Continuous and noninvasive blood pressure measurement by pulse wave velocity : a new and systematic modeling methodology

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**Continuous and Noninvasive Blood Pressure
Measurement by Pulse Wave Velocity:
a New and Systematic Modeling Methodology**

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Summary

Blood pressure (BP) provides valuable information about cardiac output, cardiac pressures and hemodynamic stability. Continuous beat-to-beat arterial BP monitoring is highly desirable during surgical procedures so that physicians can early recognize the rapid changes of BP and intervene with proper therapy as necessary. Continuous and noninvasive BP measurement has been a topic of study for years, and many commercial devices have been available. The most commonly used technologies (applanation tonometry and vascular unloading method) have a shortcoming of complex mechanical structure. In this study, to avoid the complex and high-cost sensor or control system, arterial pulse wave is acquired using the easy-to-use, low-cost and technically mature photoplethysmography (PPG) to explore a new method for continuous and noninvasive BP measurement by pulse wave velocity (PWV).

Critical parts of this study include modeling BP-PWV relationship, determining two PWV's related to systolic blood pressure (SBP) and diastolic blood pressure (DBP) respectively, and verifying the modeling methodology by practical BP measurement using PWV. Experimental setup is developed on the basis of an existing multi-channel data acquisition device for obtaining a pair of pulse waves from the ear and toe sites by clip-type PPG sensors. A new BP-PWV model is established based on the fundamental physics and

physiology together with some constrained conditions from practical considerations. Model parameters take different values for different ages and genders. In order to avoid individual calibration of model parameters in practical measurement, we propose an algorithm of model parameters identification, in which the calibration is achieved in the modeling process through determining the model parameters by statistical method. The calibrated models are called 'benchmark models'.

To verify the feasibility of the BP-PWV model and the algorithm of model parameter identification, four benchmark models of the 19 and 60 age groups (representing young and old) with both genders are developed using clinical data obtained from patients with healthy cardiovascular system. The DBP's of 20 test subjects with healthy cardiovascular system and whose ages are around 19 and 60 are measured by the four benchmark models without individual calibration. The measurement results ($DBP \leq 125 \text{ mmHg}$) meet the accuracy criteria of the Association for the Advancement of Medical Instrumentation (AAMI).

PWV related to DBP (PWV_d) is determined by the commonly used foot-to-foot method. However, it is difficult to determine proper PWV related to SBP (PWV_s) because the shape of the pulse wavecrest changes constantly and unpredictably which makes PWV_s include large random errors. A method is proposed to obtain a PWV_s appropriate for SBP measurement using our

BP-PWV model, and in the same way, verified with SBP measurements from a small population with healthy cardiovascular systems. The measurement results satisfy the accuracy criteria of AAMI.

In this thesis, a new and systematic methodology of continuous and noninvasive BP measurement by PWV is established for people with healthy cardiovascular system. After continued study and gradual improvement, this low-cost and easy-to-use method may be applicable for BP monitoring of patients in operation room in future.

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Chapter 1

Introduction

Blood pressure (BP) is the pressure applying on the walls of blood vessels caused by circulating blood. Normally, the arterial pressure of systemic circulation is considered. BP changes in different blood vessels. When human body is in horizontal position, the change of BP is usually small and slow in main arteries, but BP will drop rapidly in the small arteries, arterioles and decrease continuously as the blood flows into the terminal capillary network and veins, eventually back to the heart. But if human body is in vertical position (e.g. stand and sit), BP in small arteries and arterioles in lower limbs will be higher than that in main arteries in chest because of gravitation.

In every cardiac cycle, BP is not a constant value. It varies from the minimum to the maximum, and then back to the minimum. The highest pressure when the ventricle is pumping blood into the arteries is considered as systolic blood pressure (SBP). Oppositely, diastolic blood pressure (DBP) is considered as the lowest pressure in the arterial system, which occurs at the end of a cardiac cycle [1]. SBP and DBP are most commonly used clinical signs.

BP measured from a healthy adult human when he/she is at rest is normally about 120 mmHg for SBP and 80 mmHg for DBP. SBP and DBP are varying naturally and unequally beat-to-beat, and changing greatly with physiological factors, such as nervousness, disease, drug effect, drinking, exercise and sudden movement. When BP becomes abnormally high for a long term, it is considered as hypertension. Oppositely, hypotension is considered as the case when BP is abnormally low for a long term. BP is one of the four important vital signs that must be monitored in operation room. The other three are heart rate, respiratory rate and body temperature. In routine healthcare, BP must be measured as well.

