Ratio-Independent Arterial Stiffness-Based Blood Pressure Estimation

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A thesis submitted to the

Faculty of Graduate and Postdoctoral Studies

In partial fulfillment of the requirements for the degree

Master of Applied Science in Electrical and Computer Engineering

School of Electrical Engineering and Computer Science

University of Ottawa

Ottawa, Ontario, Canada

January 2014

Abstract

Blood pressure is one of the crucial vital signs that still lacks measurement accuracy in clinical environments. It is reported by physicians that automated non-invasive blood pressure measurement devices, which are usually based on the oscillometric method, do not provide accurate estimation of blood pressure. This problem has been addressed in this work by incorporating arterial stiffness in blood pressure measurement. Pulse transit time is first used to estimate arterial stiffness parameters. Afterwards, these parameters are fixed into a model of the oscillometric envelope which can then be used to curve fit measured data using only four free parameters: systolic, diastolic, mean blood pressure and minimum lumen area. The proposed individualized technique is independent of any experimentally determined ratio, commonly used in existing oscillometric methods. The accuracy of the proposed technique is evaluated by comparing with (1) the same model without incorporation of arterial stiffness (i.e. a purely oscillometric technique), and (2) Omron device measurements. The results are promising and meet the criteria recommended by the ANSI/AAMI SP-10 standard for non-invasive blood pressure measurement techniques.

Acknowledgments

It is my pleasure to thank the many people who made this thesis possible.

First of all, I would like to thank my supervisors Dr. Hilmi Dajnai and Dr. Izmail Batkin for their support, guidance, and assistance with the research and the writing of this thesis.

The work could also not have been completed without the support and aid of fellow research team members including Dr. Miodrag Bolic and Dr. Voicu Groza. I would also like to thank and acknowledge postdoctoral fellow Dr. Saif Ahmad and my lab mates Mohamad Forouzanfar, Mohamed Mabrouk, Milad Tannous, Huthaifa Abderahman. It has been a pleasure collaborating with each member of the team.

I owe my warmest thanks to my dear friends Niloofar Aghayan, Sahar Aghayan, Parisa Rabbani, and Mandana Javanshir Moghaddam for their encouragement. They have been really brilliant and understanding when I needed them to be.

Last but not least, I wish to express my deep gratitude to my parents who have offered unstinting support during my whole life.

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Abbreviations

AAMI	Association for the Advancement of Medical Instrumentation
ADC	Analog-to-Digital Converter
AI	Augmentation Index
ANSI	American National Standards Institutes
AS	Arterial Stiffness
BP	Blood Pressure
CFPWV	Carotid-Femoral Pulse Wave Velocity
CPP	Central Pulse Pressure
DBP	Diastolic Blood Pressure
HBMSs	Home-Based Monitoring Systems
ICU	Intensive Care Unit
MAP	Mean Arterial Pressure
MRI	Magnetic Resonance Imaging
OMW	Oscillometric Waveform
OMWE	Oscillometric Waveform Envelope
PP	Pulse Pressure

PPP Peripheral Pulse Pressure

PTT Pulse Transit Time

PWV Pulse Wave Velocity

SBP Systolic Blood Pressure

Chapter 1. Introduction

Cardiovascular disease is one of the leading causes of death worldwide. According to extensive population studies, one third of the worldwide morbidity and approximately half of deaths in Europe were associated with cardiovascular disease [1, 2]. The measurement of Blood Pressure (BP) is a highly valuable tool for managing cardiovascular disease. However, despite its paramount importance for making the right diagnostic and therapeutic decisions, it remains an imprecise measurement that is being performed in clinical environments [3].

1.1. Blood Pressure

Blood Pressure (BP) is the applied pressure on the wall of the artery during the cardiac cycle while blood is propagating through the arteries. It is measured in millimeters of mercury (mmHg). In each measurement, two numbers are reported: Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP). SBP is the maximum pressure during heart contraction (systolic phase) and ejection of the blood towards periphery. DBP is the minimum pressure exerted upon the wall of arteries while heart relaxes (diastolic phase) and heart chambers fills with the blood. BP cyclically fluctuates between maximum (SBP) and minimum (DBP) [4].

BP measurements can be done either invasively or noninvasively. The intra-arterial measurement, in which a catheter is placed inside the artery [5], is known as the most reliable and accurate method and is widely used in Intensive Care Units (ICU). However, the requirement of highly trained staff and the possibility of bleeding are two significant drawbacks.

Non-invasive methods are preferred as routine techniques in hospitals and for Home-Based Monitoring Systems (HBMSs) because they are safer, easier to use, and do not require extensive specialized training. The auscultatory method is considered as the gold standard of non-invasive measurements. This technique utilizes a stethoscope, sphygmomanometer, and cuff. The cuff is inflated to a pressure well above SBP and then deflated slowly to a level below DBP. The so-called Korotkoff sounds, are detected during cuff deflation. A trained observer listens carefully to the Korotkoff sounds produced during deflation to find SBP and DBP. SBP corresponds to the appearance of the first sound, while DBP corresponds to the last sound before silence. Disadvantages of this method are sensitivity to the noise, movements, and necessity of observer training [3, 6, 7].

The most popular technique employed in automated non-invasive BP measurement devices is the oscillometric method. In this technique, a cuff is wrapped around the arm and inflated to a level above SBP and then slowly deflated, like in the auscultatory method. Pressure oscillations in the cuff are recorded during the gradual deflation, and the cuff pressure corresponding to the maximum oscillation amplitude is regarded as the Mean Arterial Pressure (MAP). SBP and DBP are found by applying experimentally determined ratios to the MAP and then mapping back to the cuff pressure. The main advantages of this method as oppose to the auscultatory method are the relative ease of automation, and the lower susceptibility to noise and patients' movements [4, 8]. This technique relies on the amplitude of oscillations and experimental ratios to acquire MAP, SBP, and DBP. It is strongly emphasized that the amplitude of the oscillations is very sensitive to the pulse pressure (systolic pressure minus diastolic

pressure) and Arterial Stiffness (AS) and this sensitivity is a source errors in measurements [7, 9, 10].

1.2. Arterial Stiffness

Arterial Stiffness (AS) generally describes the extent of hardening of the inner wall of the artery, and so it is an indicator of vascular function and structure. The arterial system in terms of functionality and structure can be divided into two groups; (1) large arteries, which are the most elastic arteries, retain blood during systole and then release it within diastole. They provide steady blood flow towards smaller arteries, and (2) muscular arteries, which due to their composition are stiffer. These arteries regulate Pulse Wave Velocity (PWV) [4]. Therefore AS plays a crucial role in vascular hemodynamics.

AS is influenced by factors like age, BP, and atherosclerosis [11], and is quantified through a variety of indices as a function of pressure, diameter, volume, and PWV which is the inverse of Pulse Transit Time (PTT). Carotid-Femoral Pulse Wave Velocity (CFPWV) is considered as the most established technique for assessment of AS. CFPWV is the propagation speed at which the pressure wave moves between the carotid and femoral arteries. Although this indicator can be measured non-invasively, is highly reproducible, and is easily adapted for clinical use, specialized staff and equipment are required to perform it and properly locate transducers on the artery. Moreover, measurement techniques are time consuming [4, 12-15].

Imaging methods like ultrasound and Magnetic Resonance Imaging (MRI) are also used to evaluate AS, by measuring the maximum and minimum areas of vessels as a function of

pressure changes per cardiac cycle. Although these methods are non-invasive, the required equipment is quite expensive and not portable hence less applicable as a routine method [12].

Applanation Tonometry evaluates AS through recording a high fidelity pressure waveform above the carotid or radial artery. The artery is flattened via an external pressure which is equal to the intra-arterial pressure. The central pressure waveform is computed through a generalized transfer function. Central Pulse Pressure (CPP) is the summation of forward pressure waveform originating from heart contraction and reflected pressure due to impedance mismatch along arterial tree. As the artery stiffens, the reflected wave arrives back earlier to the aorta and then augments systolic pressure and lessens diastolic pressure. The augmentation index, which is the ratio between the first and second peaks of waveform, is used to evaluate AS [4, 12].

In Arteriography, as in the oscillometric method, the artery is occluded at a pressure level 35 mmHg above SBP. PWV is calculated as an indicator of AS by measuring the time difference between the pronounced peaks of the pressure waveform (first and second peaks) divided by distance. An advantage of arteriography is that it is obtained in one single location compared to the other PWV measurement techniques. Distance is found in regard to the possible location of the first reflecting point which is responsible for first peak, commonly jugulum – symphysis. Applying a pressure above SBP and wrapping cuff tightly for a short time makes patients uncomfortable. Moreover distance measurement is another limitation which is not accurate, and the patient should be completely motionless [16-18].

1.3. Motivation

Oscillometric blood pressure measurement has been becoming increasingly popular as it is easy to perform without the need for trained staff and as it is the most common technique incorporated in the automated commercially available devices [3]. The exact algorithms used in available commercial devices are usually not disclosed and so makes them difficult to validate in specific conditions. As a result, achieving a reliable and accurate measurement in a variety of conditions is still unsolved.

The oscillometric technique is less accurate in patients with stiffened arteries and high PP [19, 20]. Experimental ratios that are commonly used in existing oscillometric algorithms, and consequently SBP and DBP, are highly affected by AS [7]. The oscillometric method overestimates SBP and underestimates DBP compared to the sphygmomanometer based measurement in a normal healthy person and overestimates both SBP and DBP in individuals with stiffened arteries. These results confirm the dependency of BP estimation using the oscillometric method on AS [21]. As a result, in order to improve measurement accuracy, there is a strong need to develop a BP estimation algorithm that takes AS into account and is independent of any experimental ratios [3, 7, 9, 10, 19, 22, 23].

1.4. Objectives

In order to address the above-mentioned problem, a combined physiological-based model with the ability to quantify the vessel parameters and the incorporation of those parameters in BP measurement is proposed. Pulse Transit Time (PTT) is inversely related to the PWV which is an

indicator of arterial stiffness. PTT variation as a function of the cuff pressure is assessed with the aim of estimating arterial stiffness parameters. Afterwards, arterial stiffness values are fixed into a model of the Oscillometric Waveform Envelope (OMWE) which reduces the number of unknown parameters in the model. This helps achieve an accurate BP estimate. Mathematical-physiological based models are formulated according to the Lumen Area (LA) variation of vessel; the area through which blood passes in the artery. The proposed technique is independent of any experimental ratio which has been reported as one of the sources of BP estimation errors. To the best of our knowledge, no one has previously employed arterial stiffness measurement using Pulse Transit Time (PTT) combined with a model of the Oscillometric Waveform Envelope (OMWE), in a type of calibration and individualization of the sort recommended by American Heart Association Council on High Blood Pressure Research [3].

1.5. Thesis Overview

A comprehensive study of available methods for blood pressure estimation and arterial stiffness assessment is given in the Chapter 2. Based on the information provided in the second chapter, a novel technique of blood pressure measurement is proposed in Chapter 3. Chapter 4 shows results of the proposed method with a data set acquired from 10 healthy subjects. After that, Chapter 5 discusses the results, along with advantages and limitations of this work. To conclude, the last chapter provides a summary of the thesis, as well as its contributions, and potential future work.

Chapter 2. Background

2.1. Blood Pressure

Blood Pressure (BP) is the force exerted by the blood on the wall of vessels as it propagates through the arterial tree. When the heart ejects blood towards the periphery, the BP reaches its maximum, named Systolic Blood Pressure (SBP). On the other hand, Diastolic Blood Pressure (DBP) is related to the lowest amount of pressure, which occurs during heart relaxation, just before the next contraction. BP is recognized as a vital sign, providing us with a wealth of information about cardiovascular disease. It is usually reported as SBP over DBP, and both are clinically used to assess patients' health condition. The normal levels of SBP and DBP for adults are in the range of 120 and 80 mmHg, respectively [24, 25].

Accurate and reliable measurement of BP, an important diagnostic tool, is highly beneficial in cardiovascular risk prediction, diagnosis, and treatment [19, 22, 26]. It should be noted that there are several factors that might affect BP such as stress, sleeping, physical activity, smoking, alcohol, and nutrition. It is reported that even the time of the day can affect BP; for example; BP is typically lower in the morning than during the rest of the day [27, 28].

2.2. Blood Pressure Measurement Methods

As stated earlier, accurate BP estimation is very important for precise evaluation of the patient's health and for making significant treatment decisions [19, 22, 26]. In the following, the main blood pressure measurement techniques are discussed.

2.2.1 Invasive Method

The most accurate BP estimation technique is the direct invasive method (Intra-arterial measurement). The procedure is begun by inserting an arterial line, which is coupled with a pressure transducer, inside the artery. Beat-to-beat BP is monitored continuously for a long duration. This method allows physicians to access the BP waveform, and track any sudden changes in the cardiovascular system. It is beneficial for patients who are under intensive care at hospitals. High risk of infection, internal bleeding, the need for expensive equipment, and necessity of having trained personnel are drawbacks which discourage the use of this invasive measurement method [29, 30].

2.2.2 Noninvasive Methods

Noninvasive measurements are common in the doctor's office and have become increasingly popular in Home-Based Monitoring Systems (HBMSs). Ease of use and affordable equipment can compensate for their lower accuracy in comparison to the invasive method [29]. Noninvasive BP measurements are performed indirectly by recording the counter-pressure during the occlusion of a peripheral artery. The standard location for cuff placement is around the brachial artery in the upper arm, but some devices place the cuff around the wrist which is beneficial for very obese patients. The BP is sensitive to the location of measurement such that SBP increases and DBP decreases towards the periphery [31]. A brief description of three main non-invasive methods is given in next sections.

2.2.2.1 Palpation

The palpation method, which is mostly used in emergency situations, measures BP by placing a cuff over the brachial artery and feeling the radial pulse. The radial pulse is felt for a short period of time, until the cuff pressure reaches zero. The pressure at which pulse cannot be felt during inflation and can be felt again during deflation corresponds to the SBP .This technique gives us only an estimation of SBP. It can be performed quickly and the only requirement is a sphygmomanometer. The major drawback of this method is that the evaluation of DBP is impossible because we can only feel pressure exertion on the wall while it is at maximum and equal to the SBP [32].

2.2.2.2 The Auscultatory Method

The auscultatory method is considered as the gold standard of non-invasive measurements [3]. It was first introduced by Nikolai Korotkoff in 1905, at a scientific seminar of the Imperial Military Medical Academy [29, 33]. The necessities are the cuff, stethoscope, and one sphygmomanometer. The stethoscope is positioned at the elbow and the sphygmomanometer displays Cuff Pressure (CF) continuously during each measurement. The core of this technique is to identify acoustic sounds produced by blood propagation. The cuff is usually placed over the brachial artery and the pressure inside the cuff is increased to reach a level well above SBP, at which the artery becomes completely occluded. Then, deflation is started and pressure inside the cuff gradually decreases. At the time when blood begins to flow, the first sound corresponding to SBP is perceived. Sound related to blood flow can be heard during cuff deflation, but after a while it disappears. The last sound just before silence corresponds to DBP [3].

This method is highly sensitive to the noise and even moderate movements can cause unreliable estimation. Moreover, trained persons with good hearing are needed to identify onset and disappearance of Korotkoff sounds. Another limitation of the method is its inapplicability in HBMSs which are often important in patient care [3, 6, 7].

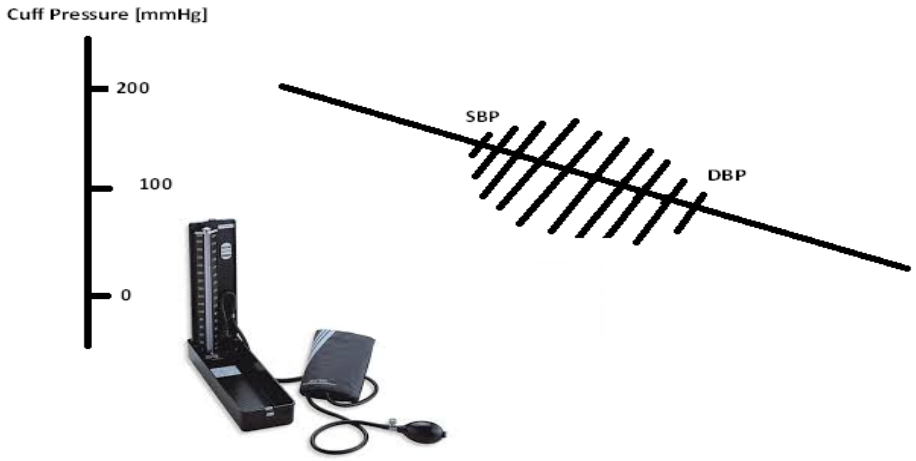

Figure 2-1. Auscultatory blood pressure measurement method. Systolic Blood pressure (SBP) is simultaneous with appearance of the first sound and Diastolic Blood Pressure (DBP) corresponds to the pressure at which silence occurs. The only requirements for this technique are a sphygmomanometer, stethoscope, and cuff [31].

2.2.2.3 Oscillometric Method

The oscillometric method is the most commonly-used technique in the automated non-invasive BP measurement devices [34], and so is widely used in HBMSs. It was first implemented by Marey in 1875, several decades before the discovery of the auscultatory method [35]. As pulsatile flow passes through an artery, it causes the wall of vessel to oscillate. These oscillations are transferred to the cuff that is placed over the artery.

The procedure is initiated by inflating the cuff to a pressure above SBP in order to occlude the artery. While the pressure is above SBP, small amplitude oscillations are transmitted to the cuff. As pressure is slowly released during deflation, oscillation amplitude increases until reaches its maximum when the cuff pressure is equal to Mean Arterial Pressure (MAP). MAP is defined as the average arterial pressure per cardiac cycle. As the cuff pressure decreases further to less than DBP, oscillation amplitude also decreases. SBP and DBP are usually determined by applying some experimentally-determined ratios (called characteristic ratios) to MAP and mapping back to the cuff pressure [36, 37].

