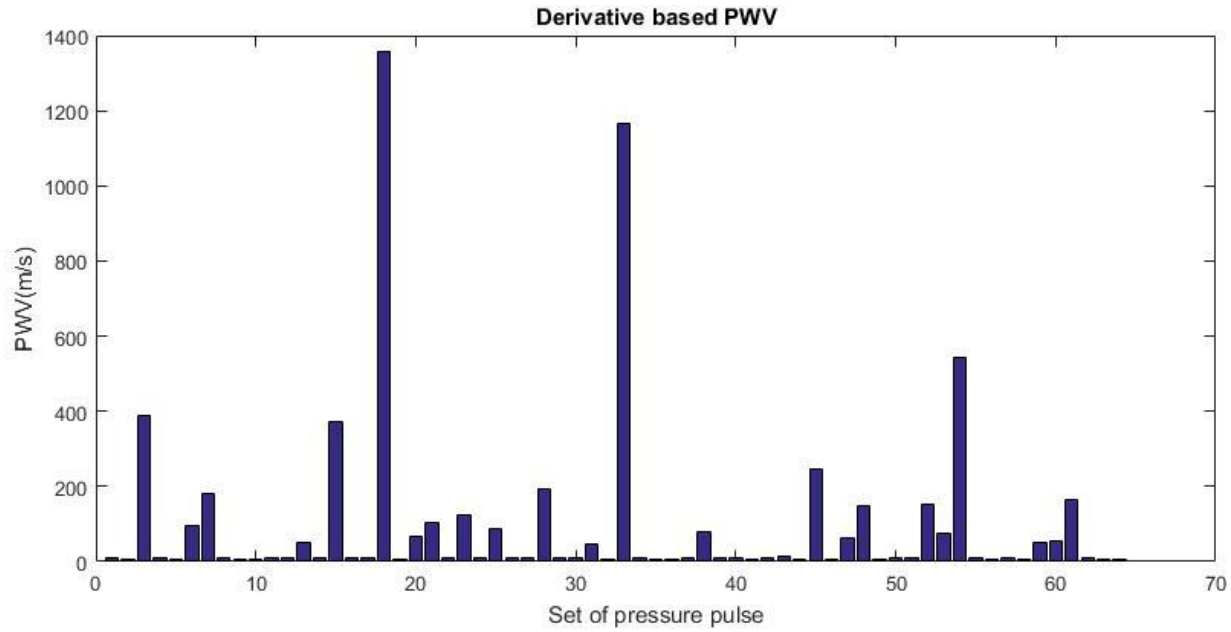


Figure 2.12 Derivate based PWV obtained from each beat in the sample set.