The history of BP measurement is more than two hundred years since the first measurement by Stephen Hales in 1733. Nowadays, BP is normally measured using a sphygmomanometer. The millimetre of mercury (mmHg) is used as the unit to reflect the value of BP [2]. Although the mercury is not really used in modern electronic device, mmHg is still considered as the unit for evaluating BP. BP can be measured directly and invasively by arteriopuncture, which gives accurate and continuous reading. But this method is too invasive to be commonly used in routine healthcare. It is usually restricted to surgery or intensive care. The noninvasive measurements, such as auscultatory and oscillometric, are easier and safer than the arteriopuncture, but they yield lower accuracy and just a single reading that is not enough for surgery as well as routine examination.

1.1 Motivation

Intermittent or continuous BP during surgical procedures is monitored to provide valuable information about cardiac output, cardiac pressures and hemodynamic stability. Patient response to anesthetic agents and surgical intervention is highly variable and unpredictable, and the combination of both commonly induces significant and rapid changes in BP. Interpretation of perioperative beat-to-beat BP is very useful because the physicians can intervene with proper therapy as necessary according to the real-time BP information. However, due to cost, complication risk or environmental circumstances, continuous and invasive intra-arterial BP monitoring is used only in cardiac surgery and in a few non-cardiac surgeries when the blood gas is required for analysis and the cardiovascular status may be unstable. In most non-cardiac surgeries, BP monitoring is accomplished using a standard patient monitor with traditional cuff technique that only provides intermittent measurements every 3-5 minutes [3]. Intermittent blood pressure measurement leads to an under-diagnosis and a delayed treatment response to perioperative hypotension and significantly increases the risk of dying either during or within 1-year after surgery [4].

Continuous measurement allows early recognition and treatment of rapid changes in BP and provides immediate feedback on the impact of interventions for optimal BP management. In the operation room today, BP is the only critical parameter that is not monitored continuously for all patients. Heart rate, respiration and oxygenation are all monitored continuously and non-invasively

for patient safety. It is therefore of considerable interest to achieve continuous and non-invasive BP monitoring.

Continuous and noninvasive BP measurement has been a topic of study for years, and many commercial devices have also been available for decades. Most of these commercial devices are based on the commonly used technologies called *applanation tonometry* and *vascular unloading method*, which acquire radial arterial pressure wave and finger arterial pressure wave respectively. Some of them, such as the T-line (Tensys Medical Systems) and CNAP™ Monitor 500 (CNSystems Medizintechnik AG), satisfy the accuracy criteria of the Association for the Advancement of Medical Instrumentation (AAMI) which stipulate that mean deviation $\leq 5\text{mmHg}$ and standard deviation $\leq 8\text{mmHg}$. Unfortunately, they are hard to be widely applied clinically due to complex mechanical structure, discommodious usage and extremely high manufacturing cost. Till now, the devices based on the two measuring technologies are generally used in clinical research and laboratory, seldom being used in operation room and routine clinical practices.

The fields where continuous and noninvasive BP measurement is most needed (e.g. operation room and intensive care unit) still lack suitable and reliable device to benefit patient and doctor.

1.1 Objectives

In this thesis, we aim to propose and validate a new and systematic methodology of continuous and noninvasive BP measurement by pulse wave velocity (PWV). For people with no evidence of cardiovascular disease,

individual calibration is not required in practical measurement. In our measuring method, a pair of pulse waves is acquired at ear and toe using the easy-to-use, low-cost and technically mature photoplethysmography (PPG) so as to avoid the complex and high-cost sensor.

In this work, there are three key problems that must be addressed.

1) Modeling the relationship between BP and PWV

In many available results, a model with different model parameters but the same pulse transit time (PTT) or PWV is used to estimate SBP and DBP. According to their results, the model parameters are changing at a fast rate when BP changes significantly and rapidly. Consequently, intermittent recalibration using external device is inevitable. Intermittent recalibration is difficult to response to the urgencies in operation room. In order to achieve the aim of fast-response and easy-to-use, we try to build a new BP-PWV model, in which SBP and DBP can be estimated by one model with the same model parameters but different PWV's. In this way, intermittent recalibration may be avoided.

2) Determining two PWV's related to SBP and DBP respectively

According to the methodology above, two PWV's related to SBP and DBP must be determined. It is commonly accepted that PWV with respect to DBP (PWV_d) is determined by the foot-to-foot method. However, how to determine PWV with respect to SBP (PWV_s) remains a problem to be solved since the shape of the pulse wavecrest changes constantly and

unpredictably. Proper PWV_s must be determined for measuring SBP using our model.

3) Verifying the modeling methodology by experimental data

SBP and DBP will be practically measured by PWV_s and PWV_d from a small population with healthy cardiovascular systems without individual calibration. The measurement results will be compared to the accuracy criteria of AAMI in order to verify the feasibility of the modeling methodology.

1.2 Major Contribution of the Thesis

The main contributions of this thesis are summarized as follows:

- A new BP-PWV model has been established based on the fundamental physics and physiology and some constrained conditions from practical considerations.
- An algorithm of model parameter identification has been proposed, in which the calibration is achieved in the modeling process by determining the model parameters using statistical method, so that individual calibration of model parameters in practical measurement can be avoided.
- The feasibility of the BP-PWV model and the algorithm of model parameter identification have been validated by DBP measurement in clinical environment without individual calibration using external device.