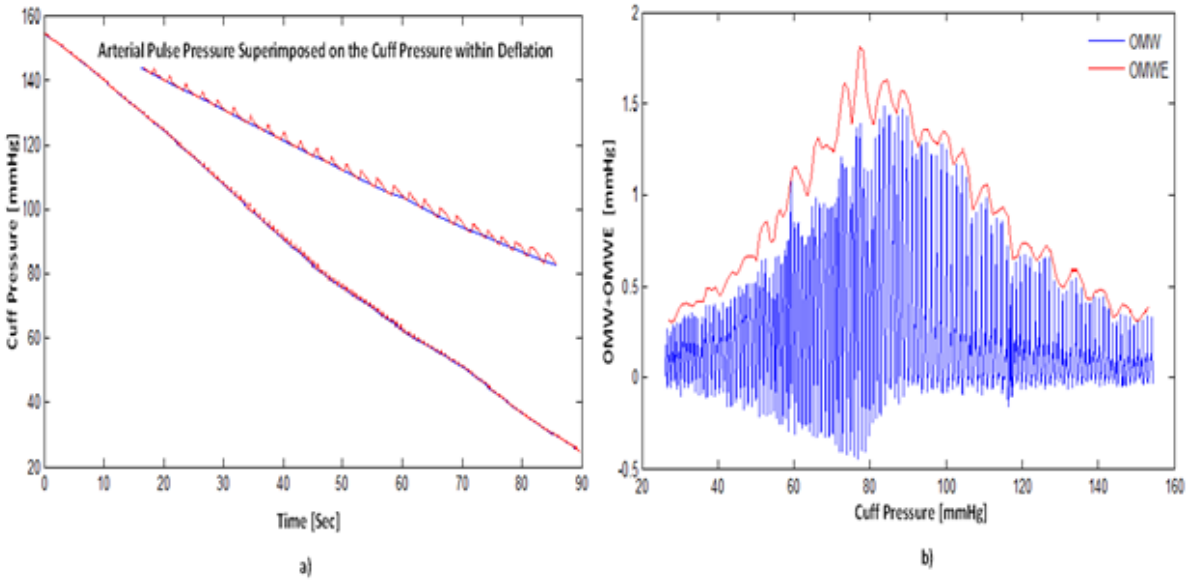

Figure 2-2. a) Representation of oscillometric technique a) Cuff is pressurized to a suprasystolic pressure level. Arterial pulse pressure, superimposed on cuff pressure, is recorded within deflation. b) Cuff pressure descending trend should be separated from signal (usually performed by filtering) to obtain Oscillometric Waveform (OMW) and the Oscillometric Waveform Envelope (OMWE) is usually found by subtraction between amplitude of peaks and troughs. Pressure at which oscillometric envelope reaches its maximum corresponds to the Mean Arterial Pressure (MAP). Afterwards, experimental ratios are applied on MAP to find the time locations of the SBP and DBP, and these are then determined by mapping back to the cuff pressure.

The major advantage of oscillometry is easy implementation in automated commercial devices. There is no need to have a trained observer and the method is less sensitive to external noise and movement compared to the auscultatory method [8]. Unlike the auscultatory method, MAP is the first parameter that is found and then SBP and DBP are estimated according to experimental ratios [4].

There have been occasional studies that have attempted to estimate the BP without using the commonly used experimental ratios. In one study, researchers have focused on the slope of oscillometric amplitude envelope to find SBP as a transition between different regions of oscillometric waveform envelope. Three regions with various slopes were found: (1) slope from beginning of deflation to Systolic (S1), (2) slope between SBP and MAP (S2), and (3) slope between MAP and DBP (S3). They have claimed that transition between S1 and S2 is SBP, with S2 less than S1. However, slope estimation is very sensitive to noise in practical situations and DBP was not distinguishable in this study [38].

It is established that any factors that could change Arterial Stiffness (AS) would consequently have an effect on the OMWE. These factors include: aging, cardiovascular disease, atherosclerosis [23].

2.2.3 Determinants of Oscillometric Method

It is known that BP measurement accuracy is subject to two types of errors; (1) errors owing to the measurement protocol (2) errors due to physiological variability within subjects [3, 28]. The first type of error can be reduced by training, using proper cuff, having correct cuff

placement, and having correct subject posture. The second type of error is more controversial, and so we will discuss it in more detail.

A variety of factors affect the accuracy of the oscillometric method including: vessel behavior during collapse, heart rate, waveform shape, and AS [7, 10]. It is found that Mean Arterial Pressure (MAP) is less affected by variation of AS while Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and consequently characteristic ratios are noticeably affected by AS [7, 39].

Furthermore, there is a tendency for overestimation and underestimation of SBP and DBP, respectively, in automated non-invasive devices compared to the sphygmomanometer. The inconsistency between the two automated devices and sphygmomanometers is even greater for some patients like diabetics who typically have AS [26]. In diabetic patients with stiffened arteries, there is overestimation of both DBP and SBP. The sensitivity of the oscillometric algorithm to AS arises from its dependence on the detected oscillations and pulse amplitude variations in the arteries [7, 9, 40].

As mentioned above, the mechanical properties of vessels play an essential role in determining BP. Therefore, there is increasing interest in exploring their role in the oscillometric algorithm. There is an imperative need to provide a method which takes AS into consideration and provides individualized BP measurements [19]. In the next section, a comprehensive review of AS, its determinants, and evaluation techniques is given.

2.3. Arterial Stiffness

Arterial stiffness (AS) in general is defined by how much the inner wall of an artery is stiffened. It is recognized that AS is affected by a large number of factors like age, hypertension, atherosclerosis, diabetes, hypercholesterolemia (high level of cholesterol in blood), and end-stage renal failure [11, 12]. In order to appreciate arterial stiffness fully, a brief description of circulatory system and arterial tree is given first.

2.3.1 The circulatory System

The circulatory system has a vital influence as blood and nutritional supplier for the whole body. This complicated system is composed of several components including, (1) Heart, (2) arteries, (3) capillaries, and (4) veins. The heart acts as a key component in the circulation system, as it sends out blood towards organs through the arterial tree. Oxygen, nutrients, and waste products are exchanged between capillaries and tissues. At the end of the cycle, non-oxygenated blood returns to the heart through the veins. An artery is considered as a viscoelastic tube composed of three layers: intima (I), media (M), adventitia (A). I is the innermost layer which consists of one layer of endothelial cells and is in direct contact with blood flow. M or tunica media is the middle layer of arteries, made up of smooth muscle cells, elastic, and collagen fibrils. Muscle cells are responsible for vessel constriction. A is the outermost layer, and contains connective tissues and bundles of collagen fibrils, which preserve the shape of the vessel. Two determinant factors affecting elastic and collagen structures are age and applied force. With advancing age, elastic fibers become thinner or fragmented resulting in the generation of new collagens. As applied force rises, elastic fiber deteriorates, and therefore more collagen is produced in order to retain the wall shape [41, 42].

The arterial system in terms of functionality can be divided into two groups; (1) The large elastic arteries, and (2) Muscular arteries. Large elastic arteries (such as the pulmonary trunk and brachiocephalic artery) act as reservoirs, and store blood during systole and release it during diastole to keep a steady flow of blood to peripheral tissues. As can be seen in Figure 2-3, the tunica media is mostly composed of elastic fibers in large arteries. Muscular arteries, on the other hand, have tunica media which is predominantly constituted of smooth muscle cells, and so are capable of adjusting muscular tone to control velocity of pulse pressure [41, 43].

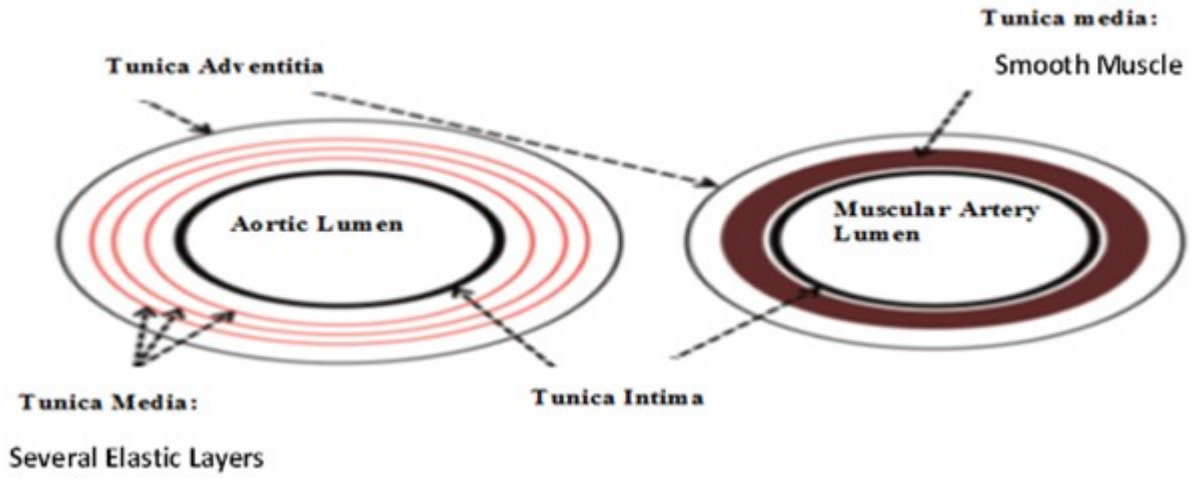

Figure 2-3. Comparison between elastic and muscular arteries. As can be seen Tunica Media in aorta is composed of several elastic layer while Tunica Media in Muscle artery is mostly composed of smooth muscle [43].

The buffering capacity of large arteries is critical to delivering steady blood flow to the periphery. Hales was the first person who measured BP and recognized the pulsatile feature of blood (1735). He also proposed the association between stiffness of large arteries and pulsating characteristics which were later modeled using the Windkessel model [41, 44, 45].

2.3.2 Mechanical Principle

Blood flow in arteries is governed by physical structure and applied forces in vessels. In this section, we aim to outline properties and fundamental laws governing elasticity of a material. Considering a material under external or internal force, we can express two types of material in terms of response after load removal: elastic and plastic [41].

Elastic substances regain their original form while plastic substances maintain a deformed shape. Force per unit area is called "stress" which leads to distortion and the amount of deformation relative to the original form is named as "strain". Young's modulus is the ratio between stress and strain. The elasticity of a material is largely determined by amount of applied force. When it comes to large forces, then no material could be considered as purely elastic substance [41].

2.4. Indices of Arterial Stiffness

A variety of indices have been introduced to evaluate arterial stiffness. In order to comprehend them; some basics need to be known about waveform propagation within arteries. As the pressure wave propagates away from large arteries, it encounters mismatch impedance owing to the different mechanical properties of the arterial tree at different locations. Once the original wave runs into an impedance mismatch and discontinuity in the periphery, two pressure waves are produced: (1) The transmitted wave (TW), and (2) The reflected wave (RW). TW keeps moving towards in the same direction as the original wave but RW goes backward to the heart in the opposite direction. RW should return to the heart in the late systolic or early diastolic phase for a normal subject in order to provide enough blood flow to the coronary arteries. As

arteries stiffen, variation in the reflected wave and transmitted wave result in inappropriate timing of reflected wave and increasing risk of cardiovascular disease [46].

If the reflected wave dose not return in a timely manner, then central systolic pressure (SBP in aorta) increases. Increase in central systolic pressure, which supplies cerebral blood flow, can cause a stroke, higher Left Ventricle Load (excessive pressure load on the left ventricle which makes heart work more and consequently hypertrophy of left ventricle), and reduction in the blood flow towards coronary arteries [47].

As mentioned earlier, the reflected wave plays a crucial role in the cardiovascular system and is considerably affected by arterial stiffness. The reflected wave can be investigated directly by two arterial stiffness evaluation indices; (1) Pulse Pressure (PP), and (2) Augmentation index (AI).

2.4.1 Pulse Pressure (PP)

Pulse Pressure (PP) is defined as the difference between SBP and DBP. PP is recommended to be obtaiend clinically by sphygomanometer which has been found to be more accurate than automated oscillometric devices [3]. This measure is an indirect indicator of pulsatile pressure, considering MAP as the non-pulsatile part [48]. PP is determined mainly by cardiac output, large artery stiffness, and wave reflection [43, 48, 49]. PP variation according to age is demonstrated in Figure 2-4.

It should be pointed out that under age 50s, DBP is better indicator of coronary heart disease than PP. DBP reaches a plateau around the age of 50-60 years. Afterwards, it starts to

decrease with advancing age. PP enhancement is noticeable in the last decades of the life [49, 50].

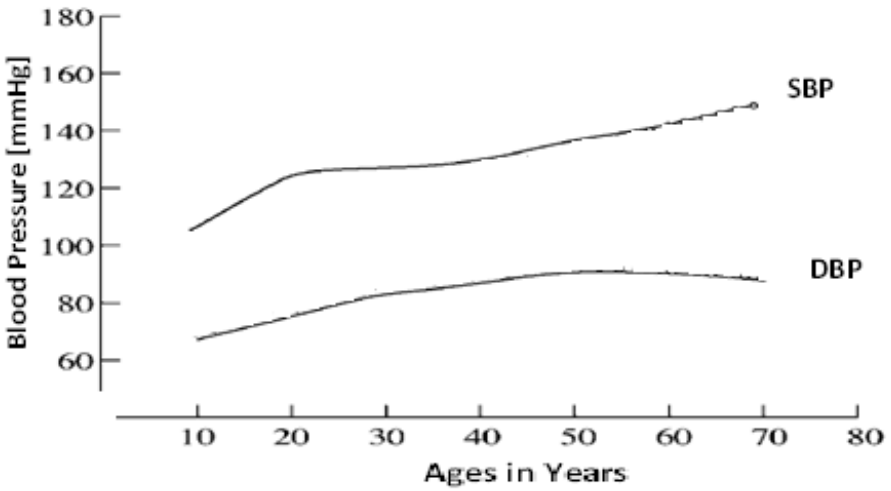

Figure 2-4. This graph illustrates relation between pulse pressure and age, where the two lines indicate SBP and DBP. Increase in pulse pressure in the last decades of life is significant [50].

It has been established that Central Pulse Pressure (CPP, commonly aortic pressure) is different from Pripheral Pulse Preesure (PPP, comonly brcahial artey) in the young and middle-aged population. This difference can go up to 20 mmHg for individuals with the same PPP. CPP and PPP have less differnece in infants and elderly due to the short body length and stiffened artery, in each group respectively. CPP provides an estimation of the systematic AS. There are some generalized transfer functions that can convert PPP into CPP with the assumption of the same arterial properties in all individuals, which is not accurate [51].

CPP is a well-known independent marker of hypertrophy and Intima Media Thickness (IMT) which is one of the major causes of atherosclerosis. IMT is the thickness of the inner two layers of the carotid artery, the intima and media. There is no doubt that PPP as a strong

predictor of cardiovascular mortality could help in making decisions in therapy but it should not be used as the only evaluation measure [52, 53]. Interestingly, it has been found lately that AS does not change necessarily in parallel with CPP. Inflammation alters stiffness by directly changing wall characteristics of arteries, without changing CPP [54].

2.4.2 Augmentation Index

Reflected waves from peripheral arteries enhance pressure towards coronary arteries. This enhancement is quantified by the augmentation index (AI). Upon arrival of the reflected wave, the first shoulder in the wave is produced and aortic pressure starts to rise till it reaches its highest peak. Blood flow begins to lessen untill aortic valve is closed. Valve closure is responsible for the second shoulder. The augumentation index as a percentage of pulse pressure is quantified by (ΔP/P) , as can be seen in Figure 2-5. When an artery is stiffened, the reflected wave tends to return earlier than in a normal artery. Consequently, SBP will be higher and this leads to a bigger augmentation index.

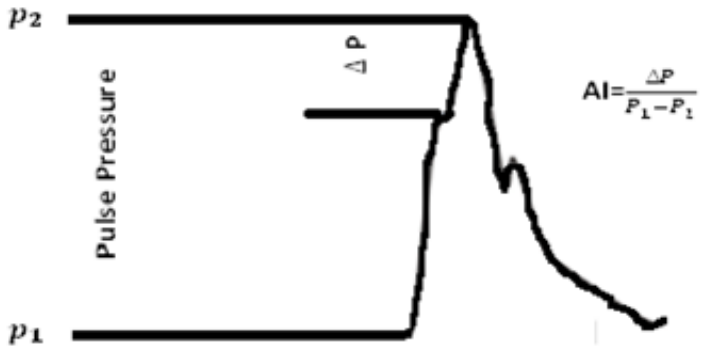

Figure 2-5. Augmentation Index (AI) as a well-known indicator of arterial stiffness is derived mathematically. AI is a presented as a percentage of Pulse Pressure (PP) [43].

AI is strongly correlated with heart rate, Pulse Wave Velocity (PWV) (which is described in the follwing section), geometry, and tone of arteries [43, 47]. AI increases until age 50, hence it is a good indicator of arterial stiffness for young patients. Radial AI has shown acceptable correlation with aortic AI [55]. This index has been employed in devices like the Sphygmocor (AtCoreMEDICAL, West Ryde NSW, Australia), and the Arteriograph (TensioMed, Budapest, Hungry) [16-18].

2.4.3 Pulse Wave Velocity (PWV)

Pulse wave velocity (PWV) is simply defined as the propagation speed of the pressure waveform along the arterial tree. It has been widely used as an effective indicator of AS, and recommended by the European Society of Cardiology (ESC) and European Society of Hypertension (ESH) for the management of arterial hypertension [12, 56, 57].