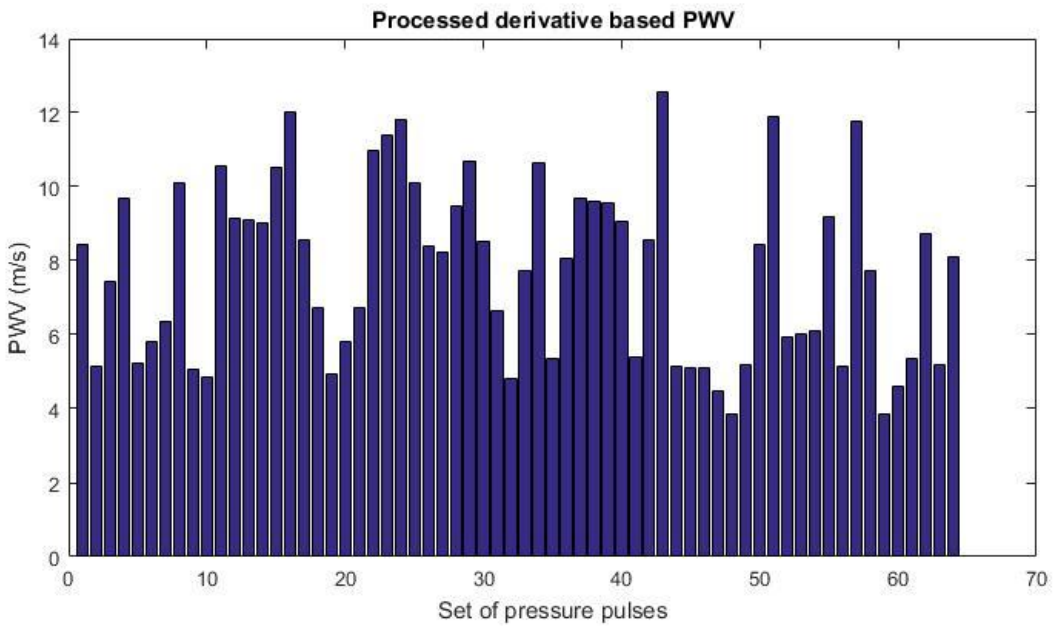


Figure 2.13 Derivative based PWV obtained from processing the data to remove outliers.

The last technique used to evaluate the data set is using the maximum rate of change obtained from the derivative to establish a region of interest per beat, and then cross-correlating the two waveforms over that region. Once we have obtained the point of maximum rate of change per heart beat from the previous method, we use this to select a window around each onset time. This window is one third of a second wide and is centered on the onset time. These individual peaks are then cross-correlated to find the delay between two PPG signals. With this delay we can estimate the PWV. The results of this operation can be seen in figure 2.14, where the PWV of each beat has been calculated and graphed. This method is the least time consuming to perform as well as the most stable automatic analysis scheme. The average PWV was detected to be 9.90 m/s with the minimum being 5.16 m/s and the maximum being 10.97 m/s.

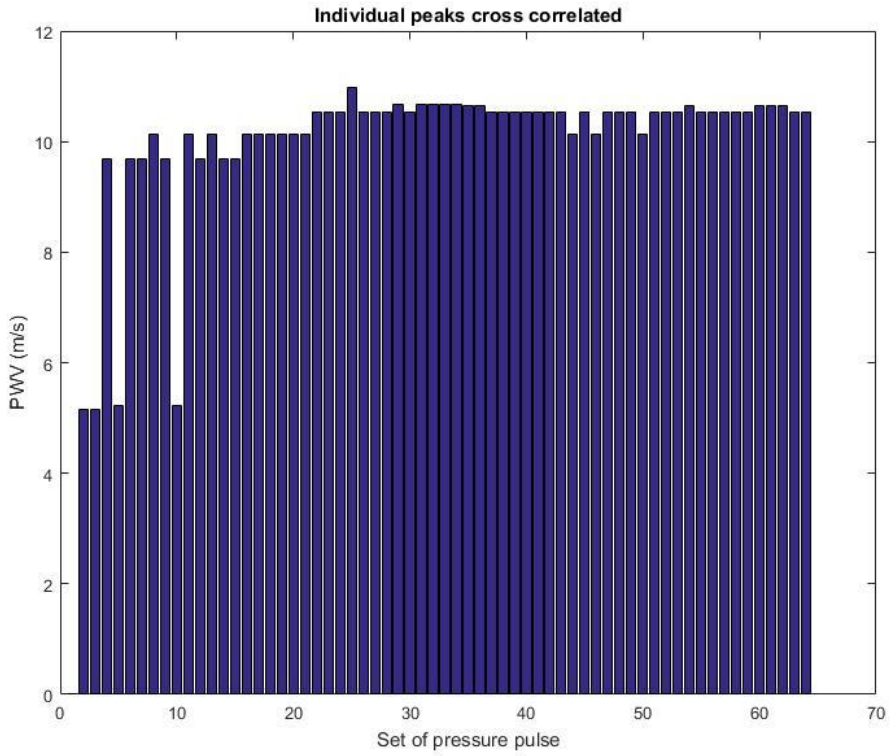


Figure 2.14 PWV resulting from cross-correlating the individual heart beats.