- Methods of identifying PTT in low, normal and high SBP conditions have been proposed and validated by experimental data.
- It is the first time that the PTT of reflected wave is determined and used in SBP estimation. By averaging the PTT's of incident and reflected waves for non-systematic error reduction, a PWV_s that is suitable for measuring SBP based on our model has been found.
- SBP and DBP are practically measured by PWV_s and PWV_d from a small population with healthy cardiovascular systems without individual calibration. The measurement results satisfy the accuracy criteria of AAMI, which verifies that SBP and DBP can be estimated by one mathematical model with the same model parameters and two separate PWV 's.
- Long-term BP measurement error by oscillometry throughout surgical operations has been analyzed statistically and compared with the accuracy criteria of AAMI. Also the probabilities of occurrence of the abnormal large errors and the clinically meaningful errors have been investigated from different aspects. We analyze the possible causes of the major errors and deduce that similar errors may happen with all oscillometric devices.

1.4 Organization of the Thesis

Chapter 1

This chapter first gives a brief introduction of the BP and its measurement, and then motivates and formulates the problem in continuous and noninvasive BP measurement. The main contributions of the thesis are

also summarized in this chapter.

Chapter 2

This chapter reviews the history of BP measurement and the traditional BP measuring principles including invasive and noninvasive methods. Standards for evaluation of BP measurement devices are also introduced in this chapter. Lastly, the limitations of the traditional non-invasive BP measurement are discussed in order to emphasize on the importance of continuous and noninvasive BP measurement.

Chapter 3

Chapter 3 summarizes the most commonly used techniques of continuous and noninvasive BP measurement based on the arterial pulse wave, which include applanation tonometry, vascular unloading method and pulse wave velocity/pulse transit time. We review the related literature, outline the advantages and disadvantages of these techniques, and explain why pulse wave velocity is used in our research.

Chapter 4

A brief literature review on the topic of pulse wave velocity and its measurement is provided in Chapter 4. The related mathematical models and the existing ways to quantify pulse wave reflections (including timing, magnitude, reflection sites and effective reflection length) are discussed since the reflected wave will be adopted in this research. The available

PWV/PTT measuring principles are summarized, and finally focus on the methods based on PPG.

Chapter 5

Chapter 5 presents the experimental setup used for signal acquisition and real-time BP measurement. The experimental setup is developed based on an existing multichannel data acquisition device. The existing parts, such as the dedicated computer, are briefly introduced. The self-designed parts, including a pair of PPG sensors and the special application software for identify PWV and calculating BP, are described in detail.

Chapter 6

In this chapter, the existing mathematical models for measuring BP by PWV/PTT are reviewed first. Then we derive a BP-PWV model based on the classical wave equation and some constrained conditions from practical considerations. The model parameters take different values for different age and gender groups. Then we propose an algorithm of model parameters identification which allows model calibration by statistical method.

Chapter 7

This chapter focuses on verification of the BP-PWV model and the algorithm of model parameters identification introduced in Chapter 6 by practical DBP measurement. A small population of subjects who have healthy cardiovascular system and in the 19 and 60 age groups

(representing young and old) of both genders is involved in experimental verification. The DBP measurement results satisfy the accuracy criteria in AAMI.

Chapter 8

Chapter 8 addresses the problem of determining proper PWV_s for SBP measurement and its identification methods in different BP conditions. The proposed PWV_s is validated by experimental data. In addition, this chapter verifies that SBP and DBP can be measured by one mathematical model with the same model parameters and two separate PWV 's.

Chapter 9

In this Chapter, BP measurement errors (oscillometry vs invasive method) throughout the surgical operations are investigated and compared with the accuracy criteria of AAMI. In addition, the probabilities of occurrence of the abnormal large errors and clinically meaningful errors are assessed. These errors are worthy of attention so as to avoid misdiagnosis and wrong/delayed treatment.

Chapter 10

Last chapter concludes our work and suggests possible topics for future research.

Chapter 2

Review of Traditional Blood Pressure

Measurement

2.1 Background

BP measurement has a history of more than two hundred years. Reverend Stephen Hales was given credit for inventing the first blood pressure measurement device in 1733. He inserted a brass pipe into the artery of a horse, and connected the pipe to a 274cm glass tube in which the blood level caused by pressure force can be observed [5, 6]. In 1828, Jean-Louis-Marie Poiseuille used a U type mercury column to replace the brass pipe and glass tube so that arterial BP could be measured by a 200mm mercury column. Until now, the unit of measure BP is millimeters of mercury. The first human BP measurement was performed by doctor Faivre in 1856 by inserting catheters directly into the artery. These early surgical procedures were too invasive to be used in a clinical setting. Patients might suffer from the infection and a mass of blood loss. Till now, the invasive catheterization is seldom used for BP measurement.