Carotid-Femoral PWV (CFPWV) is considered as the most established technique for AS determination [58, 59]. The waveform at the carotid artery is recorded by applanation tonometry while a cuff is used on the femoral artery to register the waveform. In Applanation tonometry carotid artery is compressed in such a way to make it flat and then internal pressure and external applied pressure are equal. Applntation tonometry provides a high fidelity pressure waveform. However, this method needs a trained operator [12]. CFPWV greater than 12 m/s for middle-aged hypertensive patients is regarded as an indicator of high cardiovascular risk and damage [60]. In another study, based on a 20% shorter anatomical distance than direct carotid-femoral distance, the threshold is suggested to be 10 m/s [61]. The Moens-Kortweg equation represents the relation between PWV and elasticity:

$$PWV = \sqrt{[Eh/2\rho R]}$$ Equation 2-1

Where h denotes arterial wall thickness and R is radius of the artery. E and ρ are Young's modulus of arterial wall and blood density, respectively.

Experts believe AI and PP are surrogate markers of AS, but PWV can be considered as a direct indicator. There are a variety of devices available to measure PWV, like Sphygmocor (AtCoreMEDICAL, West Ryde, NSW, Australia) and Complior (ALAMMEDICAL, Paris, France), with different applied methods, which leads to variation in the result even for the same patient. Consequently, they cannot be used interchangeably [44].

PWV-based methods assume a homogenous structure in the arterial tree whereas there is always reflection due to mismatch impedance at structural discontinuities. In one study, it is recommended to limit wave reflection effects on PWV by using troughs in the waveform to calculate propagation time and PWV. Troughs occurs in the early diastolic phase when there is a minimum amount of reflection from peripheral sites [62].

PWV is commonly obtained using two regions of arterial tree possessing dissimilar vessel wall characteristics: Carotid and femoral or Carotid and brachial. The research conducted by Mitchell et al. within the Framingham Heart Study revealed interesting results, can be seen in next Figure. This study was conducted on the middle-aged and elderly population. They demonstrated that CFPWV is significantly affected by age while CBPWV changes smoothly with advancing age. This figure shows that CFPWV is lower than CBPWV in individuals aged fewer than 50. Central arteries become stiffer with advancing age in comparison to peripheral

ones. Central and peripheral stiffness were compared according to variation of CFPW and CBPWV [63].

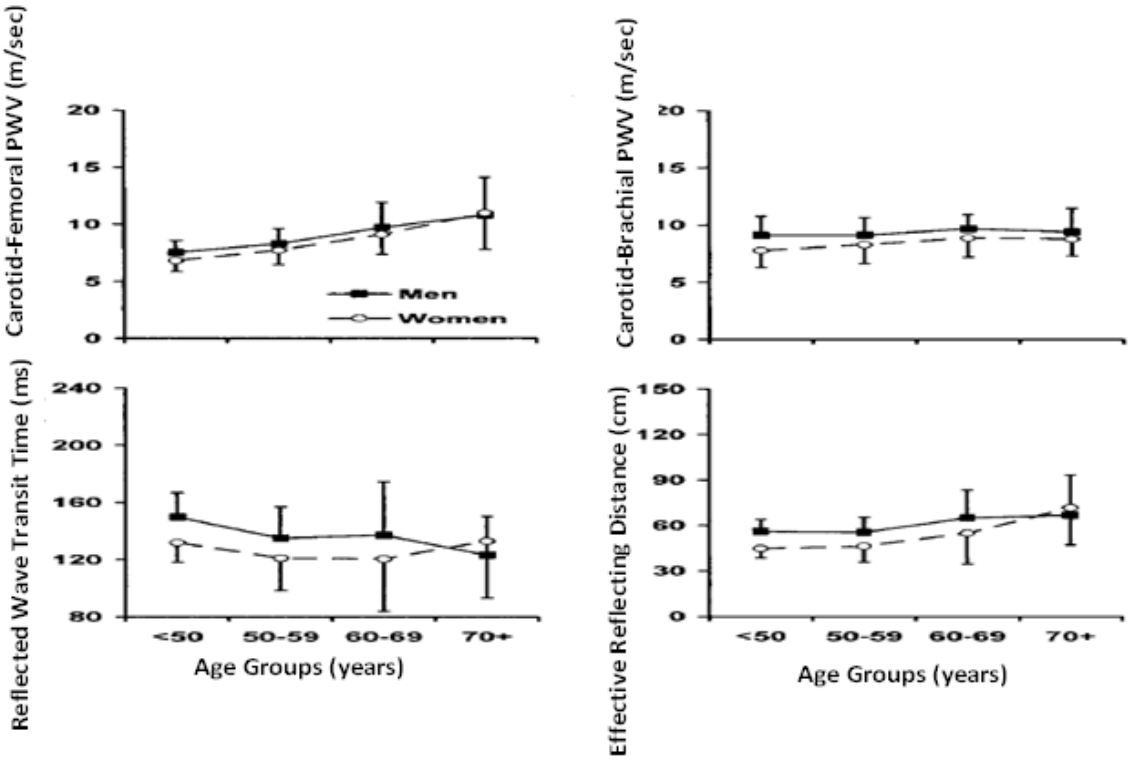

Figure 2-6. Carotid-Femoral Pulse Wave Velocity (CFPWV) is significantly changing with age while Carotid-Brachial Pulse Wave Velocity (CBPWV) is less sensitive to the age variation. For subjects aged more than 60s, CFPWV becomes equal or more than CBPWV and Pulse transit time is decreasing for population aged less than 60s. After 60s, reduction in Pulse Transit Time (PTT) is less due to shifted mismatch impedance point (closer to peripheral) [63].

Figure 2-7 represents forward pressure, reflected wave (RW) and augmentation index changes according to age. The RW diminishes with advancing age due to reduced impedance mismatch [63].

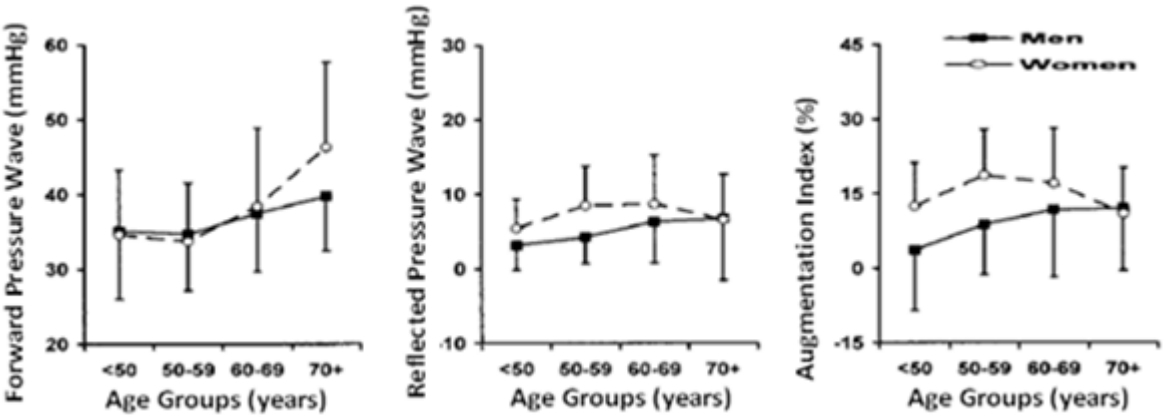

Figure 2-7. This figure illustrates forward pressure wave, RW and AI variation according to age [63]. Due to having more stiffened arteries in central, impedance mismatch is less and consequently more forward wave, less RW and less AI for older population.

2.4.4 Brachial-ankle Pulse Wave Velocity

Brachial-Ankle Pulse Wave Velocity (BAPWV) is obtained simply by placing four cuffs around peripheral arteries in the four extremities. This index is well correlated with aortic PWV. The longer pathway used to obtain this index has as its advantage that it can reflect more accurate vessel condition. Peripheral arterial disease might influence BAPWV more than aortic PWV. In comparison with CFPWV, the patient doesn't need to remove clothing and there is no need to use applanation tonometry, which clinicians can find difficult [64].

2.4.5 Pulse Transit Time (PTT)

Pulse Transit Time (PTT) is pulse propagation time between two points, usually the heart and a site in the periphery. Extensive research has confirmed the relation between PTT and AS. PTT decreases considerably as an individual gets older [65-68]. We have already discussed how PWV is related to AS, and that PTT inversely related to PWV.

$$PWV = \frac{L}{PTT}$$ Equation 2-2

where L indicates length of the artery.

In order to calculate PWV, length should be manually measured or estimated based on height and weight. Length measurements are less accurate for older subjects because their aorta becomes sinuous due to atherosclerosis. Errors in estimating propagation distance can give imprecise information about cardiovascular condition [69]. Our group presented a PTT-based physiological model which estimates BP independent of experimental ratios. This method has the potential to quantify AS using PTT-CP curve [70], as is fully described in the following chapter.

2.4.6 Cardio-Ankle Vascular Index (CAVI)

The Cardio-Ankle Vascular Index (CAVI) is a measure which employs logarithmic changes of SBP over DBP and variation of distensibility (relative change in diameter for a given pressure change). AS sometimes shows variation only due to momentary changes in BP, and not due to decreased or increases elasticity of vessel wall. CAVI is claimed to be theoretically independent of this BP variation due to the application of logarithmic ratio. It is calculated as follows [62]:

$$\frac{D}{\Delta D} = \left(\frac{2\rho}{\Delta P}\right) * (PWV^2)$$ Equation 2-3

where D is the diameter of artery , ΔD is variation in diameter, ρ is blood density and ΔP is pulse pressure (difference between systolic pressure and diastolic pressure). PWV represents pulse wave velocity between aortic valve and ankle.

β is a local stiffness parameter in which variation in diameter according to arterial pressure changes is assessed. However, using this index is limited because it needs sonographic equipment to measure relative diameter changes.

$$\beta = \frac{ln\frac{P_{sys}}{P_{Dia}}}{\frac{D_s - D_d}{D_d}}$$ Equation 2-4

where D_s is diameter in systolic, D_d is diameter in diastolic, P_{Sys} is systolic pressure, and P_{Dia} is diastolic pressure [62].

$$CAVI = a\beta + b$$ Equation 2-5

in which a and b are constants.

Substituting equation (2.3) and (2.4) into (2.5) gives us equation (2.6) [62].

$$CAVI = a\left[\left(\frac{2\rho}{\Delta p}\right).(ln)\frac{P_{sys}}{P_{Dia}}.PWV^2\right] + b$$ Equation 2-6

CAVI has shown its potential in assessing AS for patients who have atherosclerosis, coronary heart disease, diabetics, and hypertension [62].

2.4.7 Oscillometric-Based method

Automated oscillometric BP devices are widely used in home monitoring and clinical environments. This simple and broadly available approach for assessing BP can be used for daily monitoring of hemodynamic parameters such as large arteries stiffness. On the other hand, the arterial stiffness might possibly be used as an approach for the validation and calibration of these devices [71-73]. Oscillometric-based methods can be divided into two groups according to the applied algorithm: (1) mathematical-based models, and (2) waveform feature extraction based methods.

2.4.7.1 Mathematical-based Model

It is well-established that the relation between cuff pressure as it decreases and the corresponding arterial volume can be modeled as a sigmoid curve, where the slope of this sigmoid curve is a function of arterial stiffness [7, 8, 22]. The slope of this curve is regarded as an indicator of arterial stiffness in such a way that for a less stiffened artery, the slope is steeper [71]. Studies on isolated arteries have also demonstrated dependency of the volume-pressure curve on the arterial stiffness [74, 75], where volume can be estimated from oscillometric waveform.

In a recent study [10], the volume-pressure relationship for negative and positive transmural pressure was evaluated. Normal AS indices for negative transmural pressure, called a, and positive transmural pressure, called b, were determined as 0.11/mmHg and 0.03/mmHg respectively. The role of these two parameters will be described in detail in Chapter 3. The volume-pressure relationship for different levels of arterial stiffness is illustrated in Figure 2-8.

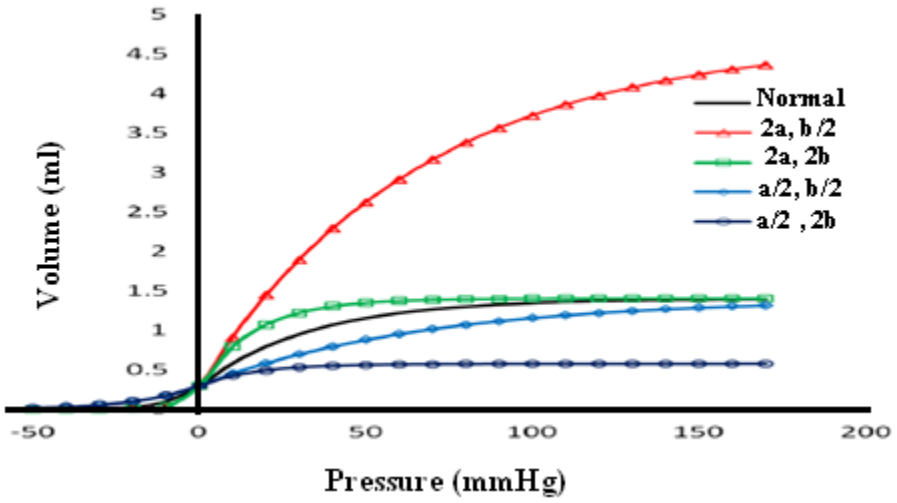

Figure 2-8. Volume-pressure relationship is strongly affected by AS. Increasing a/b ratio results in a more elastic artery while decreasing means more stiffened arteries. As a/b is increasing, maximal distension goes up. These parameters will be described more in Chapter 3 [10].

2.4.7.2 Waveform Feature Extraction

This method relies on the amplitude of the oscillometric waveform. In one study, the maximum amplitude of the oscillometric envelope and 80 percent of maximum during deflation and inflation are located. The pressure difference between these two points is regarded as arterial stiffness. It is found that a stiffened artery has more pressure difference between these two above mentioned points than a non-stiffened artery in normal individuals. Amplitude sensitivity to the artifacts like patient motion and irregularity due to cardiovascular disease is reduced by employing recursive regression [39].

2.4.8 Non-Invasive Vascular Ultrasound

Ultrasound is known as one of the most widely and clinically accepted methods to measure arterial dimension changes, blood flow, and wall thickness using high frequency acoustic waves [41, 71, 76].

The ultrasound method has been applied for assessment of the stiffness of arteries such as: carotid, femoral, brachial, and abdominal arteries. The maximum and minimum of arterial diameter per cardiac cycle, within SBP and DBP, are found, and BP is measured at the same time. Diameter–pressure dependent variations are employed to find arterial wall characteristic [50, 77].

This technique has the advantage of not involving any mathematical model. However, due to the low resolution of the video-image analysis, it is often difficult to find small variations in arterial diameter. Therefore, Magnetic Resonance Imaging (MRI) is occasionally used as an alternate imaging method. However, because of the high operating costs and training that is required, these approaches are not in common use [77].

2.4.9 Variability of Arterial Stiffness Indices

A variety of indices have been used in the assessment of the arterial wall, although it was out of scope of this thesis to detail them all. Several indices that have not been discussed above are summarized in the next table.

Table 2-1. A summary of several arterial stiffness indices that have not been described in previous sections [12].

Index	Definition
Elastic Modulus	Pressure required to reach 100% stretch from resting diameter ($\Delta P*V/\Delta V$) in mmHg
Young's modulus	Pressure required to reach 100% stretch from resting diameter per unit area; Elastic modulus per unit area ($\Delta P*V/\Delta V*h$) in mmHg/cm
Distensibility	Relative change in diameter for a given pressure change; inverse of elastic modulus $\Delta D/(\Delta P*D)$ (1/mmHg); a fraction of arterial compliance; Recommended to be used when vessels of different size are under investigation.
Arterial Compliance	Absolute diameter change for a given pressure change ($\Delta D/\Delta P$) in cm/mmHg

Chapter 3. Methodology

This chapter explains the proposed blood pressure measurement technique, which combines two models, one based on the Oscillometric Waveform Envelope (OMWE) and another based on the Pulse Transit Time (PTT). It starts with description of equations governing vessel behavior under external pressure, which considers arterial stiffness and its effects on the oscillometric waveform. Afterwards, a model of the OMWE is described which is based on the arterial Lumen Area (LA) variation as a function of the applied pressure that incorporates Arterial Stiffness (AS). A model of the PTT, which gives us the possibility of arterial stiffness estimation and incorporation of this estimate into the OMWE model, is fully described. Details of the study population, which is used to test the performance of the proposed technique, are given. Experimental procedures, which include: signal registration by a prototype device and data analysis, are also described.

3.1. Arterial Stiffness

The accuracy of noninvasive blood pressure measurement devices is influenced by the mechanical properties of vessels and by the pulse pressure. Several theoretical studies have confirmed the dependency of the oscillometric waveform on Arterial Stiffness (AS) [22, 36, 78, 79]. It is found that as the arteries stiffened, the characteristic ratio for SBP increases while DBP is less affected, resulting in 20-50% of the error [8]. Pulse pressure is also found as a strong factor affecting the oscillometric waveform in such a way that as pulse pressure increases, the characteristic ratio for both SBP and DBP decreases. Pulse pressure is also affected by arterial

stiffness, whereby as artery stiffness increases, pulse pressure increases especially for elderly population [8]. Considering both pulse pressure and arterial stiffness, as a person gets older and arteries stiffen and pulse pressure increases, there is possibility of having overestimation of SBP and DBP [8]. An experimental procedure has been performed on diabetic patients who possess stiffened arteries, and overestimation of SBP and DBP has been reported with automated oscillometric devices [21]. One study has formulated the error and its dependency on arterial stiffness as follows [22]:

$$E = \left(k + \frac{b}{a-b}\right) \Delta P \qquad \text{Equation 3-1}$$

where E is error, a and b are stiffness indices measured in $mmHg^{-1}$ and which are used in our technique (as described below), ΔP is pulse pressure difference between SBP and DBP, and K is a shape index based on MAP, SBP and DBP defined as:

$$k = \frac{p_m - p_d}{p_s - p_d} \qquad \text{Equation 3-2}$$

where p_m is mean arterial ressure , p_d is diastolic blood pressure and and p_s is systolic blood pressure.