In summary, the best method was the cross-correlation of individual heart beats. The derivative method is sensitive to signal clarity and noise levels in the data recording and thus can get erroneous results. The manual detection is labour intensive and is only as viable as the skill of the operator. The average results of the best method was 9.9 m/s, which is comparable to average PWV of 11.14 m/s in the radial artery, for people between ages 25-30 [60]. The three methods are summarized in table 2.2.

Table 2.2 Summary of the 3 analysis methods

Method	Min	Max	Average	Standard deviation
Manual	4.69 m/s	28.79 m/s	9.29 m/s	4.25 m/s
Derivative	3.86 m/s	12.56 m/s	7.74 m/s	2.73 m/s
Cross-Correlation	5.16 m/s	10.97 m/s	9.90 m/s	1.81 m/s
		Age average	11.14 m/s	4.7 m/s

2.8 Additional data

In the following section, PWV is estimated in a group of five people, over two days. The same methods as were discussed in the previous sections were used to determine PWV. All five subjects were between 25-30 years old, were not obese and did not suffer from any cardiovascular disease. All sample sets were 60 seconds long.

To determine the reliability of the system, PWV was measured on a group of people with two measurements taken one day apart. The results are presented in table 2.3.

Table 2.3 Table of the pulse wave velocity obtained from the 5 test subjects (in m/s) in three different ways. The standard deviation of each measurement has been included as well. The standard deviation of the population is calculated as well.

Day 1		Manual		Derivative		Cross Correlation	
		Average	SD	Average	SD	Average	SD
	Subject 1	7.83	2.85	8.46	1.72	9.20	1.18
	Subject 2	9.20	3.67	8.55	2.61	10.10	0.17
	Subject 3	6.76	4.47	7.37	2.48	6.96	1.15
	Subject 4	9.06	2.62	7.86	2.02	8.40	1.14
	Subject 5	8.00	5.16	7.61	2.16	8.81	0.15
	Standard deviation in population						
		0.998198		0.519182		1.15537	
Day 2		Manual		Derivative		Cross Correlation	
		Average	SD	Average	SD	Average	SD
	Subject 1	9.71	3.39	8.14	1.10	8.62	0.14
	Subject 2	7.57	3.61	6.90	1.95	7.53	1.4
	Subject 3	11.01	4.65	9.92	2.30	10.96	1.46
	Subject 4	13.92	8.31	10.93	0.88	10.97	0.14
	Subject 5	9.98	6.96	8.63	1.58	9.03	0.31
	Standard deviation in population						
		2.313908		1.566183		1.511479	

The age average of PWV for the age group selected is 11.14 m/s with a standard deviation of 4.7. All the test subjects fall within this range. The best method for detection was the cross correlation. A paired T-test was also run between both the subjects per day and between literature and the average PWV per subject. The first T-test between the two populations yielded a p-score of 11.8%, and the T-test between the literature and the average subject PWV yielded a p-score of 16.2%.

The difference detected in PWV from day to day can be attributed to a lack of a rigorous testing protocol, such as limiting caffeine and exercise before testing.

Chapter 3

Conclusions & future work

With the high importance of blood pressure measurement for determining overall cardiovascular health in individuals of any age, especially in the developed world, the improvement of measurement techniques is of vital importance. Furthermore, with increasing advances in portable and wearable technologies, there is opportunity for the enhancement in quality of life, and reduction of medical costs associated with hypertension. As part of a drive to develop a wearable continuous blood pressure monitor, this thesis focuses on obtaining pulse wave velocity locally, to eventually be combined with ultrasonic arterial diameter determination.

To this effect, the dynamics of the arterial system were investigated and a model combining arterial diameter and pulse wave velocity to continuously determine blood pressure was developed. To obtain the pulse wave velocity of a small segment of artery, several options of detection techniques were considered, with the final selection being photoplethysmography.

The PPG system was then designed, constructed and tested to determine if a local estimation of PWV was possible. Our estimations fell within acceptable range for the physical characteristics of the test subject, according to literature. Given these promising results, future testing, including arterial diameter, is planned with the help of UBC Okanagan's School of Health Sciences. We hope these future studies will show that a non-invasive blood pressure estimation scheme using only PPG and ultrasonics is valid and new technologies will be born as a result.