Physicians and scientists began looking for a noninvasive method of measuring blood pressure. Italian physician Scipione Riva-Rocci developed the mercury sphygmomanometer in 1896, which used an inflatable cuff on the upper arm to block and release the blood flow and measure BP [7]. In 1905, Nikolai Korotkoff found the relationship between the sounds made by arteries and BP, and then developed the auscultatory method to measure DBP and SBP [8]. The auscultatory technique was used till now and considered as the standard for the noninvasive BP measurement.

In order to increase reproducibility and reduce the operation difficulty, a microphone was used instead of human listening in automated devices. The most commonly used automated technique is oscillometric. Unlike auscultatory, oscillometric devices only can measure the mean blood pressure (MBP). SBP and DBP are obtained by estimation [5, 9]. Most commercialized sphygmomanometers are based on auscultatory and oscillometric. Some other methods, such as infrasound technique, ultrasound techniques and arterial tonometry, are also occasionally used to determine BP.

In recent years, ambulatory blood pressure monitoring (ABPM) has been paid attention gradually in order to obtain the BP of patient that well represents the patient's lifestyle instead of just one measurement in clinical setting. ABPM reflects patients' BP over a long period (typically 24 hours) so that it helps to identify the white coat hypertension as well as the circadian rhythm of BP [10]. From ABPM, the number of patients who are mislabeled as hypertensive can be reduced.

2.2 An overview of traditional BP measuring principles

2.2.1 Auscultation

Auscultation is the act of listening to sounds made by the blood by placing a stethoscope on the brachial artery. The sphygmomanometer includes a cuff placing around the upper arm of a subject. The cuff is inflated to a pressure higher than the subject's SBP when no sound can be heard. Then cuff pressure is slowly released. When there is a little blood flowing in the artery, a pounding caused by the turbulent flow can be identified. SBP correspond to the cuff pressure when the first sound is heard. The pounding sounds continue to be heard when the cuff pressure falls further, as long as the cuff pressure is between SBP and DBP. Eventually, the cuff pressure drops until there is no sound can be heard, at DBP [5, 8]. Figure 2.1 [11] shows the auscultation techniques for measuring SBP and DBP.

Figure 2.1 Auscultation techniques for measuring BP [11]

Korotkoff sounds actually include five different phases[12, 13].

Phase 1: The first appearance of clear pounding sounds. SBP is heard for at least two consecutive beats.

Phase 2: The softening of sounds which may become swishing or murmurs.

Phase 3: The return of sharp and crisp sound. The intensity is between phase 1 and 2.

Phase 4: The distinct abrupt muffling of sounds at pressures within 10 mmHg above DBP.

Phase 5: The disappearance of sound as the cuff pressure drops below DBP. DBP is considered as the cuff pressure at the end of phase 4 or the beginning of phase 5.

In manual devices, a rubber bulb is repeatedly squeezed to inflate a cuff and then the cuff pressure is slowly released. Korotkoff sound is listened by an examiner using a stethoscope. He/she can read from a mercury column and then determine the cuff pressure. In automatic devices, the stethoscope is replaced by microphones and the Korotkoff sounds are detected and analyzed by algorithms so as to determine the associated cuff pressure [9].

The measurement error may come from many factors. For instance, the Korotkoff sounds indicating real SBP may disappear but come out again at a lower point. This phenomenon is called auscultatory gap that may lead to an underestimation of SBP and/or an overestimation of DBP [14]. The way of determining DBP may be another source of error. Generally, DBP is the pressure at which the fourth Korotkoff sound is just barely heard. However, recently the fifth Korotkoff sound (i.e. silence) is used more often to recognize the DBP because this has been felt to be more reproducible[15].

Although the Korotkoff sounds may have individual differences, the auscultatory method is the most commonly used method in clinical BP measurement for more than 100 years [16].

2.2.2 Oscillometry

The oscillometric method predates the method of Korotkoff but it is not originally as popular. In this technique, the oscillation of cuff pressure which caused by pulse and related to BP is detected [17]. The cuff pressure oscillation is measured automatically using a proper-sized cuff with a pressure transducer (sensor), and interpreted electronically. Similar to the auscultatory method, the cuff is initially inflated to a pressure higher than SBP when the artery is compressed with no blood flow. Then the cuff pressure decreases and the arteries start to emit pulsations. During the decrease of pressure in the cuff, the oscillations will increase until a maximum amplitude ($A_{\max}$) which related to the mean blood pressure (MBP) [5, 18]. Then the oscillations will become smaller and smaller with the decrease of cuff pressure, until they disappear.