Reducing errors relatd to variation in arterial stiffness is the focus of our work. In order to improve blood pressure estimation accuracy, it is of crucial importance to involve arterial stiffness in the blood pressure measurement.

It has been found by experimental and theoretical analysis that the Lumen Area (LA), which is the cross-sectional arterial area through which blood passes, is highly dependent on the stiffness of arteries. As the artery stiffens, more pressure is needed to make small changes in lumen area. The slope of the arterial lumen area-cuff pressure exponential curve represents arterial stiffness [7, 22, 36, 71]. As mentioned in the previous chapter, studies on isolated arteries have also confirmed the dependency of the lumen area-pressure curve on arterial stiffness [74, 75].

As mentioned in Section 2.4.3, Pulse Wave Velocity (PWV) is a strong predictor of arterial stiffness. The Bramwelll and Hill equation has shown dependency of PWV on volume variation according to the applied pressure on the vessel [80] as formulated in Equation 3-3:

$$PWV \propto \frac{dV}{dP} \qquad \text{Equation 3-3}$$

where $\frac{dV}{dP}$ is the variation of volume as a function of the pressure.

The volume is the product of multiplication between the cross-sectional area (Lumen Area) and length of the artery. Since we are investigating signals on only one segment of the artery (beneath the cuff), the length of the artery remains the same and the volume is only affected by the cross-sectional area (lumen area). Therefore:

$$\frac{dV}{dP} \propto \frac{dA}{dP} \qquad \text{Equation 3-4}$$

where $\frac{dA}{dP}$ is lumen area variation as a function of the applied pressure.

The lumen area is modeled using an exponential equation for both positive and negative transmural pressures [81]. The slopes of these equations are regarded as arterial stiffness. The model is expressed as follows:

$$A(t) = \begin{cases} A_0\, e^{a\, p_t(t)} & p_t(t) \ll 0 \\ A_m + (A_0 - A_m)e^{-b p_t(t)} & p_t(t) \gg 0 \end{cases} \qquad \text{Equation 3-5}$$

where A(t) represents lumen area, A_0 is lumen area when transmural pressure is zero, A_m is lumen area when the vessel is entirely distended, and a and b are arterial stiffness parameters. These two parameters are measured in $mmHg^{-1}$while the units of A_0 and A_m are cm^2.

The Oscillometric Waveform Envelope (OMWE) is the main focus of the oscillometric technique; consequently, a model of OMWE that is based on lumen area variation gives us the possibility of taking into account the values of arterial stiffness. The OMWE model includes five parameters: SBP, DBP, MAP, A_0, A_m , and the two arterial stiffness parameters. This work has been conducted by a member of our team, and is described in more detail below [82].

In order to fix arterial stiffness values in the OMWE model, we need to estimate arterial stiffness values prior to blood pressure estimation. Since, the PTT is inversely related to PWV and PWV has been shown according to Equation 3-3 and Equation 3-4 to be related to the lumen area-cuff pressure variation, a model of the PTT based again on the lumen area-cuff pressure variation is used to first estimate the two arterial stiffness parameters. Work on this model has

also been conducted by a member of our group and is described in more detail below and in [70]. In this thesis, we have proposed a new method that is based on the combination of the two aforementioned models, since, they are both based on the same exponential model (Equation 2-5). A summary of the method proposed in this thesis is given in Figure 3-1.

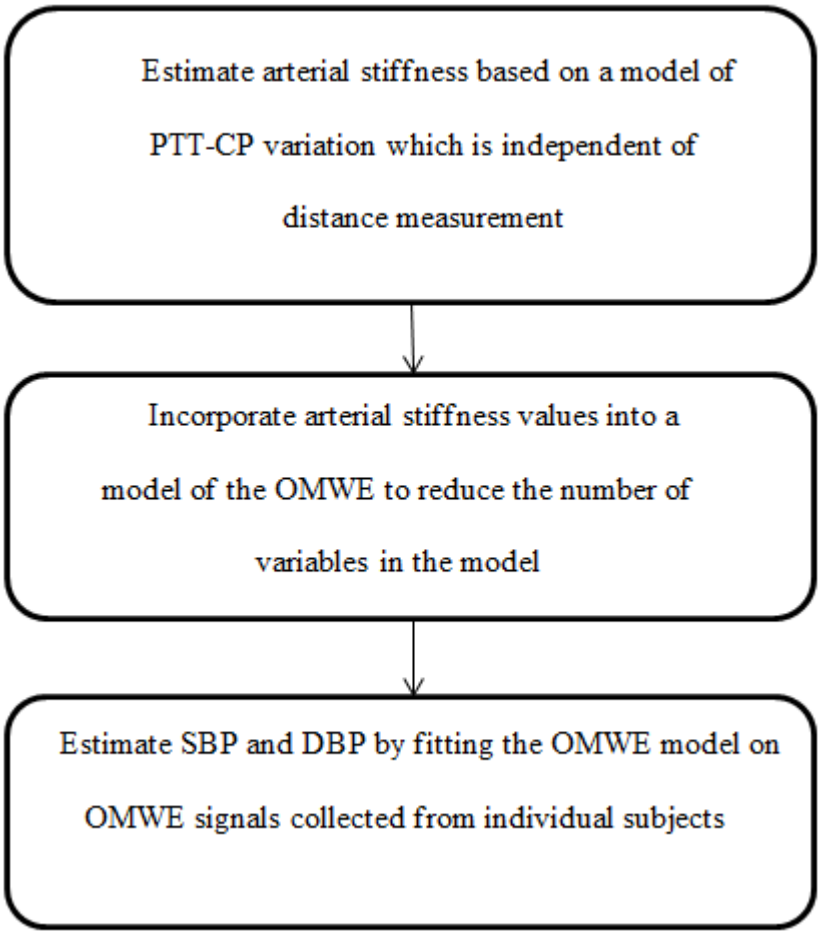

Figure 3-1. A summary of the work presented in the thesis, which derives from arterial stiffness being one of the determinant factors of oscillometric method and its governing equation. This helps to estimate arterial stiffness and find appropriate model for blood pressure estimation.

Based on the above-mentioned discussion, the two important signals that are employed in this proposed techniques are: (1) Oscillometric Waveform (OMW) (2) Electrocardiogram (ECG). First, Pulse Transit Time (PTT) is obtained using ECG and OMW. Afterwards, arterial stiffness indices are estimated by curve fitting on the PTT. Arterial stiffness estimation is then fixed into a model of Oscillometric Waveform Envelope (OMWE) to improve the accuracy of Blood Pressure (BP) estimation.

3.2. Transmural Pressure

The interaction between the Cuff Pressure (CP) and arteries is of great importance in BP estimation. In oscillometric methods, the cuff is placed over the brachial artery and inflated to a supra-systolic pressure level. Afterwards, the cuff is deflated to reach a sub-diastolic pressure level. Assuming an artery without an attached cuff, there is only internal arterial pressure exerted on the artery wall. Placing a cuff over the brachial artery produces a counter pressure in the opposite direction of internal pressure, as shown in Figure 3.2.

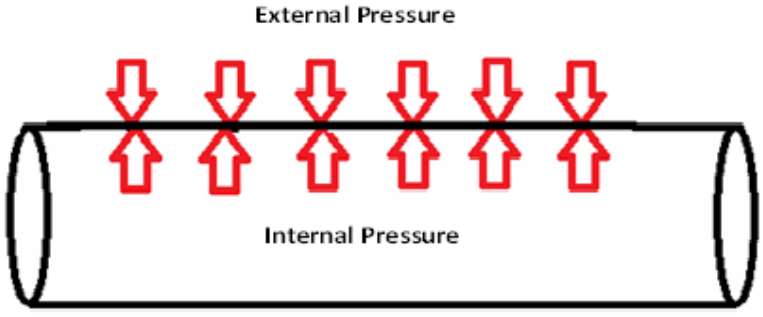

Figure 3-2. External and internal pressures are applied on the wall of the artery.

The transmural pressure is defined as the difference between the external applied pressure and intra-arterial pressure:

$$P_t(t) = P_a(t) - P_c(t) \quad \text{Equation 3-6}$$

where t indicates time, P_t represents transmural pressure, P_c is cuff pressure and P_a is intra-arterial pressure.

Considering a linear deflation over time, CP is formulated as:

$$P_c(t) = SSP - r.t \quad \text{Equation 3-7}$$

where r is deflation rate and which is assumed to be a constant between 1 and 4 ($\frac{mmHg}{Sec}$). SSP (Supra Systolic Pressure) is the pressure at which deflation is started [83].

3.3. Lumen Area (LA) model

Arteries are composed of the Lumen Area (LA) through which blood passes and the arterial wall which is composed of three layers, described previously in Section 2.3.1. LA varies in accordance with internal pressure and applied external pressure (i.e. with transmural pressure). When no external pressure is applied, LA is small at diastolic pressure and reaches its maximum area during systolic pressure. When external pressure is higher than internal pressure, the vessel almost or fully collapses [13, 84]. The brachial artery, as the standard location for the cuff placement, undergoes complete collapse, partial collapse and then recovery in LA during application of the oscillometric method [10, 85]. It has been established that the effect of CP on

the LA varies significantly between normal subjects and hypertensive patients in a way that lumen area-pressure curves are shifted towards larger pressures for hypertensive patients. As artery is stiffened, more pressure is needed to make lumen area smaller, as can be seen in Figure 2-8 [10].

As discussed in the previous chapter, arterial stiffness is significantly associated with diameter variation and consequently lumen area variation. The behavior of arteries at different levels of pressure gives us important information about the vessel's state of health. While instantaneous assessment of internal pressure for a short period of time is not currently possible noninvasively, employing a cuff gives us the ability to investigate lumen area variation for each level of applied cuff pressure.

Lumen area variation will affect the cuff volume and produce oscillometric waveform oscillation. Some researchers have introduced the exponential function to model the non-linear relationship between lumen area and cuff pressure for positive transmural pressures [75, 86].The model expressed in Equation 3-5 is used here to drive the equation for Oscillometric Waveform (OMW) [81], and it is shown here again to avoid any confusion.

$$A(t) = \begin{cases} A_0\, e^{a\, p_t(t)} & p_t(t) \ll 0 \\ A_m + (A_0 - A_m) e^{-b p_t(t)} & p_t(t) \gg 0 \end{cases} \qquad \text{Equation 3-8}$$

where A(t) is lumen area, A_0 is lumen area when transmural pressure is zero, A_m is lumen area when vessel is entirely distended, and a and b are arterial stiffness parameters measured in $mmHg^{-1}$and A_0 and A_m are measured in cm^2.

This model has been used extensively in the oscillometric technique to investigate the Lumen area-Cuff pressure dependency [8, 10, 87]. The Lumen Area (LA) can be used interchangeably with volume, which is the product multiplication of lumen area and artery length, because during deflation, the length of the artery is constant and only lumen area is changing. In order to have a differentiable equation in zero transmural pressure, the following relationship should be valid between a and b [88].

$$a = b\left(\frac{A_m}{A_0} - 1\right) \qquad \text{Equation 3-9}$$

Equation 3-8 of Lumen Area (LA) has been used to model the Oscillometric Waveform Envelope (OMWE) such that arterial stiffness is taken into account as one of the determinant factors. This model is described in the following section.

3.4. Oscillometric Waveform (OMW) Model

The Oscillometric Waveform (OMW) elicited from the cuff is directly proportional to the lumen area variation [8, 36, 89-91]. It is assumed that the tissue under the cuff is almost incompressible so LA oscillations are transferred to the cuff. Researchers have demonstrated strong similarity between OMW and LA oscillations [8, 36, 90, 91]. LA oscillations are

commonly extracted by applying a high–pass filter with cut-off frequency of 0.3 Hz to the recorded CP signal [36]. The Lumen Area (LA) consists of the combination of two main components; (1) a slow-varying component mainly due to the cuff pressure deflation, and (2) oscillations as a result of variations of arterial pulse pressure per cardiac cycle:

$$A(t) = \tilde{A}(t) + \bar{A}(t) \qquad \text{Equation 3-10}$$

where $\tilde{A}(t)$ represents lumen area oscillations and $\bar{A}(t)$ is the slow-varying component.

As mentioned earlier, OMW is directly proportional to the lumen area oscillations as follows:

$$OMW(t) \propto \tilde{A}(t) \qquad \text{Equation 3-11}$$

Therefore:

$$OMW(t) = \varphi\,(A(t) - \bar{A}(t)) \qquad \text{Equation 3-12}$$

where φ is a proportional factor.

A model of OMW is derived based on the lumen area function. Slow-varying components which originate from cuff deflation can be obtained by setting intra-arterial pressure equal to Mean Arterial Pressure (MAP) (non-pulsatile part) in Equation 3-8 which results in eliminating pulsatile effects on LA:

$$\bar{A}(t)=\begin{cases} A_0 e^{a(\mu-p_c(t))} & \text{for} \quad (\mu-p_c(t)) \le 0 \\ A_m + (A_0 - A_m)e^{-b(\mu-p_c(t))} & \text{for} \quad (\mu-p_c(t)) \ge 0 \end{cases} \qquad \text{Equation 3-13}$$

where μ represents MAP. The remaining variables in this equation have been defined earlier.

Therefore, OMW (t) is obtained by subtracting Equation 3-13 from Equation 3-8 according to Equation 3-12. The OMW is then formulated as the following differentiable model [82]:

$$\text{OMW}(t) = \varphi * \begin{cases} A_0\left(e^{ap_t(t)} - e^{a(\mu-p_c(t))}\right) \\ \text{for } p_a(t) \le p_c(t) \text{ and } \mu \le p_c(t) \\ A_0 e^{ap_t(t)} - A_m - (A_0 - A_m)e^{-b(\mu-p_c(t))} \\ \text{for} \\ p_a(t) \le p_c(t) \le \mu \\ A_m + (A_0 - A_m)e^{-b\,p_t(t)} - A_0(e^{a(\mu-p_c(t))}) \\ \text{for} \\ p_a(t) \ge p_c(t) \ge \mu \\ (A_0 - A_m)(e^{-b\,p_t(t)} - e^{-b\,(\mu-p_c(t))}) \\ \text{for } p_a(t) \ge p_c(t) \text{ and } p_c(t) \le \mu \end{cases} \qquad \text{Equation 3-14}$$

As stated earlier, the deflation rate is typically between 1 and 4 ($\frac{\text{mmHg}}{\text{Sec}}$). On the other hand, intra-arterial pressure varies between SBP and DBP within 0.6 to 1.2 seconds; therefore, the effects of deflation on OMW within each heartbeat are negligible.

The Oscillometric Waveform Envelope (OMWE) is the result of subtraction between peaks and troughs of the OMW [10]. As mentioned earlier, the OMW is proportional to the lumen area variation; therefore, we can conclude that subtraction of the troughs (when DBP is happening) of lumen area from its peaks (when SBP is happening) is equivalent to the OMWE by involving the proportional factor. The mathematical model of the OMWE is defined as follows:

$$\mathrm{OMWE}(t) = \varphi\ ((A(t)\ |p_a(t) = \mathrm{SBP}) - (A(t)\ |p_a(t) = \mathrm{DBP})) \qquad \text{Equation 3-15}$$

Where the vertical bar signifies "at". The rest of variables are defined previously.

By substituting (3.8) into equation (3.15), the next equation is derived [82];

$$\mathrm{OMWE}(t) = \varphi * \begin{cases} A_0\left(e^{a((\mathrm{SBP}-p_c(t))} - e^{a(\mathrm{DBP}-p_c(t))}\right) \\ \text{for } \mathrm{SBP} \le p_c(t) \\ A_m + (A_0 - A_m)e^{-b\,(\mathrm{SBP}-p_c(t))} - A_0\left(e^{a(\mathrm{DBP}-p_c(t))}\right) \\ \text{for } \mathrm{DBP} \le p_c(t) \le \mathrm{SBP} \\ (A_0 - A_m)\left(e^{-b(\mathrm{SBP}-p_c(t))} - e^{-b(\mathrm{DBP}-p_c(t))}\right) \\ \text{for } p_c(t) \le \mathrm{DBP} \end{cases} \qquad \text{Equation 3-16}$$

As discussed earlier, the OMWE has a maximum at zero transmural pressure. This means that the second term of Equation 3-16 should have a maximum when CP equal to the MAP. Thus taking the derivative of this equation and setting it equal to zero gives the next equation:

$$A_m = A_0\left(\frac{SBP-DBP}{MAP-DBP}\right)$$ Equation 3-17

3.5. Pulse Transit Time (PTT)

The PTT is inversely related to the pulse wave velocity (PWV) and so is a marker of arterial stiffness. According to the Bramwell and Hill equation, PWV is linked to arterial stiffness as follows [93]:

$$PWV = \frac{1}{\sqrt{\rho * Distensibilty}}$$ Equation 3-18

$$Distensibility = \Delta D / (\Delta P * D)$$ Equation 3-19

where ρ represents blood density, ΔD is the diameter variation corresponding to the pressure changes ΔP. The assumption underlying this equation is an elastic vessel with incompressible liquid [12, 92-94]. Distensibility, as one of the markers of arterial stiffness, is defined as the relative change in arterial volume for a given pressure change [92, 95-97].

To the best of our knowledge, PTT variation as a function of cuff deflation has not been evaluated with the aim of vascular assessment. A model of PTT-CP, used to estimate BP, has been developed by one of the group members [70]. Our work is inspired by this model to evaluate arterial stiffness.

The PTT is composed of two main components: (1) PTT from the heart to brachial artery which is not affected by CP, and so can be considered as a constant, and (2) PTT underneath the cuff which is locally affected by external pressure.

$$\tau(t) = \tau_0\,(t) + \tau_c\,(t) \qquad \text{Equation 3-20}$$

where $\tau_0(t)$ is the time propagation from the heart to brachial artery, and $\tau_c(t)$ is the propagation time underneath the cuff. As discussed earlier, the PTT is inversely related to PWV as follow:

$$\tau = \frac{PWV}{L} \qquad \text{Equation 3-21}$$

where L is propagation length.