3.1 Discussion

The pulse wave velocity measured for the author of this thesis was found to be comparable to values typical for the author's age demographic [61]. However, direct validation could not be performed due to lack of access to other direct measurement techniques and devices to establish PWV. The PWV obtained from our system will be used in conjunction with direct arterial diameter measurements to prototype a method to directly estimate blood pressure.

3.2 Future work

Future experimentation using this testing apparatus and analysis in conjunction with ultrasound measurements of arterial diameter has been underway. However, further work is still required in order to obtain better signal quality and ease of use. Some of these suggested improvements are covered here, along with a more detailed account of the next stages of experimentation.

Work is in progress to improve the hardware configuration of the PPGs to include the TI AFE 4404 [62], which is an analog front end designed for optical bio sensing applications. The AFE has an integrated LED driver with programmable current output, supporting up to three LEDs simultaneously. It also has an integrated transimpedance amplifier and an ADC, which can be read through an I^2C interface. With the PPGs redesigned to include this chip, the gain and intensity controls can be programmed to be fully automatic to raster through the gain settings until the best signal clarity can be detected. Furthermore, the LED "on" time can be set and pulse width modulated, which leads to lower power draw. Another benefit of pulse width modulation is that the reduced "on" time would allow for higher intensity light to be used without damaging

the LED. The PD can be sampled before and after the LED "on" time to detect the ambient light. This can be used to lower the impact of noise interference from ambient light.

In the current iteration of the PPG system, the two sensor heads are independent of each other, and thus for each test subject the distance between the sensors needs to be measured. As the work progresses, we hope to secure the sensors with a fixed distance between them that will be able to work for a wide variety of forearm sizes. With increased signal sensitivity and automatic gain stage control, such a task would be simplified. Furthermore, as the signal processing and volumetric blood volume detection improves, the distance between the sensors can decrease. Thus, if the signal quality is good enough, and the sample rate high enough, the distance between the sensors can decrease. A fixed distance system would require a structure that is flexible enough to accommodate a wide variety of forearm shapes, without being so rigid that the placement is uncomfortable, or impedes the measurement, yet stiff enough that the distance remains constant and placement secure.

During this process of increasing the effectiveness of the PWV system, work has progressed to refining the model to describe blood pressure, given arterial diameter and pulse wave velocity. This procedure is done in collaboration with the School of Health and Sciences (HES) of UBC Okanagan. With the help of HES, we have also secured ethics approval for human testing on 30 individuals under the age of 40, with equal distribution between genders. This testing consists of using an ultrasonic imaging system to determine arterial diameter, along with a Finometer, which is a plethsymographic finger cuff system to measure BP continuously, as described in chapter 1, to track blood pressure during the procedure. Along with the Finometer, an oscillometric cuff blood pressure measuring system is used to ensure that the

signal tracking from the Finometer does not drift. The combination of these two systems sets a reference blood pressure waveform. Thus, the collaboration with HES has two main objectives:

1) To determine the accuracy of tracking blood pressure using the modified form of the Moens-Korteweg equation, as seen in equation 1.10, and to see if it is feasible with our system, to increase the systems appeal to a larger audience. To test the accuracy, the difference in blood pressure estimated by equation 1.10 will be compared to the Finometer monitored pressure. Any differences will be noted and the samples will be cross referenced with trials from other patients to determine if it is reoccurring between individual, and if so, if there is any commonality between the subjects that could describe the connection.

2) To determine if there is a way that we can, through modeling, eliminate the need for diastolic pressure in equation 1.10. If such a model can be determined, the need for calibration would be removed. This model would be based on the characteristics of the individuals tested, such as age, gender and other similar features.

References

[1] M. Karamanoglu *et al*, "An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man," *Eur. Heart J.,* vol. 14, *(2),* pp. 160-167, Feb, 1993.