It may be suspected that the onset of the oscillation occurs at SBP and the disappearance of the oscillation occurs at DBP [19, 20]. In fact, the onset of oscillation actually occurs before the cuff pressure reaches SBP, and the oscillation does not disappear when the cuff pressure drops below DBP. The values of SBP and DBP can only be estimated indirectly according to some empirically derived algorithm instead of directly measuring from the oscillogram.

Figure 2.2 demonstrates an algorithm of estimating SBP and DBP [18]. Empirical and theoretical work has shown that SBP and DBP occur when the

amplitudes of oscillation are certain fractions, PIP_{SBP} and PIP_{DBP} respectively, of A_{max} [21]:

SBP is the cuff pressure when $PIP_{SBP} = 0.55$

DBP is the cuff pressure when $PIP_{DBP} = 0.85$

Figure 2.2 Oscillometry techniques for measuring BP [18]

Nowadays, most commercial automatic and semiautomatic sphygmomanometers preferentially use the oscillometric technique. Comparing with auscultatory method, oscillometry needs no transducer placed over the brachial artery so that placement of the cuff is not critical. In addition, the influence of external noise is less (but it may be still sensitive to the mechanical vibration, such as body movement) and the patient can remove and replace the

cuff by themselves. The oscillometric method has been used widely in ABPM in clinical setting as well as at home.

It is noted that the oscillometric devices produced by different manufacturers can use different algorithms to calculate SBP and DBP. So far, there is no standard algorithm for oscillometric method. Only a few commercial devices are recommended by professional societies such as the Association for the Advancement of Medical Instrumentation (AAMI) and British Hypertension Society (BHS) [16]. As the reliability of many oscillometric devices have not been confirmed, attention must be paid when these devices are used in clinical settings and intensive care (ICU). Even for those devices satisfying accuracy criteria of AAMI or BHS, their long-term BP measurement error during surgical operations or intensive care may still exceed the accuracy criteria set by AAMI or BHS. This may be because the conditions of BP monitoring in operation room and ICU are much more complex and unpredictable than the conditions stipulated by AAMI or BHS for sphygmomanometer validation. In addition, only the data from population is analyzed. The individual factors have not come into notice. Therefore, a patient monitor which has passed the validation criteria can still include consistent error in a number of individuals.

Shahriari M et al [16] had tested five different oscillometric manometers. The results showed that none of the tested manometers fulfilled the criteria set by the BHS. They suggested that these devices should be tested against the auscultatory recordings in every single patient when these devices were used at home. In the clinical wards, especially during surgeries, it was important for the doctors to be aware of the measuring accuracy if oscillometric measurements were used without calibration by the auscultatory measurements.

2.2.3 Intra-arterial cannulation

The theoretical concept of intra-arterial BP measurement has been established hundreds years ago, but it is not commonly used in clinical setting untill 1960's when the electromechanical devices become popular [22]. Intra-arterial cannulation is accurate and valuable but it has inherent risk. Consequently, anaesthetist with competent knowledge is required to make sure the safe and effective use of this BP monitoring tool.

The direct measurement of BP is quite invasive. A cannula needle is inserted into an artery (usually at brachial, femoral, dorsal or radial). Figure 2.3 [23] illustrates the intra-radial cannulation. A pressurized flush bag is utilized to obtain the arterial pulse. Generally, the flush bag is 500 mls of 0.9% sodium chloride solution (normal saline) and is connected to the transducer via tubing. This bag is placed in a pressure sleeve. When the pressure sleeve is inflated to 300 mmHg, there is a continues flow of 3 to 5 milliliters/hour in the pressurized flush bag. In this way, arterial blood will not climb along the tubing and the tubing will not be blocked [24].

Figure 2.3 Intra-radial cannulation [23]

The cannula is inserted in the opposite direction to the flow of the blood, as shown in Figure 2.4 [23].

Figure 2.4 Insertion of cannula [23]

There is a diaphragm in the transducer that can detect pulsation inside the fluid column and convert the pulsation to be a visible waveform. Besides measuring the beat-to-beat BP, the blood gas samples can also be obtained by the transducer that has been calibrated to atmospheric and hydrostatic pressures so as to ensure the accuracy of BP [25]. Generally, the transducer is placed near the insertion site of the arterial cannula, or it is fixed on a pole at the head of the patient's bed for security. The transducer is connected to a monitor for displaying and processing BP information. Usually, SBP, DBP, MBP as well as the pulsatile waveforms will be displayed simultaneously.

Since severe bleeding may occur if the transducer is disconnected, close supervision is required for patients undergoing invasive BP monitoring.

As the arterial cannula is directly inserted into the artery and usually the arterial blood gas samples is required to ensure the reliability of the BP measurement, when the cannula is removed, blood may splash on the eyes and mouth of the nurse which is potentially dangerous for them to be infected by contagious disease. Therefore, invasive arterial monitoring is not very

commonly used. It is only reserved for patients who need intensive care and a rapid variation of BP are suspected.