It is well-know that PWV depends mainly on the elasticity of the vessel, according to the Equation 3-18, and as discussed in Chapter 2 [80]. Based on the Bramwell and Hill equation, PWV from the heart to brachial (v_0), and PWV beneath the cuff (v_c) is formulated as follow [80]:

$$v_0\,(t) = \sqrt{\frac{A(t)}{\rho}\frac{\partial p_t(t)}{\partial A(t)}\,|\,p_c(t) = 0} \qquad \text{Equation 3-22}$$

$$v_c\,(t) = \sqrt{\frac{A_c(t)}{\rho}\frac{\partial p_t(t)}{\partial A_c(t)}} \qquad \text{Equation 3-23}$$

where ρ represents blood density and it is equal to 1060 kg/m^3.

Assuming L_0 is length from heart to brachial artery and L_c is length of the artery beneath the cuff (cuff width), the following equation is derived:

$$\tau(t) = L_0 \sqrt{\frac{\rho}{A(t)} \frac{\partial A(t)}{\partial p_t(t)} \Big| p_c(t) = 0} + L_c \sqrt{\frac{\rho}{A_c(t)} \frac{\partial A_c(t)}{\partial p_t(t)}} \qquad \text{Equation 3-24}$$

By inserting p_c=0 in Equation (3-8), A (t) is obtained as:

$$A(t) \Big|_{p_c(t) = 0} = A_m + (A_0 - A_m)\, e^{-b\, p_a(t)} \qquad \text{Equation 3-25}$$

Then by taking the derivative of Equation 3-25, the following equation is obtained:

$$\frac{\partial A(t)}{\partial p_t(t)} \Big|_{p_c(t) = 0} = (A_m - A_0)\, b\, e^{-b\, p_a(t)} \qquad \text{Equation 3-26}$$

The pressure transmission ratio is defined as the ratio between pressures at the outer surface of brachial artery divided by applied pressure on the arm surface. Researchers have realized that even similar external applied pressures over the arm surface do not guarantee the same pressure transmission ratio at all points [8, 90]. This transmission ratio is reduced up to 30% from the center to the cuff boundaries. It is realized that when the artery is completely collapsed in the center, it is still open at the edges, and thus less pressure is transferred to the artery located at the edges of the cuff [90]. Based on the above discussion, Equation 3-8 is modified as follows:

$$A_c(t) = A(t) + A_{cst} = \begin{cases} A_{cst} + A_0 e^{a\,p_t(t)} & \text{for } p_t(t) \le 0 \\ (A_{cst} + A_m) + (A_0 - A_m)e^{-b\,p_t(t)} & \text{for } p_t(t) \ge 0 \end{cases}$$ Equation 3-27

where A_c is the total average lumen area under the cuff, A_{cst} is the average unoccluded area, while the area at the center of cuff is zero. $\frac{\partial A_c(t)}{\partial p_t(t)}$ is achieved by taking the derivative of Equation 3-27:

$$\frac{\partial A_c(t)}{\partial p_t(t)} = \begin{cases} a\,A_0 e^{a\,p_t(t)} & \text{for } p_t(t) \le 0 \\ (A_m - A_0)\,b\,e^{-b\,p_t(t)} & \text{for } p_t(t) \ge 0 \end{cases}$$ Equation 3-28

Substituting Equation 3-28, Equation 3-27, Equation 3-26, and Equation 3-25 into Equation 3-24 result in the following formula:

$$\tau(t) = \tau_0(t) + \begin{cases} \tau_{c1}(t), & \text{for } p_t(t) \le 0 \\ \tau_{c2}(t), & \text{for } p_t(t) \ge 0 \end{cases}$$ Equation 3-29

Where

$$\tau_0(t) = L_0 \sqrt{\rho b \left(\frac{1}{1 - \frac{A_m - A_0}{A_m} e^{-b\,p_a(t)}} - 1\right)}$$ Equation 3-30

$$\tau_{c1}(t) = L_c \sqrt{\rho a \left(1 - \frac{1}{1 + \frac{A_0}{A_{cst}} e^{a\,p_t(t)}}\right)}$$ Equation 3-31

$$\tau_{c2}(t) = L_c \sqrt{\rho b \left(\frac{1}{1 - \frac{A_m - A_0}{A_m + A_{cst}} e^{-b\, p_t(t)}} - 1 \right)}$$ Equation 3-32

As can be seen, $\tau_{c1}(t)$ and $\tau_{c2}(t)$ are functions of the transmural pressure. $\tau_0(t)$ is the time from the heart to brachial artery and is independent from cuff pressure. Parameters a and b are the arterial stiffness indices which are always greater than zero.

According to the derived equations, it is as expected the negative transmural pressure (cuff pressures more than mean arterial pressure) increases towards zero during deflation, PTT increases. Conversely, $\tau_{c2}(t)$ decreases as transmural pressure increases in the positive region (cuff pressures less than mean arterial pressure). This leads to the conclusion that there is a maximum at $p_t(t) = 0$ or $p_c(t) = p_a(t)$. The first function for $\tau_0(t)$ in Equation 3-30 is a function of intra-arterial pressure and thus fluctuates as intra-arterial pressure varies between maximum and minimum within each heartbeat. PTT obtained via troughs (PTT_D), peaks (PTT_S) and zero-crossings (PTT_{MAP}) have maxima close to SBP, DBP and MAP, which was the focus of previous work by our group [70]. In this thesis, the relation between pulse transit time and cuff pressure is applied to estimate arterial stiffness, and then fix arterial stiffness indices into Oscillometric Waveform Envelope (OMWE) model described in Section 3.4.

3.6. Study Population

The performance of the proposed method is evaluated on real data, obtained from 10 healthy subjects aged from 24 to 63 years (six males and four females) without any history of cardiovascular disease or hypertension. All subjects provided their informed consent in

accordance with the guidelines of the Institutional Research Ethics Board. This data was collected in a previous study in our group [98].

3.7. Prototype Device

A prototype multi-parameter monitoring device has been developed in our group which is able to simultaneously register the Electrocardiogram (ECG) and Cuff Pressure (CP) during cuff deflation (named InBeam prototype) [98, 99]. The prototype device, shown in Figure 3-3, is equipped with the required software and hardware to record ECG and (CP) synchronously.

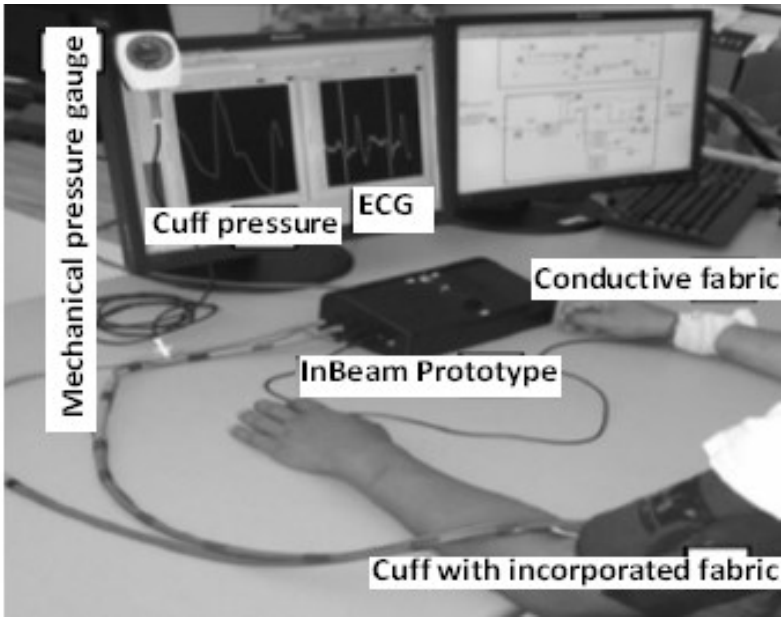

Figure 3-3. InBeam prototype, shown acquiring ECG and CP for a male subject. The cuff is equipped with a conductive fabric. A second ECG electrode is placed inside the wristband. A mechanical pressure meter is used for pressure calibration [98].

ECG is recorded by employing two electrodes. The first one is incorporated inside the cuff, while the second one is incorporated inside a wristband. A flexible conductive fabric is

incorporated inside the cuff which is folded over the subject's left arm. The cuff provides one of the required electrodes for the ECG along with its ability to sense arterial pulse pressure as illustrated in Figure 3-4.

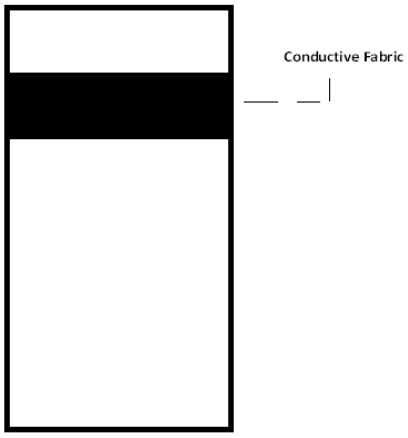

Figure 3-4. Conductive fabric incorporated inside the cuff [99].

For a second electrode, another conductive fabric is placed inside a wristband which is worn on the right wrist of the subject. As shown in Figure 3-3, the cuff and wristband are connected to the prototype device via two air hoses and two electrical leads, respectively.

The Cuff Pressure (CP) signal is acquired using the cuff, which is placed over the brachial artery. One of the two air hoses is attached to a sphygmomanometer through a T connector for the purpose of pressure calibration. National Instruments (Austin, TX) data acquisition hardware is used to connect the prototype device to a Personal Computer (PC) for further analysis and data storage.

The InBeam prototype is composed of four essential components including; (1) an analog ECG amplifier, (2) an analog pressure transducer, (3) a mini DC air pump, and (4) a screw-controlled manual pressure release valve. The main part of the ECG amplifier is composed of an

instrumentation amplifier (INA-129, Texas Instruments, Dallas, TX, USA) in combination with circuitry for voltage stabilization and signal conditioning. The ECG amplifier is fed with ±5 Volt DC power supply.

A Vernier pressure transducer (BPS-BTA, Beaverton, OR) is used for transforming mechanical vibration due to the pressure oscillation inside the cuff into voltage. The 5V DC voltage is needed to operate this pressure transducer.

The mini DC air pump, which is attached to the hose, is used to inflate the cuff. The screw-controlled pressure release valve, in conjunction with cuff, is manually used for deflation rate adjustment.

Analog output voltage from the ECG amplifier and Vernier pressure transducer output are fed into two simultaneously sampled analog channels of the National Instruments C Series 9239 analog input module (NI-9239) mounted on the Compact DAQ data acquisition board. When voltage signals are applied to the NI-9239, they are conditioned, buffered and sampled by a 24-bit delta-sigma Analog-to-Digital Converter (ADC). The digitized signal is then transferred to a personal computer via a USB cable.

The voltage supply for the Vernier pressure transducer is provided by a National Instruments C Series 9263 4-Channel, 16-bit, ±10-V analog output module (NI-9263) mounted on the Compact DAQ data acquisition board. In addition, two external voltage batteries are also incorporated for supplying the ECG amplifier and mini DC air pump. Since the pressure transducer is attached to the NI-9263 module, it receives a constant and steady voltage level. As batteries are employed for the ECG amplifier power supply, the effect of 60 Hz noise on ECG signal is diminished.

The National Instruments LabVIEW environment is used for acquiring the ECG and CP signals, which are sampled at 1000 Hz. Further signal processing and analysis is performed using a program written in Matlab® (The MathWorks Inc., Natick, MA, USA). More details on the measurement set-up are found in [98].

3.8. Reference Device

OMRON HEM-790IT

Ideally, validation should be achieved by comparing the BP estimation results with the highly accurate intra-arterial blood pressure measurement. However, it was not possible to conduct invasive measurements as part of this study. The Omron HEM-790IT is a commercial home-based BP monitoring device which is approved by Food and Drug Administration (FDA). This device is used as a reference to be compared with our results.

3.9. Experimental Procedure

All subjects were sitting during experiments, and were asked to have minimum movement. First, the BP was recorded by the Omron device to obtain a reference value with a cuff placed on the right arm. Subsequently, the InBeam prototype was applied on the subject with the cuff positioned on the left arm and wrist-band on the right wrist. This procedure was then repeated five times. Although in patients with cardiovascular diseases there is sometimes a difference between BP measured in each arm, in healthy subjects any such difference would be expected to be minimal.

A gap of 1 minute is recommended by the American Heart Association (AHA) between recordings [3]. Since the experiments were performed 5 times plus one more time using the Omron device, it seems more suitable to have a gap of 3 minutes between data registration sessions. The data was collected on three different days (not necessarily subsequent days) with five measurements per day, which resulted in a data set of 150 recordings. The InBeam prototype was inflated to a pressure of about 150 mmHg and then deflated at a rate of 1.5-3.5 mmHg/sec, until reaching a pressure of 20 mmHg. All signals were registered during deflation. The measurement procedure is summarized in the next block diagram:

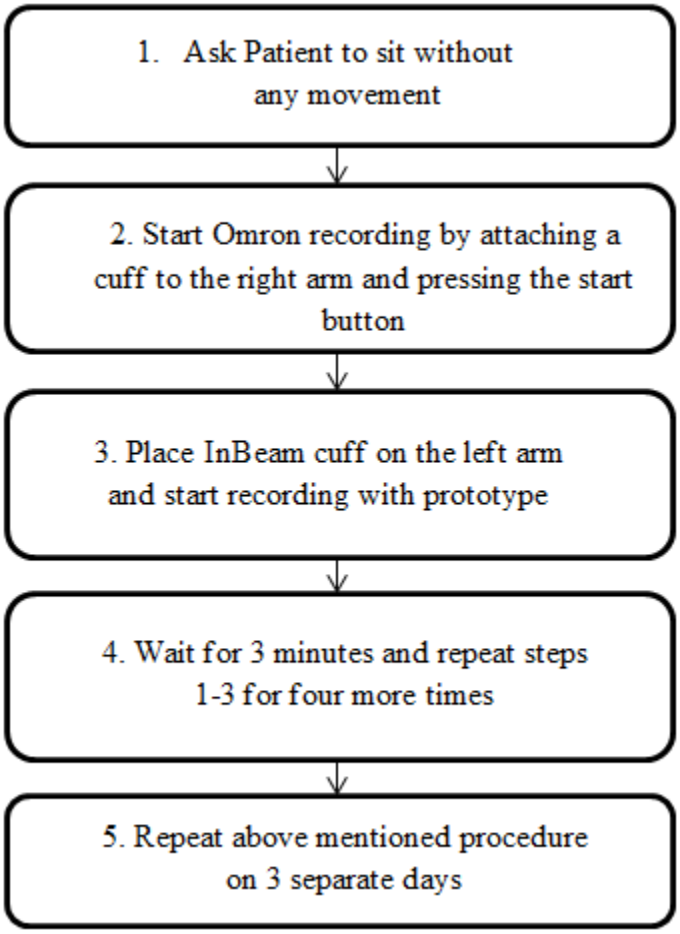

Figure 3-5. Summary of the experimental procedure.

3.10. Waveform Feature Extraction

The Oscillometric Waveform (OMW) was constructed with the aid of the ECG. Noise in the cuff pressure signal, irregular cardiac rhythms in conditions like arrhythmia, or when recorded pulses are weak like in obesity make it difficult to find the OMW [100]. These difficulties can be overcome through an ECG- based approach [98], in which the peaks of the ECG signal (known as the R-peaks) assist us in more accurate localization of the pressure pulses.

3.10.1 ECG R-Peak Detection

The first Step in the ECG-assisted approach is to identify R-peaks locations. Linear interpolation, at 256 Hz sampling rate, is performed on the ECG signal and then R-peak detection is carried out by using the MIT / PhysioNET MATLAB QRS onset detector software [101-103]. This software employs a band-pass filter (3-35 Hz) to suppress muscle noise, 60-Hz noise, baseline wander, and T-wave interference.

Afterwards, the signal is differentiated to emphasize the QRS complex. Following differentiation, squaring is performed to make higher frequencies prominent. The waveform is integrated via a moving window whose length depends on the QRS width and sampling rate. After that, a threshold is applied to locate the maximum slope and consequently R-peaks [103]. As an example, identified R-peaks superimposed over the ECG are displayed in Figure 3-6.

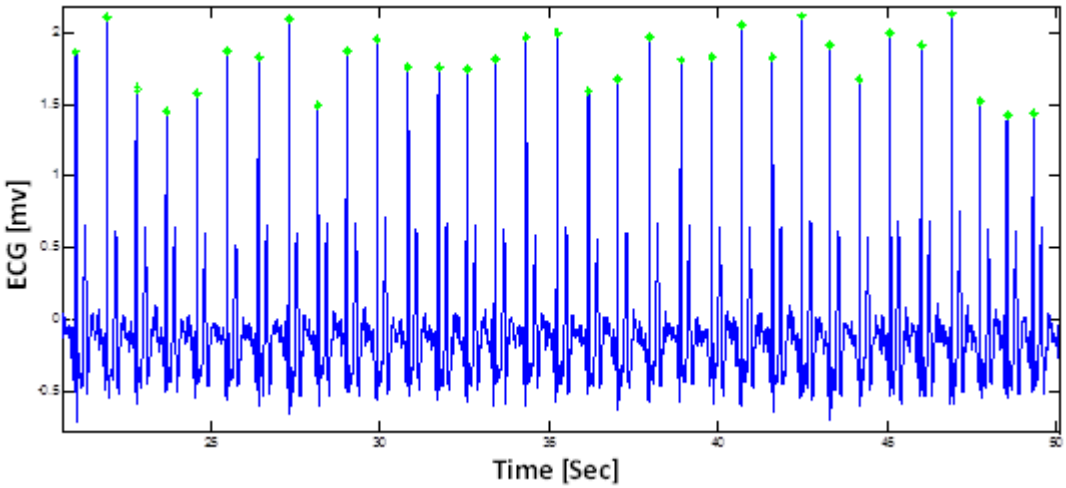

Figure 3-6. Representation of detected R-peaks pointed out in green dots.