[2] T. G. Pickering *et al*, "Recommendations for blood pressure measurement in humans and experimental animals: Part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research," *Hypertension,* vol. 45, *(1),* pp. 142-161, Jan, 2005.

[3] C. Robitaille *et al*, "Diagnosed hypertension in Canada: incidence, prevalence and associated mortality," *Cmaj,* vol. 184, *(1),* pp. E49-56, Jan 10, 2012.

[4] A. V. Chobanian *et al*, "The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report," *Jama,* vol. 289, *(19),* pp. 2560-2571, 2003.

[5] W. Nichols, M. O'Rourke and C. Vlachopoulos, *McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles.* CRC Press, 2011.

[6] W. H. O. Staff, *The World Health Report 2002: Reducing Risks, Promoting Healthy Life.* World Health Organization, 2002.

[7] J. Handler, "The importance of accurate blood pressure measurement," *Perm. J.,* vol. 13, *(3),* pp. 51-54, Summer, 2009.

[8] T. G. Pickering *et al*, "How common is white coat hypertension?" *Jama,* vol. 259, *(2),* pp. 225-228, 1988.

[9] R. S. Vasan *et al*, "Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study: a cohort study," *The Lancet,* vol. 358, *(9294),* pp. 1682-1686, 11/17, 2001.

[10] (2014, August 04). *Understanding Blood Pressure Readings* [Online]. Available: http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/AboutHighBloodPressure/Understanding-Blood-Pressure-Readings_UCM_301764_Article.jsp#.V6uH7PkrJhF.

[11] K. Davis, "Expenditures for Hypertension Among Adults Age 18 and Older, 2010: Estimates for the US Civilian Noninstitutionalized Population," 2013.

[12] (2014, August 04). *Low blood pressure*. Available: http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/AboutHighBloodPressure/Low-Blood-Pressure_UCM_301785_Article.jsp#.V6uNaPkrKUl.

[13] P. A. Iaizzo, *Handbook of Cardiac Anatomy, Physiology, and Devices.* Springer Science & Business Media, 2009.

[14] S. Lorsomradee *et al*, "Uncalibrated arterial pulse contour analysis versus continuous thermodilution technique: effects of alterations in arterial waveform," *J. Cardiothorac. Vasc. Anesth.,* vol. 21, *(5),* pp. 636-643, 2007.

[15] B. V. Scheer, A. Perel and U. J. Pfeiffer, "Clinical review: complications and risk factors of peripheral arterial catheters used for haemodynamic monitoring in anaesthesia and intensive care medicine," *Critical Care,* vol. 6, *(3),* pp. 1, 2002.

[16] E. P. McCutcheon and R. F. Rushmer, "Korotkoff sounds. An experimental critique," *Circ. Res.,* vol. 20, *(2),* pp. 149-161, Feb, 1967.

[17] G. M. Drzewiecki, J. Melbin and A. Noordergraaf, "Arterial tonometry: review and analysis," *J. Biomech.,* vol. 16, *(2),* pp. 141-152, 1983.

[18] J. D. Humphrey *et al*, "Fundamental role of axial stress in compensatory adaptations by arteries," *J. Biomech.,* vol. 42, *(1),* pp. 1-8, 1/5, 2009.

[19] J. D. Humphrey, *Cardiovascular Solid Mechanics Cells, Tissues, and Organs.* Springer New York, 2002.

[20] T. C. Gasser, R. W. Ogden and G. A. Holzapfel, "Hyperelastic modelling of arterial layers with distributed collagen fibre orientations," *J. R. Soc. Interface,* vol. 3, *(6),* pp. 15-35, Feb 22, 2006.

[21] G. A. Holzapfel, T. C. Gasser and R. W. Ogden, "A new constitutive framework for arterial wall mechanics and a comparative study of material models," *Journal of Elasticity and the Physical Science of Solids,* vol. 61, *(1-3),* pp. 1-48, 2000.

[22] D. H. Bergel, *The Visco-Elastic Properties of the Arterial Wall.,* 1960.