2.3 Evaluation standards

International Electrotechnical Commission (IEC) proposed safety standards for BP measurement devices in 1995. Performance standards for evaluation of BP measurement devices are recommended by three principle societies. Association for the Advancement of Medical Instrumentation (AAMI) published ANSI/AAMI SP10 in 2003, which is American National Standard for validation of electronic or automated sphygmomanometers [26]. According to ANSI/AAMI SP10, when auscultatory method is used as the reference, the subject database shall contain no fewer than 85 subjects with more than three measurements in each subject. A minimum of 255 observations ($=3 \times 85$) must be obtained and used to evaluate the performance of an automated sphygmomanometer. When intra-arterial method is used as the reference, tests shall be conducted in no fewer than 15 subjects and a minimum of five and a maximum of ten paired measurements per subject shall be made. The minimum number of entries of paired values, taking all subjects into consideration, shall be 150. For SBP, DBP and mean BP, treated separately, the mean deviation of the difference of the paired measurements shall be within ± 5 mmHg with a standard deviation ≤ 8 mmHg.

A protocol British Hypertension Society (BHS) has been drawn up to evaluate the device of BP measurement in 1990, and with some subsequent

revisions in 1993. This protocol includes most of the AAMI standard recommendations, but it includes some other features, such as inter-device variability, strict criteria for observer training, performance characteristics and a new system of analysis for grading the device under testing. The different categories or differences that determine the grade of classification are 5, 10, 15 mmHg [27, 28]. In 2002, European Society of Hypertension (ESH) [29] published the International Protocol. This protocol simplifies those from AAMI and BHS and includes a lot of validation studies. It uses the category differences that are similar to the BHS as the validation criteria. Considering that adults of the age over 30 years are the majority population who have hypertension, the validation is limited to this population. There is no recommendation for elderly, children, pregnant women and other special groups. In addition, this protocol is lack of investigation on some special circumstances such as during exercise, or abnormal pathophysiological circumstances, such as atrial fibrillation or arterial stiffness.

In our study, experiments are done in strict accordance with the ANSI/AAMI SP10, and the BP measurement results are evaluated based on the accuracy criteria recommended by AAMI.

2.4 Limitations of non-invasive BP measurement

2.4.1 Measurement accuracy

Non-invasive methods of BP measurement (auscultation and oscillometry) have been used for more than a hundred years and robust in theory [5, 30]. The

mercury manometer based on auscultation gives an absolute reading without need for calibration and thus considered as the gold standard. Oscillometric method gives reliable results for people with no evidence of cardiovascular disease. However, for patients who have heart and circulation problems, such as preeclampsia, arterial sclerosis, pulsus alternans, arrhythmia and pulsus paradoxus, the oscillometric method may give wrong readings.

Clinical research results have indicated that the non-invasive methods based on an inflatable cuff have a general tendency to underestimate true SBP independent of device [31-33]. In addition, it has always been known that noninvasive BP measurement using upper arm cuff has a bad performance for those obese patients who have large and cone-shaped upper arms. Usually, invasive measurement will be used for super obese patients to ensure the reliability[34]. Moreover, a few individuals may invariably have very big measurement errors which cannot be avoided by repeated measurements if the inflatable cuff technique is used to measure their BP.

An important point is that the measuring accuracy of any non-invasive sphygmomanometer in a single patient is unpredictable and the measurement error is inevitable. However, for two independent measuring principles, their resulting measurement errors have different sources, and thus the large errors should distribute in different populations. Measuring BP in a single patient based on two different non-invasive principles may be a way to recognize large errors. For instance, in certain BP measurement, two independent non-invasive methods are applied together and their measurement results are compared. If the results are similar, it indicates that the errors of both methods should be small and the measurement results are reliable. If the results are quite different, it

means that one of them has large measurement error. Although it is difficult to determine which method is accurate in this case, the results at least can alert doctors so that certain misdiagnosis can be avoided.

To date, auscultatory measurement is considered as the touchstone in judging the accuracy of an oscillometry sphygmomanometer [16, 35]. However, strictly speaking, auscultation and oscillometry are based on similar measuring principles which depend on cuff pressure [6, 16, 36, 37]. Alberto has pointed out that the features of the the oscillogram and Korotkoff sounds are closely related to specific levels of cuff pressure which are used to represent invasive pressure [6], as given in Figure 2.5 [38]. Consequently, auscultation and oscillometry have some common errors. Unfortunately, there is still no reliable measuring principle that is completely independent with cuff technique.