3.10.2 Oscillometric Waveform Detection

The Oscillometric Waveform (OMW) should be extracted from the recorded CP signal. As mentioned above, the CP signal is composed of a slow downward trend due to deflation and arterial pulse oscillations. In order to extract the OMW, the descending trend due to deflation should be found and subtracted from the CP signal. This task is performed by; (1) locating pressure pulses corresponding to R-peaks in the CP signal, and forming the descending line, and (2) subtracting this constructed line from the CP signal.

An example of identified pressure pulses corresponding to R-peaks and the interpolated descending line is shown in Figure 3-7. The resulting OMW is shown in Figure 3-8. The advantage of the ECG-based method over filtering techniques is that peaks and troughs might shift in position due to filtering.

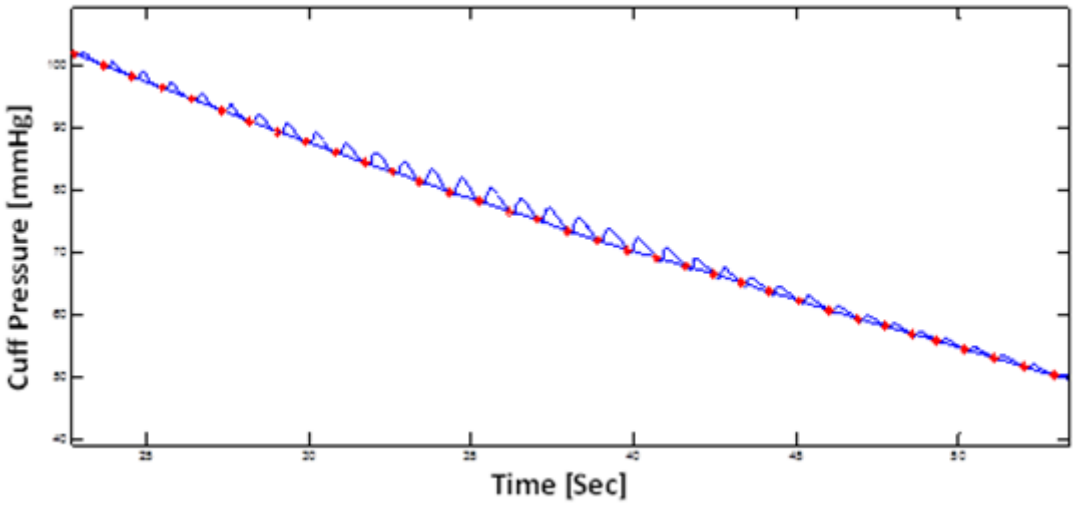

Figure 3-7. The dots in this graph show the temporal position of R-peaks superimposed over the recorded cuff pressure. The interpolated descending trend line connecting the dots is also shown.

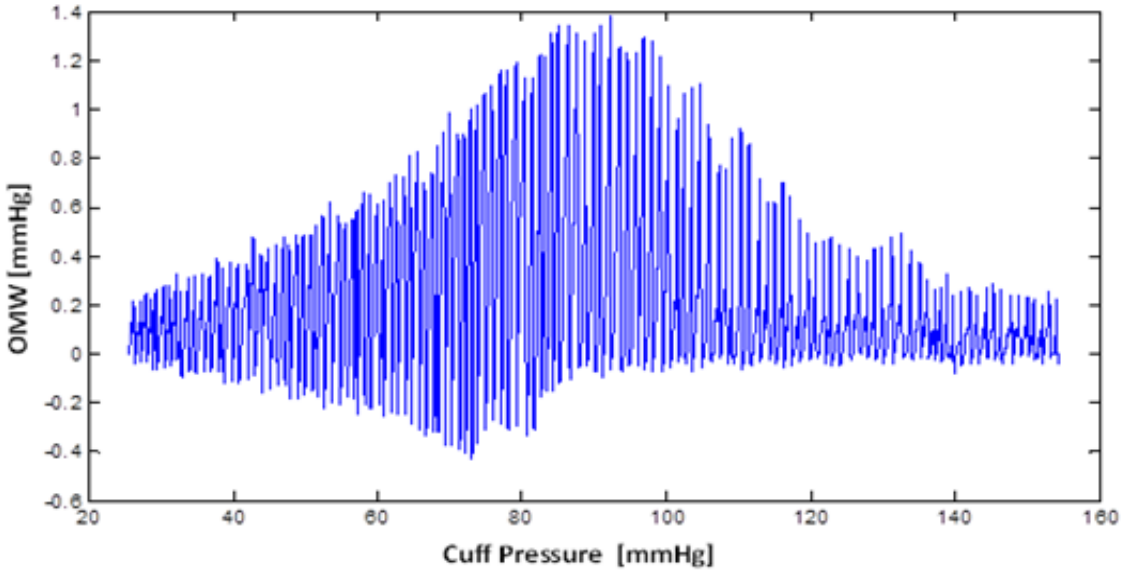

Figure 3-8. The obtained OMW after subtraction of the descending line from recorded cuff pressure signal.

The peaks and troughs of the OMW are then detected with the aid of R-peaks. The maximum and minimum amplitude of the recovered OMW between two successive R-peaks are found and assigned as peak and trough illustrated in Figure 3-9.

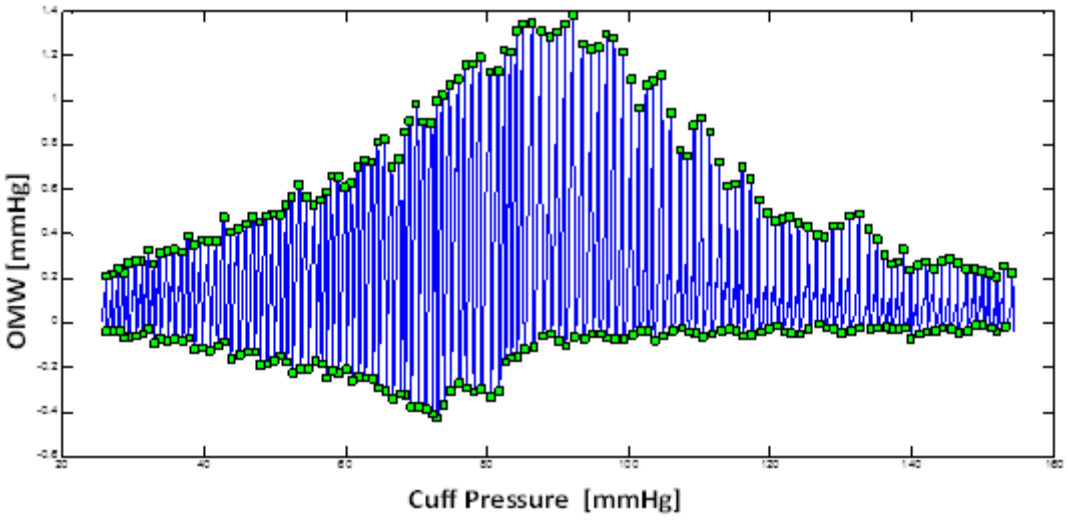

Figure 3-9. Peaks and troughs in the Oscillometric Waveform (OMW) are identified with help of ECG R-peaks.

The zero-crossings of oscillometric waveform in ascending part are found by employing a different approach, because the ECG-assisted method cannot completely exclude the slow-varying component of the CP signal. To address this issue, low-pass filtering using a 2nd order Butterworth filter with cutoff frequency 0.2 Hz is employed to find the descending line in the CP, which is then subtracted from the recorded CP. After that, the minima of the absolute value of all data points within each cycle, from trough to peak, are calculated and regarded as zero crossing points. These are shown in Figure 3-10 superimposed on the OMW signal.

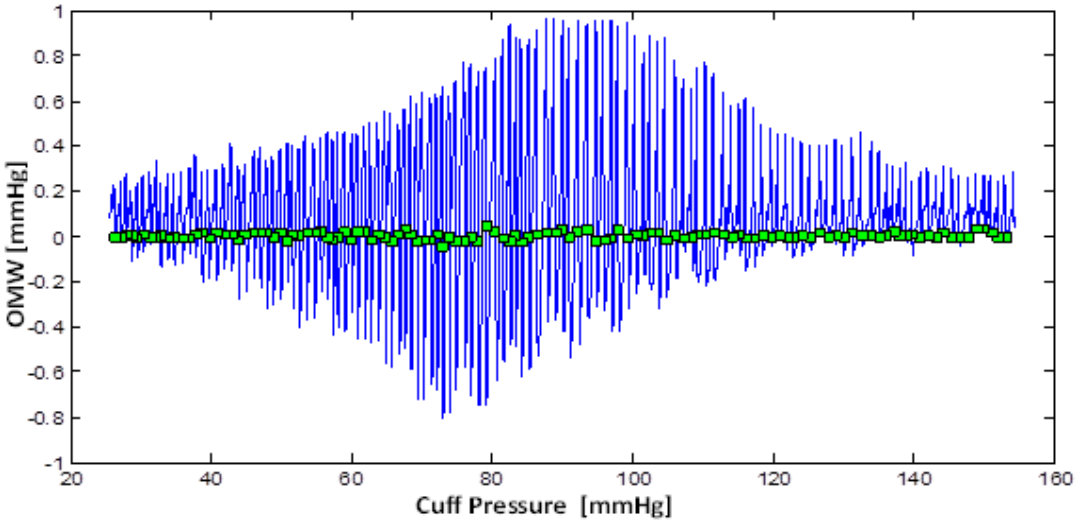

Figure 3-10. Zero-crossings shown superimposed on the OMW signal.

3.10.3 Oscillometric Waveform Envelope Construction

The Oscillometric Waveform Envelope (OMWE) is constructed by subtracting troughs from peaks in the OMW. Smoothing is performed in two stages; (1) data is smoothed by applying a seven-point moving-average filter, and then (2) fitted with a cubic spline function with a smoothing parameter of 0.1. The result of these operations is shown in Figure 3-11.

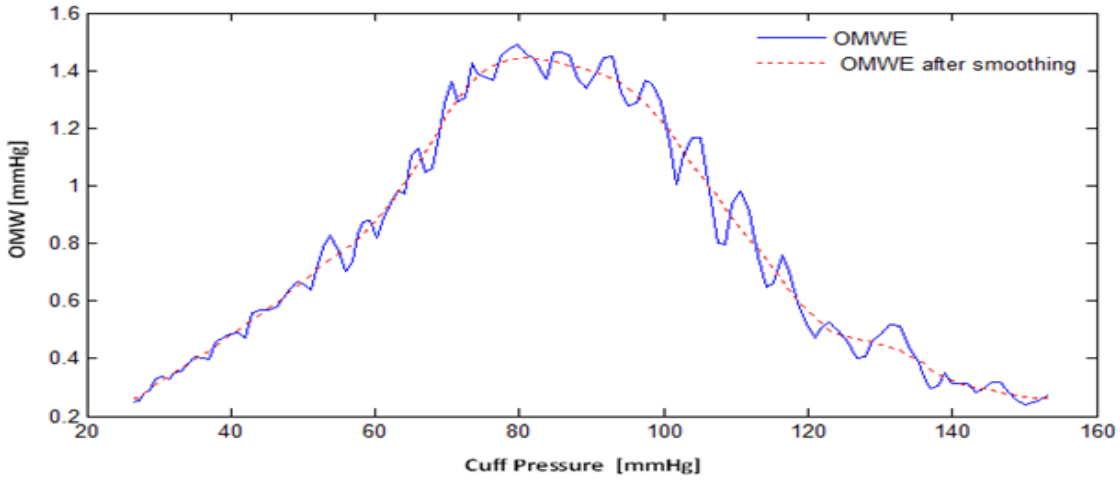

Figure 3-11. OMWE obtained by subtraction between peaks and troughs of the OMW signal. The red curve shows OMWE after smoothing.

3.10.4 Pulse Transit Time Measurement

The Pulse Transit Time (PTT) can be measured as the time delay between the onset of R-peak and peaks (τ_p), troughs (τ_t) or zero-crossings of the OMW (τ_z) [104]. Therefore, as explained previously in Section 3.5, there are three possibilities to estimate arterial stiffness depending on the selected point on the Oscillometric Waveform (OMW). Since MAP (at zero transmural pressure) is the point at which transition between negative and positive transmural pressure is occurring, and based on the exponential model of lumen area-cuff pressure and volume-cuff pressure, arterial stiffness will change at zero transmural pressure (i.e. at MAP) [22], with different slopes at two sides of the curve. Therefore two different sets of arterial stiffness indices should be devoted to these two regions, the one below and the above Mean Arterial Pressure (MAP). Based on the models for pulse transit time, and only when we are using zero-crossing

points, two separate models are provided for these two regions, expressed in Equation 3-30 to Equation 3-32. [22, 70]. Consequently, given the above discussion, the arterial stiffness is estimated using zero-crossings. Another reason to use zero-crossings to estimate PTT is that troughs and peaks were to be used, then SBP and DBP should be fixed into the model, which is not possible in our case since we are aiming to estimate them.

When zero-crossings are employed to estimate PTT, and hence the arterial stiffness parameters, mean arterial pressure should be fixed into the model. MAP is easily obtained by finding maximum pressure that corresponds to the maximum amplitude of PTT [70]. As expected, the employing arterial stiffness using zero-crossings experimentally results in more reliable estimation of blood pressure measurement as shown in the following chapters. The estimation of PTT based on zero-crossings in the OMW is shown in Figure 3-12.

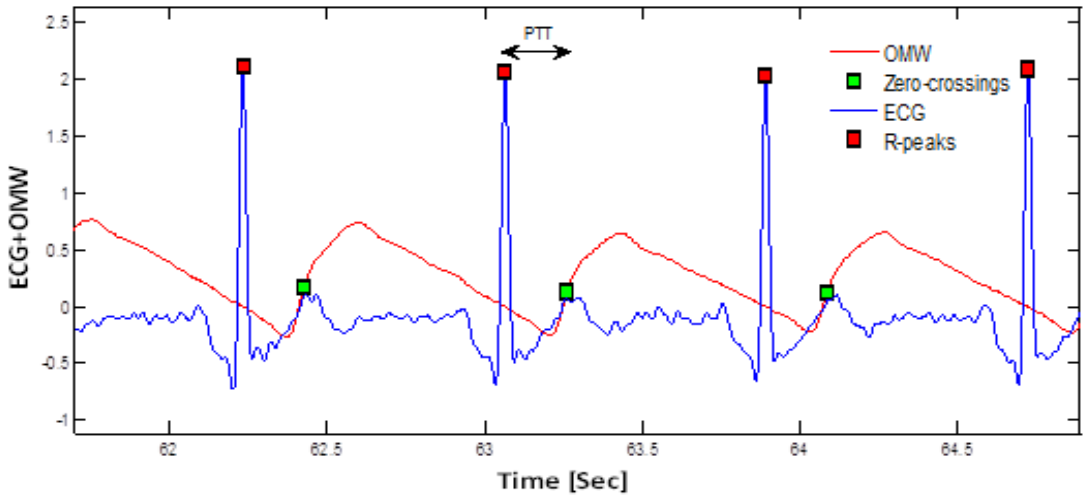

Figure 3-12. Pulse transit time is obtained as the difference between R-peaks and zero-crossings.

The PTT obtained using these points is smoothed with a moving-averaging window of span 5, as illustrated in Figure 3-13.

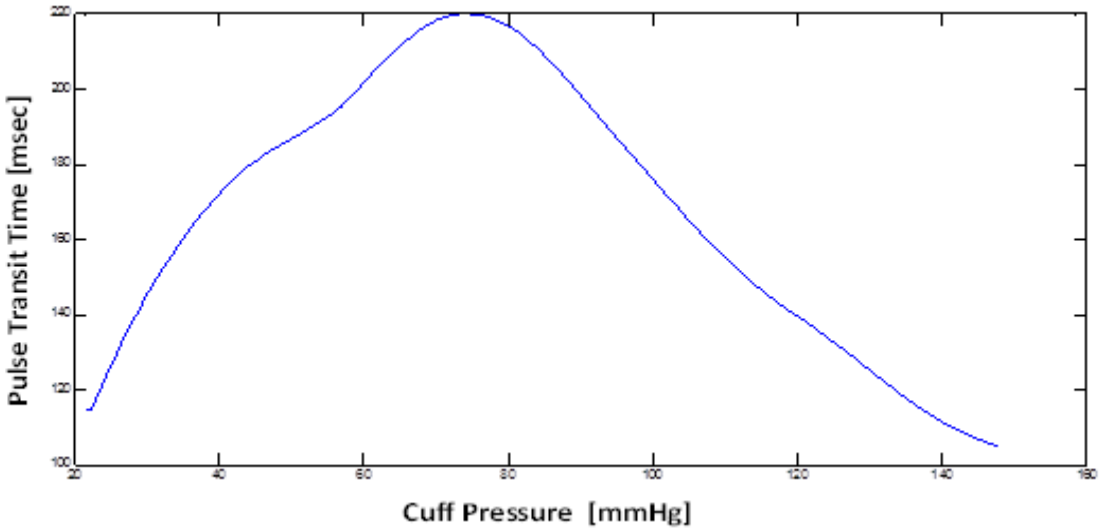

Figure 3-13. This graph illustrates the smoothed PTT obtained using zero-crossings.

The exponential model proposed in Equation 3-29, Equation 3-30, and Equation 3-31 is employed to estimate stiffness index, a, for negative transmural pressure region. Afterwards, b is estimated according to Equation 3-9.