[23] P. B. Dobrin, "Mechanical properties of arterises," *Physiol. Rev.,* vol. 58, *(2),* pp. 397-460, Apr, 1978.

[24] J. C. Kim and E. B. Shim, "Hemodynamics," in Anonymous 2010, . DOI: 10.1007/978-4-431-99703-0_14.

[25] M. O'Rourke, "Arterial stiffness, systolic blood pressure, and logical treatment of arterial hypertension," *Hypertension,* vol. 15, *(4),* pp. 339-347, Apr, 1990.

[26] R. G. Gosling and M. M. Budge, "Terminology for describing the elastic behavior of arteries," *Hypertension,* vol. 41, *(6),* pp. 1180-1182, Jun, 2003.

[27] J. Vappou *et al*, "Non-invasive measurement of local pulse pressure by pulse wave-based ultrasound manometry (PWUM)," *Physiol. Meas.,* vol. 32, *(10),* pp. 1653, 2011.

[28] L. M. Van Bortel *et al*, "Non-invasive assessment of local arterial pulse pressure: comparison of applanation tonometry and echo-tracking," *J. Hypertens.,* vol. 19, *(6),* pp. 1037-1044, 2001.

[29] D. J. Hughes *et al*, "Measurements of Young's modulus of elasticity of the canine aorta with ultrasound," *Ultrason. Imaging,* vol. 1, *(4),* pp. 356-367, Oct, 1979.

[30] T. Pereira, C. Correia and J. Cardoso, "Novel methods for pulse wave velocity measurement," *Journal of Medical and Biological Engineering,* vol. 35, *(5),* pp. 555-565, 2015.

[31] L. M. Van Bortel *et al*, "Clinical applications of arterial stiffness, Task Force III: recommendations for user procedures," *Am. J. Hypertens.,* vol. 15, *(5),* pp. 445-452, May, 2002.

[32] M. F. O'Rourke *et al*, "Clinical applications of arterial stiffness; definitions and reference values," *American Journal of Hypertension,* vol. 15, *(5),* pp. 426-444, 2002.

[33] T. E. H. OTHMANE *et al*, "Effect of sevelamer on aortic pulse wave velocity in patients on hemodialysis: a prospective observational study," *Hemodialysis International,* vol. 11, *(s3),* pp. S13-S21, 2007.

[34] P. Salvi *et al*, "Validation of a new non-invasive portable tonometer for determining arterial pressure wave and pulse wave velocity: the PulsePen device," *J. Hypertens.,* vol. 22, *(12),* pp. 2285-2293, 2004.

[35] M. W. Rajzer *et al*, "Comparison of aortic pulse wave velocity measured by three techniques: Complior, SphygmoCor and Arteriograph," *J. Hypertens.,* vol. 26, *(10),* pp. 2001-2007, Oct, 2008.

[36] S. Laurent *et al*, "Expert consensus document on arterial stiffness: methodological issues and clinical applications," *Eur. Heart J.,* vol. 27, *(21),* pp. 2588-2605, Nov, 2006.

[37] J. Baulmann *et al*, "A new oscillometric method for assessment of arterial stiffness: comparison with tonometric and piezo-electronic methods," *J. Hypertens.,* vol. 26, *(3),* pp. 523-528, Mar, 2008.

[38] L. Joly *et al*, "Pulse wave velocity assessment by external noninvasive devices and phase-contrast magnetic resonance imaging in the obese," *Hypertension,* vol. 54, *(2),* pp. 421-426, Aug, 2009.

[39] J. Allen, "Photoplethysmography and its application in clinical physiological measurement," *Physiol. Meas.,* vol. 28, *(3),* pp. R1, 2007.

[40] B. Jani and C. Rajkumar, "Ageing and vascular ageing," *Postgrad. Med. J.,* vol. 82, *(968),* pp. 357-362, Jun, 2006.

[41] M. Djelic, S. Mazic and D. Zikic, "A novel laboratory approach for the demonstration of hemodynamic principles: the arterial blood flow reflection," *Adv. Physiol. Educ.,* vol. 37, *(4),* pp. 321-326, Dec, 2013.