Figure 2.5 Comparison of auscultation and oscillometry [38]

2.4.2 Discontinuous

In the process of surgery, BP monitoring is essential to provide information about hemodynamic stability and cardiac output. Tracking the perioperative BP is important so that the surgeon and anaesthetist will intervene with proper treatment according to the BP information. In addition, the effects of anesthetic medications on the cardiovascular system must be specifically monitored during surgery to ensure the safety of patient. The perioperative BP which is sensitive to the anesthetic medications becomes a direct feature to indicate the effects of anesthetic medications. For subjects who have cerebrovascular disease, beat-to-beat BP monitoring becomes especially desirable because they may suffer from rapid and severe blood loss in surgical procedure and the hemodynamic instability is highly suspected.

Normally, continuous and invasive intra-arterial BP monitoring is required in cardiac surgery. For non-cardiac surgery, continuous and invasive BP is only measured when cardiovascular instabilities are expected. It has been reported that BP is monitored using a standard cuff-based BP monitor (oscillometry is used in most cases) in 82% of non-cardiac surgeries, in which the intermittent measurement is provided in every 3-5 minutes [3]. In the US, nearly 35 million non-cardiac surgeries are conducted per year. However, the invasive BP measurement is not used in most surgeries because of the cost and complication. According to the interviews and literature analysis, some patients undergoing non-invasive monitoring suffered from complications, which may be caused by unrecognized hypotensive episodes during or after surgery. Unfortunately, hypotension is difficult to be identified before and even during the surgical procedure. Measuring BP intermittently may lead to an under-diagnosis of or a

delayed treatment response to perioperative hypotension. As a result, patients will suffer from the risk of dying either in the process of surgery or within 1-year after surgery [4].

In addition, noninvasive measurements are commonly used in routine examinations for BP management and hypertension diagnosis. It is a fact that hypertension is the number one killer in the world, and it is not well managed by the conventional noninvasive means. The number of victims keeps increasing. The existing noninvasive method only captures BP based on one single heartbeat. A single reading at home or at the clinic does not represent a patient's BP over a long period. It is important to have patients' BP pattern profiled or tracked over 24 hours at regular intervals to have a better picture of the BP fluctuations. Ambulatory BP monitoring is an evidence-based approach to the management of hypertension as it records the BP fluctuations for 24 hours or longer.

2.5 Summary and conclusion

BP is a very important physiological parameter that reflects the conditions of cardiovascular system. Normally, methods of measuring BP can be classified into two categories: invasive method and non-invasive method. The invasive method, which usually needs arterial cannulation, is continuous and accurate. But it is only limited to certain clinical situations because of the cost, complication risk and environmental circumstances. The noninvasive methods, normally referring to auscultatory and oscillometry, are easier and safer than invasive method because less expertise is required and they are more pleasant

for the patient. In terms of routine BP management and hypertension diagnosis, auscultatory and oscillometry are more welcome. However, noninvasive methods generally have lower accuracy. For a few individuals such as these patients, the noninvasive methods have systematic differences which cannot be avoided by repeated measurements. In addition, they have a common disadvantage of discontinuousness which cannot meet the requirement of serious clinical situations, especially for surgery.

All of these are showing that the continuous, non-invasive, reliable, and easy-to-use BP monitoring is highly desirable.

Chapter 3

Continuous and Non-invasive Blood Pressure

Measurement Based on Arterial Pulse Wave

3.1 Background

In medicine, one's pulse represents the tactile pulsation of arteries resulting from the heartbeat. The pulse may be measured in any place, usually at the neck (carotid artery), at the wrist (radial artery), on the inside of the elbow (brachial artery), and at the fingertip (peripheral artery). The history of arterial pulse is long and distinguished. It had been applied in the diagnosis of disease by physicians from many ancient countries, such as Chinese, Greek, Roman and Indian [39, 40]. In traditional Chinese medicine, the radial pulse had been palpated and used as a important observation for more than 3,000 years [40, 41]. In Modern Medicine, John Floyer (1649–1734) developed a pulse watch that could count the number of pulses for sixty seconds. This was the first invention for identifying the pulse rate [42, 43]. Jules Herisson invented the *sphygmometer* that could detect the pulse and relate it to the regularity, rhythm force, etc [42, 44]. In 1860, Etienne Marey (a French

physiologist) modified Herisson's *sphygmometer* and introduced his *sphygmograph*. This new device was able to record the radial pulse graphically and the pulse rate and rhythm could also be interpreted [45]. After that, Marey's sphygmographs were improved upon by Mahomed whose sphygmograph was able to record the pressure of the pulse wave in a quantitative manner [46]. According to Postel-Vinay's review [47], the first cuff sphygmomanometer was introduced by Riva-Rocci [7, 48] in the late 19th century. In 1963, the arterial pressure waves shapes were measured by Pressman and Newgard using a new technique called applanation tonometry [49]. This technique was widely used to measure the peripheral pressure wave shape noninvasively [50, 51]. Other methods like vascular unloading and photoplethysmography were introduced later for measuring continuous BP based on arterial pulse[52].