It has been found that PWV at SBP pressure levels is more correlated with arterial stiffness [105]. We therefore concluded that PTT, which is inversely related to PWV, would follow the same trend. Hence, arterial stiffness at high pressure is estimated using PTT. For pressures lower than the mean arterial pressure, arterial stiffness, b, is estimated using the relation between stiffness indices and maximum lumen area, while artery is completely distended and lumen area is assumed at zero transmural pressure, expressed in Equation 3-9. Moreover, based on the experimental results, finding b (for pressures lower than MAP) using Equation 3-9 was found to give a more accurate BP estimation.

Nonlinear least-squares curve fitting based on the trust reflective region was used to find the required parameters [106]. Least-squares fitting is based on minimizing the sum of square of errors between real data and the fitted curve. Coefficients are estimated according to the best curve fitted to the data. The procedure is started with an initial set of values along with the range of values for unknown parameters, and finishes with the estimated values for those parameters that result in the best fit curve. Initial values for PTT, $\frac{A_0}{A_{cst}}$, and a were chosen as 100 ms, 5, and 0.09 $mmHg^{-1}$, respectively, based on the values mentioned in the [70]. Ranges for these variables were set at (0-500), (0-∞) and (0-∞), respectively. The curve fit is illustrated in Figure 3-14.

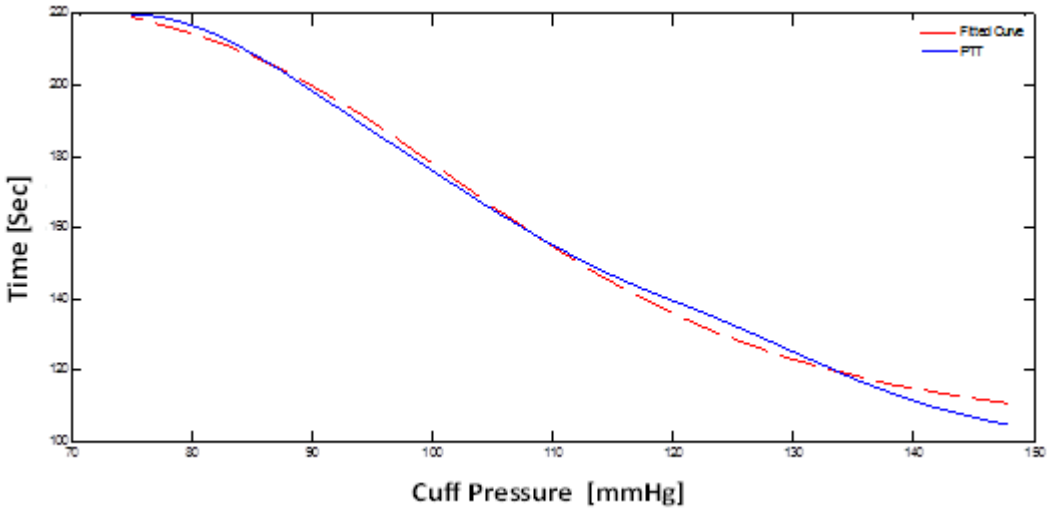

Figure 3-14. This figure illustrates PTT and the curve fit to obtain estimates of the arterial stiffness parameters a and b.

Equation 3-16 is fit to the recorded OMWE by incorporating the two stiffness parameters obtained from the PTT model. The SBP and DBP values which minimize the sum of squares of errors are estimated based on the OMWE model (see Figure 3-15). Initial values for SBP, DBP and MAP, and A_0 were 120, 80, 90 and 0.1 and the ranges used were (70-150), (40-100) (50-110), and (0 - ∞), respectively based on the recommended values in [70] . However, different set of ranges and initial values were examined and the method was not sensitive to the examined the initial values and ranges. An illustration of the fitting the OMWE model to real data is shown in Figure 3-15.

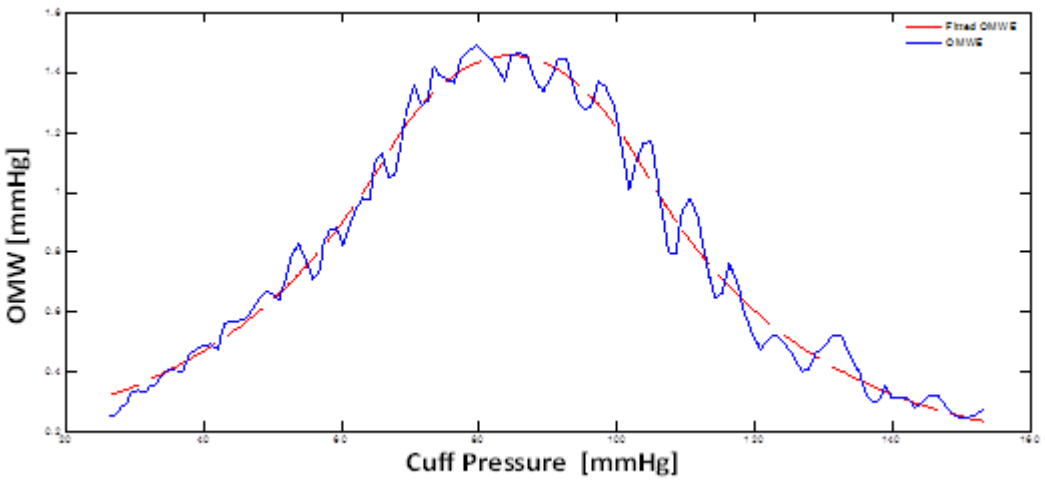

Figure 3-15. An illustration of curve fitting the OMWE model to OMWE obtained from real data to estimate SBP and DBP.

The algorithm was repeated after smoothing the OMWE and there was little change in the results, so the technique is insensitive to the smoothing function. In order to clarify the proposed method's sensitivity to the incorporation of arterial stiffness values in the OMWE model, data from one of the subjects is chosen to illustrate how method works by incorporating arterial stiffness. As Figure 3-16 and Figure 3-17 show, the fit in the SBP region (i.e. at cuff pressures

higher than the MAP) is much improved by fixing arterial stiffness into the model, while the fit in the DBP is less sensitive. This is in agreement with overall results that were obtained, and which are described in the following chapter.

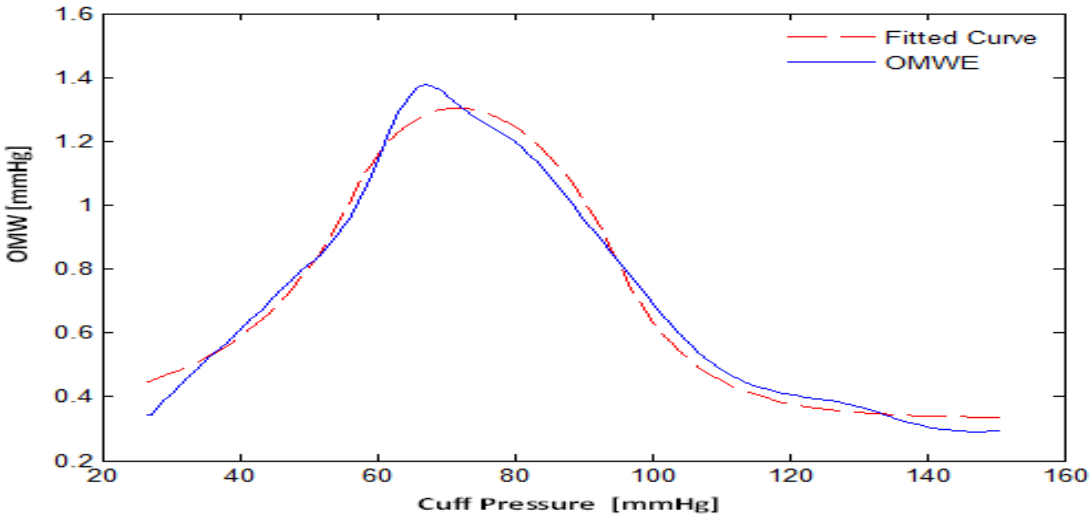

Figure 3-16. OMWE curve fitting with the incorporation of the arterial stiffness values estimated from PTT-CP curve.

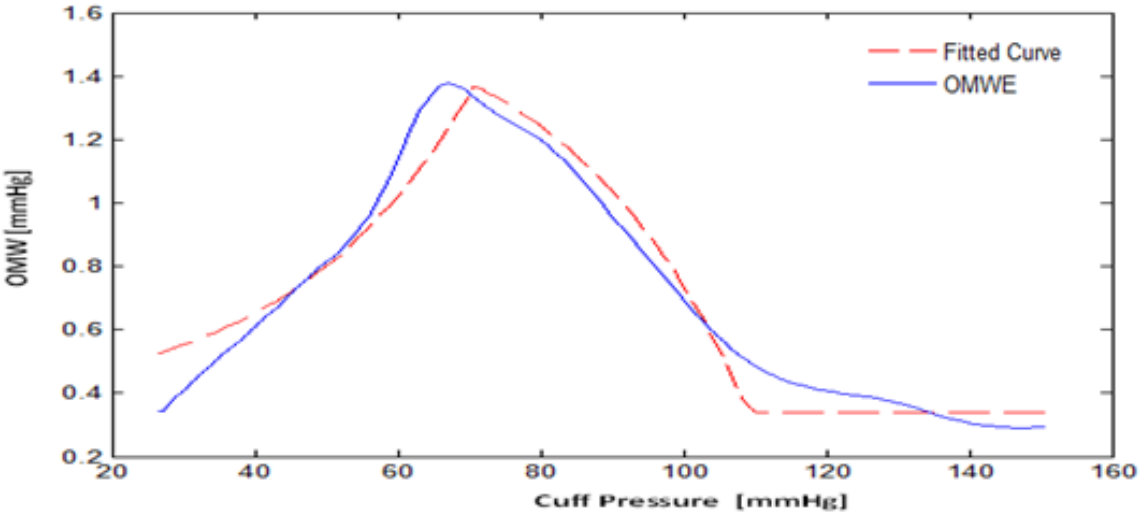

Figure 3-17. OMWE curve fitting without the incorporation of the arterial stiffness values estimated from PTT-CP curve.

Chapter 4. Results

This chapter presents the results obtained the proposed method from the entire data set, which was described previously in Section 3.6. To assess the performance of the proposed method the following error measures are used: Standard Deviation of the Error (STDE), Mean Absolute Error (MAE) and Mean Error (ME). Error is defined as the difference between estimated BP and the reference value in mmHg. STDE refers to the standard deviation of the error. MAE refers to the mean of the absolute value of the error. The model performance is tested in two conditions; (1) without estimating arterial stiffness parameters using Pulse Transit Time (PTT), and (2) with estimating arterial stiffness parameters from PTT. The results are summarized in the following tables and figures, first for the case where the two arterial stiffness parameters were not fixed in the OMWE model using the Pulse Transit Time (Table 4-1 and Figure 4-1), and then for the case when the arterial stiffness parameters were first estimated using the PTT and then incorporated in the OMWE model (Table 4-2 and Figure 4-2).

Table 4-1. Estimates of SBP and DBP with OMWE model in which arterial stiffness values are not fixed in the model using the Pulse Transit Time (PTT). MAE, STDE, ME correspond to the mean absolute error, standard deviation and mean error (in mmHg).

	MAE	**STDE**	**ME**
SBP	11.51	13.42	5.75
DBP	6.9	8.71	-1.59

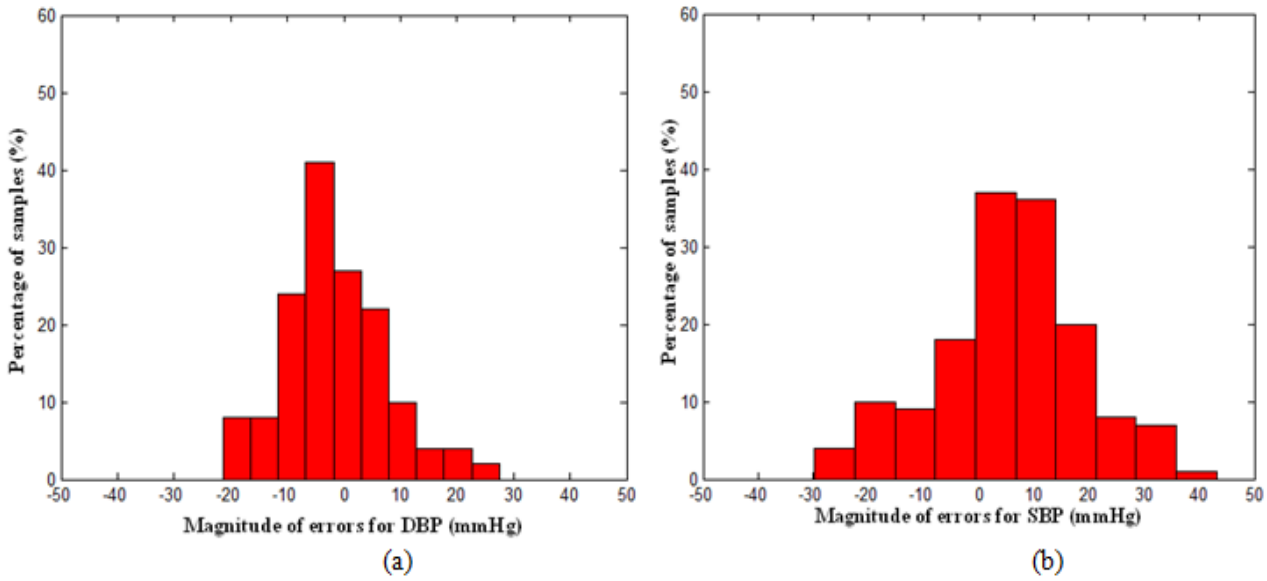

Figure 4-1. Error distribution with OMWE model in which arterial stiffness values are not fixed using Pulse Transit Time (PTT) (a) DBP errors (b) SBP errors.

In terms of the overall errors when the arterial stiffness parameters were not fixed using the PTT model, 63% of absolute errors were greater than 5 mmHg and 34% were greater than 10 mmHg.

Table 4-2. Estimates of SBP and DBP in which arterial stiffness values were first estimated by curve fitting the PTT and the fixed into OMWE model. MAE, STD, and ME corresponds to mean absolute error, standard deviation and mean error (in mmHg).

	MAE	**STDE**	**ME**
SBP	4.95	6.31	-1.23
DBP	5.40	7.38	2.60

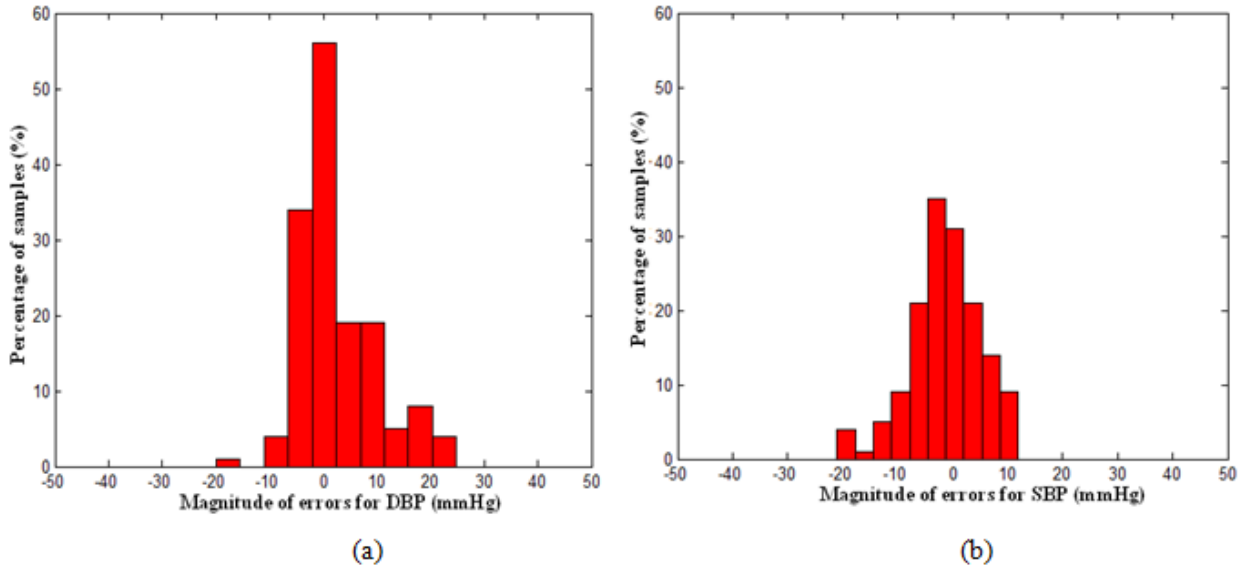

Figure 4-2. Error distribution for the combined model of PTT and OMWE in which arterial stiffness values are first estimated by curve fitting the PTT and then fixed in OMWE model. (a) DBP errors (b) SBP errors.

In terms of the overall errors when the arterial stiffness parameters were fixed using the PTT model into OMWE model , 37% of absolute errors were greater than 5 mmHg and 13% were greater than 10mmHg.

In Figures 4-3 to Figure 4.6, Bland Altman plots are constructed to explore how well the proposed method performs compared to the reference method. Figure 4-3 and Figure 4-5 relate to the case where the arterial stiffness parameters were not estimated first using the PTT, while Figure 4-4 and Figure 4-6 relate to the case where the arterial stiffness parameters were first estimated using the PTT and then fixed into the OMWE model. The difference between each the result of proposed method and the reference value is plotted against the mean of the proposed method and the reference value. The limits of agreement are computed by calculating the mean of the difference ± 1.96 the standard deviation of differences and these are shown as horizontal lines.