[42] J. Steppan *et al*, "Vascular stiffness and increased pulse pressure in the aging cardiovascular system," *Cardiol. Res. Pract.,* vol. 2011, pp. 263585, 2011.

[43] T. Shokawa *et al*, "Pulse wave velocity predicts cardiovascular mortality-findings from the Hawaii-Los Angeles-Hiroshima study," *Circulation Journal,* vol. 69, *(3),* pp. 259-264, 2005.

[44] P. Boutouyrie *et al*, "Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients a longitudinal study," *Hypertension,* vol. 39, *(1),* pp. 10-15, 2002.

[45] J. Blacher *et al*, "Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients," *Hypertension,* vol. 33, *(5),* pp. 1111-1117, May, 1999.

[46] W. B. Murray and P. A. Foster, "The peripheral pulse wave: information overlooked," *J. Clin. Monit.,* vol. 12, *(5),* pp. 365-377, 1996.

[47] H. Fukushima *et al*, "Estimating heart rate using wrist-type photoplethysmography and acceleration sensor while running," in *2012 Annual International Conference of the IEEE Engineering in Medicine and Biology Society,* 2012, pp. 2901-2904.

[48] V. Vizbara, "Comparison of green, blue and infrared light in wrist and forehead photoplethysmography," *Biomedical Engineering 2015,* vol. 17, *(1),* 2013.

[49] T. Tamura *et al*, "Wearable photoplethysmographic sensors—past and present," *Electronics,* vol. 3, *(2),* pp. 282-302, 2014.

[50] Y. Maeda, M. Sekine and T. Tamura, "The advantages of wearable green reflected photoplethysmography," *J. Med. Syst.,* vol. 35, *(5),* pp. 829-834, 2011.

[51] Y. Maeda *et al*, "The effect of contact pressure to the photoplethysmographic sensor during walking," *生体医工学,* vol. 51, *(Supplement),* pp. R-307-R-307, 2013.

[52] K. Budidha and P. Kyriacou, "The human ear canal: investigation of its suitability for monitoring photoplethysmographs and arterial oxygen saturation," *Physiol. Meas.,* vol. 35, *(2),* pp. 111, 2014.

[53] Y. K. Lee, J. Jo and H. S. Shin, "Development and Evaluation of a Wristwatch-Type Photoplethysmography Array Sensor Module," *IEEE Sensors Journal,* vol. 13, *(5),* pp. 1459-1463, 2013.

[54] M. Maguire and T. Ward, "The design and clinical use of a reflective brachial photoplethysmograph," 2002.

[55] D. Lee *et al*, "Ultrasound evaluation of the radial artery for arterial catheterization in healthy anesthetized patients," *J. Clin. Monit. Comput.,* vol. 30, *(2),* pp. 215-219, 2016.

[56] J. E. Sharman *et al*, "Validation of a generalized transfer function to noninvasively derive central blood pressure during exercise," *Hypertension,* vol. 47, *(6),* pp. 1203-1208, Jun, 2006.

[57] OSRAM, ""SFH7050 BioMon"," 2016.

[58] Texas Instruments, ""AFE4404 Development Guide"," 2015.

[59] National Instruments, ""Bus-Powered M Series Multifunction DAQ for USB - 16-Bit, up to 400 kS/s, up to 32 Analog Inputs, Isolation"," 2014.

[60] A. Ferreira *et al*, "Determination of radial artery compliance can increase the diagnostic power of pulse wave velocity measurement," *Physiol. Meas.,* vol. 25, *(1),* pp. 37, 2003.

[61] J. S. Fulton and B. A. McSwiney, "The pulse wave velocity and extensibility of the brachial and radial artery in man," *J. Physiol.,* vol. 69, *(4),* pp. 386-392, Jun 27, 1930.

[62] Texas Instruments, ""AFE4404 Ultra-Small, Integrated AFE for Wearable, Optical, Heart-Rate Monitoring and Bio-Sensing"," 2016.