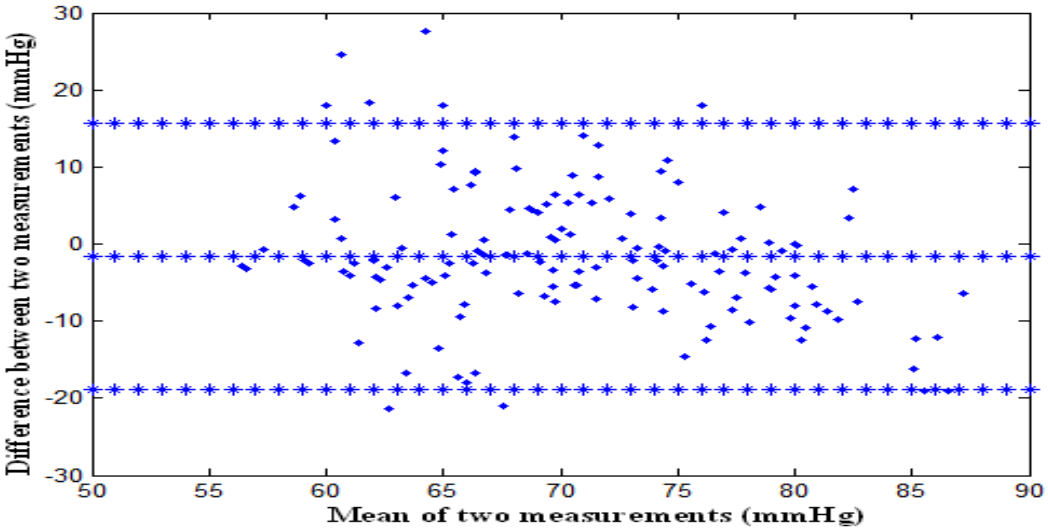

Figure 4-3. Bland Altman plot which compares DBP estimation from OMWE model without fixing the arterial stiffness parameters using Pulse Transit Time (PTT) and the reference Omron measurements. In this plot Bias is -1.59 mmHg and Limits of agreement are from -18.86 to 15.66 mmHg.

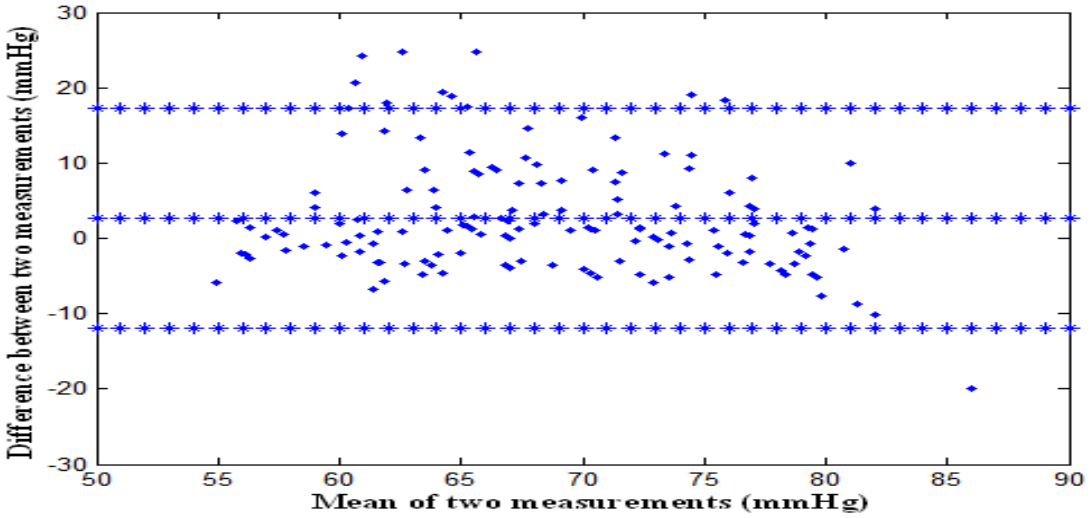

Figure 4-4. Bland Altman plot which compares DBP estimation from OMWE model with arterial stiffness parameters first estimated from the Pulse Transit Time (PTT), and the reference Omron measurements. In this plot Bias is 2.06 mmHg and Limits of agreement are from -12.01 to 17.23 mmHg.

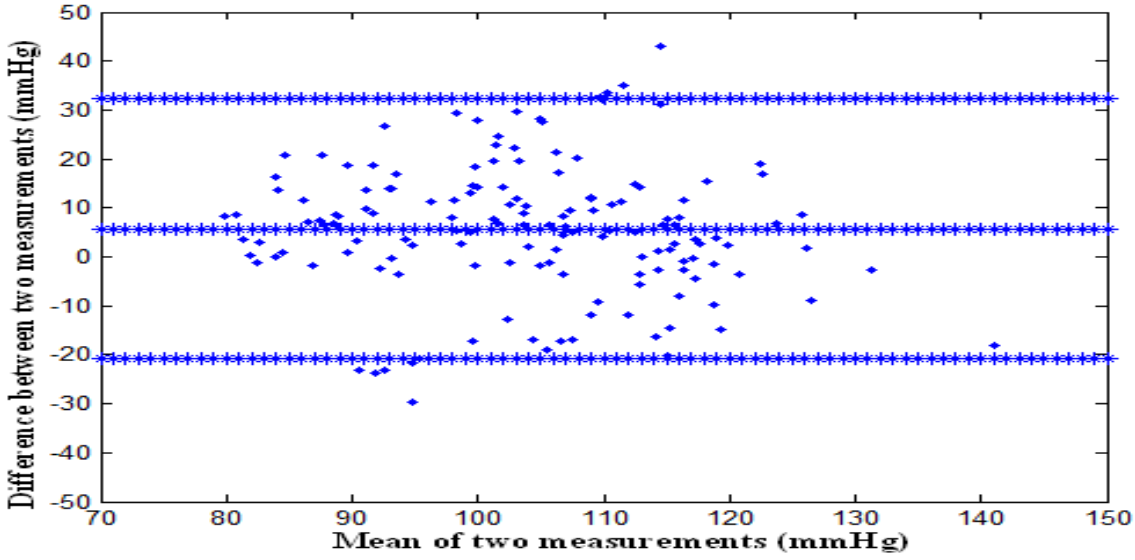

Figure 4-5. Bland Altman plot which compares SBP estimation from OMWE model without fixing the arterial stiffness parameters using Pulse Transit Time (PTT) and the reference Omron measurements. In this plot Bias is 5.75 mmHg and Limits of agreement are from -20.83 to 32.34 mmHg.

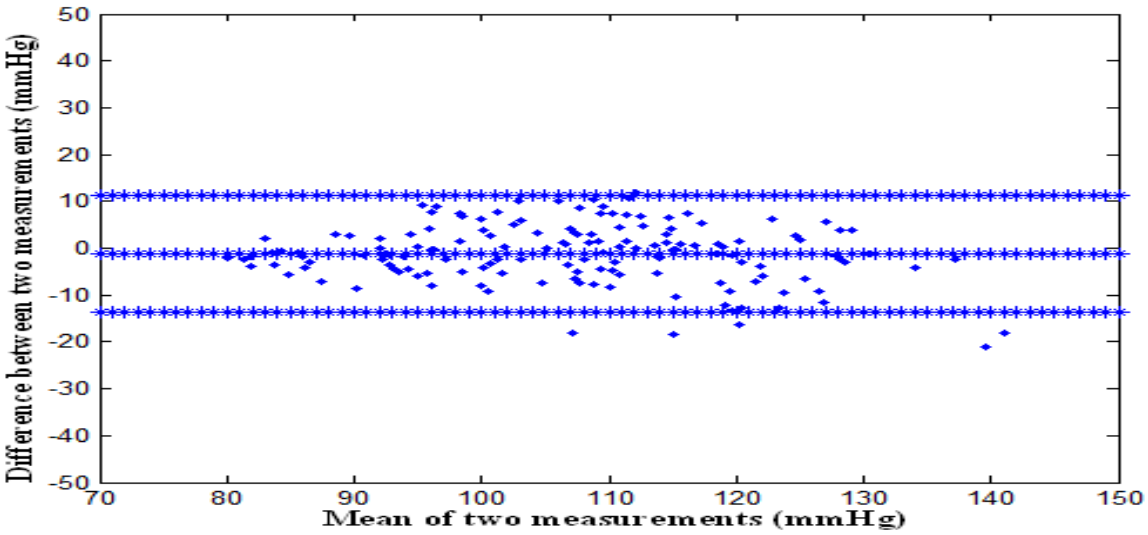

Figure 4-6. Bland Altman plot which compares SBP estimation from OMWE with arterial stiffness parameters first obtained from the Pulse Transit Time (PTT) and the reference Omron measurements. In this plot, Bias is -1.23 mmHg and Limits of agreement are from -13.75 to 11.28 mmHg.

Chapter 5. Discussion

In the previous chapter, the proposed algorithm was validated by testing on real-world data and by comparing the results to reference values. A mathematical model optimized for each individual subject and independent of any experimentally-derived ratio is proposed. By taking arterial stiffness into account, the number of model parameters is reduced by two, which improves the reliability and robustness of blood pressure measurement. By applying arterial stiffness, the method is less sensitive to the initial values used to optimize the model with only SBP, DBP, MAP and minimum area of vessel in zero transmural pressure left as free parameters. The accuracy of blood pressure measurement is significantly influenced by arterial stiffness, as it is found that changes in arterial stiffness can cause errors up to 15-20% in SBP and DBP [8].

The Pulse Transit Time (PTT) is the time taken for the arterial pulse to propagate between two points of the arterial tree. The ability of the arterial wall for expansion and compression considerably affects the PTT. As mentioned earlier, the inverse of the pulse transit time is related to pulse wave velocity, which is regarded as an important marker in the assessment of arterial stiffness [50]. In this work, PTT variation with deflating cuff pressure is used to estimate arterial stiffness using a mathematical model and curve fitting. The PTT model was derived based on the Bramwell-Hill equation and its dependency on the lumen area variation, cuff pressure, and intra-arterial pressure.

In cuff-based models of arterial stiffness, a constant transmission ratio has been assumed from the cuff borders to the center of the cuff while as mentioned in Chapter 2, the transmission may degrade by up to 70%. This has been considered in the model used for pulse transit time-cuff pressure variation [90] in Equation 3-27 which is expected to improve the accuracy of estimation of arterial stiffness.

The parameters representing arterial stiffness are incorporated into Oscillometric Waveform Envelope (OMWE), which was modeled according to lumen area variation. The combined model was tested first without fixing arterial stiffness values into the oscillometric envelope model. Mean Absolute Error (MAE), Standard Deviation of the Error (STDE) and Mean Error (ME) for SBP were 11.51, 13.42 and 5.75 mmHg respectively, and for DBP they were 6.9, 8.71 and -1.59 mmHg respectively. When, stiffness values estimated from the PTT-CP model were fixed into OMWE model. MAE, STDE, ME for SBP were 4.9, 6.31 and -1.23 mmHg respectively, and for DBP were 5.40, 7.38, and 2.60 mmHg respectively. Therefore, a smaller error is obtained when estimates of arterial stiffness are fixed in the OMWE model The errors obtained using the proposed method meet the criteria set by the Association for the Advancement of Medical Instrumentation (AAMI) and American National Standards Institutes (ANSI) in the ANSI/AAMI SP-10 standard for new blood pressure measurement techniques [107]. According to this standard, STDE should be less than 8 mmHg and ME less than 5 mmHg which are achieved when arterial stiffness parameters are estimated and fixed in the OMWE model.

According to the Bland Altman analysis, there is also better agreement between the proposed method and the reference method when the arterial stiffness values are first fixed in the

model. All stiffness parameter estimates were in the expected range and the coefficient b was always less than a, which is confirmed by other research findings [10] .

Based on the obtained results, Systolic Blood Pressure (SBP) is much more sensitive to arterial stiffness than Diastolic Blood Pressure (DBP). However, another study has obtained opposite results, as they concluded that SBP estimation is influenced by pulse pressure and not arterial stiffness [10]. Never-the-less, based on the literature survey we have done, pulse pressure is itself affected by arterial stiffness variation. Although it may be possible that pulse pressure can change without a corresponding change in arterial stiffness, a changing arterial stiffness will certainly cause pulse pressure to change. Therefore, we conclude that arterial stiffness should affect both SBP and DBP. The above-mentioned study (i.e. [10]) is the only previous research work that we found in the literature in which arterial stiffness was obtained using the oscillomtric envelope. However, this study did not test the algorithm on real-world data and validation was only performed by using cuff pressure oscillations simulated using a matrix of different levels of SBP and DBP and known levels of pulse pressure. A more important difference between their method and our proposed approach is that they used Oscillometric Waveform Envelope (OMWE) to estimate arterial stiffness coefficients. In contrast, we used the PTT, which is obtained by simultaneously recording the ECG and the oscillometric waveform, to estimate arterial stiffness parameters from another channel of information which is separate from the OMWE. We expect that using these two sources of information in our method would add to the reliability and accuracy of the blood pressure estimates.

The PTT is inversely related to PWV which is used in the evaluation of vessel properties [10]. Based on one study, PWV as an indicator of arterial stiffness at SBP level is much more

correlated with vessel characteristic than PWV at DBP. It can therefore be concluded that SBP is much more influenced by arterial stiffness than DBP, which is in agreement with our findings [105].

It should be noted that although we estimated arterial stiffness using curve fitting of the PTT, other approaches to estimating arterial stiffness may also be useful for improving models of the OMWE. Pulse Wave Velocity (PWV), which is arguably the most common measure used for arterial stiffness estimation, requires distance measurement and an appropriately trained device operator. However, distance can only be approximated and not precisely measured. Our method of Arterial Stiffness (AS) estimation is independent of any distance measurement and does not need a trained operator to perform the measurement. Therefore, the proposed approach could be readily incorporated into an automated blood pressure measurement device, such as the prototype described earlier, in which has capability to simultaneously measure ECG.

Our proposed individualized method, which considers the physical properties of the arterial vessel, is independent of any experimentally-determined ratios that are commonly used in current oscillometric approaches to blood pressure estimation. Therefore, it has the potential to achieve more accurate and more reliable blood pressure measurements.

Chapter 6. Conclusion

Blood pressure is one of the essential measures used to evaluate a person's health. Small measurement errors can translate into risk misclassification of the individual. It has been found that a 3-4 mmHg rise in systolic blood pressure means 20% higher risk of stroke mortality and 12% higher risk of ischemic heart disease mortality [108]. Prehypertension, which occurs at the high end of normal range of blood pressure, confirms the paramount importance of accurate blood pressure measurement [3, 109]. An accurate automated non-invasive method of blood pressure estimation in different health conditions is still missing [3].

The oscillometric method employs some characteristic ratios relative to the maximum envelope pressure amplitude in order to estimate Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP). These characteristic ratios are experimentally determined based on large population studies, and so likely vary among subjects with different disease conditions and vessel properties. Arterial stiffness is recognized as a critical factor that can result in an error of up to 15-20% in blood pressure estimation.

In this thesis, a simple and noninvasive approach is proposed which relies on lumen area variation of the vessel under the cuff during cuff deflation while simultaneously measuring the Pulse Transit Time (PTT) [8].

The PTT measurement is used to estimate two arterial stiffness parameters, by fitting the measured PTT to a physiologically-based model. Subsequently, the estimated arterial stiffness values are incorporated into a model of the Oscillometric Waveform Envelope (OMWE) with

only four parameters (SBP, DBP, and MAP and A_0). The values of SBP and DBP are then determined using a best fit curve to the measured OMWE. Validation of the results before and after fixing the arterial stiffness parameters was achieved by comparing with reference blood pressure values obtained using a commercially-available validated non-invasive blood pressure measurement device. The results show that incorporating the arterial stiffness-values into the OMWE model improves measurement accuracy compared to a purely oscillometric method without incorporation of arterial stiffness. We conclude that our approach can be used as a first step towards creating an individualized oscillometric method that is independent of experimental ratios.

6.1. Contributions

The main goal of this thesis was to improve the accuracy of the oscillometric algorithm by incorporating estimates of arterial stiffness in the measurements. The contributions therefore include:

- Incorporation of arterial stiffness estimates into the oscillometric waveform envelope model which results improve the accuracy of blood pressure measurement.
- An individualized approach to non-invasive systolic and diastolic blood pressure estimation that is independent of any experimentally-determined ratios. In addition to improving blood pressure accuracy, compared to a purely oscillometric technique without incorporation of arterial stiffness, this approach is likely less sensitive to variations between different individuals and health conditions compared to methods based on the experimental ratios.

- A new method of arterial stiffness estimation based on the variation of pulse transit time during the cuff deflation. This method is independent of distance measurement which is one of the main causes of error in arterial stiffness evaluation techniques.
- Validation of the individualized arterial stiffness-based blood pressure measurement approach on real-world data.

6.2. Future Work

The present study proposes a new technique of blood pressure measurement, which has some limitations that can be addressed in the future work. The main limitation of this work is the validation method. The validation of this work was performed by comparing the result with a validated non-invasive commercial Omron device. However, the invasive (intra-arterial) method of blood pressure measurement is considered as the gold standard. Comparing the results of the proposed approach with intra-arterial would give a more definitive validation. Even the auscultatory method with a trained observer may provide more reliable reference values for validating the proposed method. However, it should be noted that if the proposed method is not subject to consistent bias, then using a less accurate reference, such as the commercial device used in this study, for validation would be expected to contribute additional random errors to the validation results. Therefore, it is quite possible that the errors that are associated with our method are reality smaller than we reported.

This technique has been tested on 10 healthy subjects. A larger study population would provide much needed data. Moreover, none of the subjects have a history of cardiovascular disease. Since the basis of this technique is to involve arterial stiffness in BP measurement,

including individuals with different levels of arterial stiffness could help to assess the reliability of the technique.

The first phase of the proposed technique is to estimate arterial stiffness. Since this technique is easily applicable in automated oscillometric devices and there is no need for trained staff, it has the potential capability as a method for assessing vascular health. However, this needs to be validated with one of the clinically accepted approaches for arterial stiffness evaluation.

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