3.2 An overview of continuous and non-invasive BP measuring principles based on arterial pulse wave

3.2.1 Applanation tonometry

Initially, applanation tonometry is developed for determining the fluid pressure inside the eye called intraocular pressure (IOP) [53, 54]. According to Imbert-Fick law, the force needed for flattening a constant area of the cornea is interpreted as IOP [55]. In recent years, this technique has been widely applied in detecting the arterial pressure pulse noninvasively as well as measuring the BP [6]. Theoretically, the arterial applanation is very similar to

the ocular application. By exerting pressure on the superficial artery locating near the bone, the curved surface of artery is flattened, at this moment, the tension of arterial wall is almost reduced to zero and the internal BP is nearly equal to the external pressure that can be measured using a transducer. Pressman and Newgard [49, 56] developed a tensiometer as illustrated in Figure 3.1. A plate is pressed on the skin outside the artery. The side plate makes the skin appanate so that the pressure in vertical direction entirely comes from the arteriopalmus. An artery plate that is narrower than the diameter of the artery is connected to a transducer so that the tiny changes of the radial pressure in the artery can be detected. The pressure on skin is adjusted to obtain the maximum pressure wave. Now the transmural pressure is reduced to zero and the pressure detected by the transducer is almost equal to the mean BP. The pressure at the peak of the pulse wave corresponds to SBP and that at the foot of the pulse wave corresponds to DBP.

Figure 3.1 Schematic diagram of arterial applanation tonometry [56]

Theoretically, applanation tonometry is able to give an accurate BP measurement result as long as the contact stress can be eliminated [55]. However, the practical application of this does not come easy.

This method has very high requirement on the placement of the sensor, as discussed below.

- 1) There must be a rigid support for the artery. It is common accepted that the wrist is a suitable and accessible location. The examiner can palpate the radial pulse easily on the carpal bone.
- 2) The sensor type may be a hand-held pencil-type holder or an intelligent system that can be strapped over the wrist [57, 58] to detect arterial pulse wave.
- 3) Sufficient and suitable hold-down force should be applied to make the artery appanate and obtain zero contact stress.
- 4) The sensor should be vertical to the horizontal axis of the artery so that no additional deformational stress is detected.
- 5) The sensor is easy to be displaced when the subject moves. The motion artifact may lead to loss of the pulse signal. This will increase the difficulty in long-term measurement.

It is assumed that if the sensor is perfectly placed and there is no displacement, the measurement result may still be unreliable. When the physiological status of the subject changes, the external pressure may not closely follow the mean BP and then the measurement error will occur [51]. So far, tonometric technique is not to be compared with the cuff sphygmomanometer in accuracy and ease of use [57]. However, this method can record the peripheral pulse which reflects the time-related change of BP [59, 60]. Some commercial devices combine the cuff sphygmomanometer and pulse

wave analysis to achieve the continuous and non-invasive BP measurement. For example, HealthSTATS International Pty Ltd use a watch-type sensor (Bpro), a cuff sphygmomanometer and a software (Pulse Traxer) for pulse wave analysis to monitor the beat-to-beat BP [61].

Other devices, such as the T-line tensymetry made by Tensys Medical Systems, can measure BP continuously and non-invasively without calibration by the cuff sphygmomanometer. T-line tensymetry consists of a non-invasive sensor that can detect and process the radial arterial pressure waveform using the advanced electronics and signal processing algorithms [62]. Initially, the atmospheric pressure is compensated automatically by the system inside the sensor. Then the system scans over the radial artery and determines an optimum position for pressure sensing. When the best site is found, the system will compress the radial artery and look for the mean BP by applanation dynamically. Once the mean BP is determined, the patient's BMI is used to scale the pulse waveform properly. Eventually, the SBP and DBP are determined by a proprietary algorithm.

3.2.2 Vascular unloading

Vascular unloading method or volume compensation method was proposed originally by Penaz [52] in 1973 to determine the continuous BP. A reference pressure is initialized to make the artery in unloading condition, so that the pressure inside the cuff is considered to be equal to the inner-arterial pressure. The reference pressure suggested by Penaz is the cuff pressure when arterial volume reaches $\frac{1}{3}$ of its maximum value. Figure 3.2 illustrates the vascular unloading method in which a simple PPG is included in the Task Force Monitor

(a sophisticated clinical cardiovascular assessment device) for continuous and noninvasive pulse detection and BP measurement [52].

Figure 3.2 The vascular unloading method with a simple PPG for continuous and noninvasive pulse detection and BP measurement

In 1980, Yamakoshi successfully measured BP in human fingers by this technique using a hydraulic to set the reference pressure [63]. FinapresTM was also introduced in the early 1980s for measuring finger arterial pressure [64]. Many methodological and comparative studies on this technology have been published. Imholz et al gave a extensive review [65]. The block diagram of Kawarata's finger sphygmomanometer is shown in Figure 3.3 [66]. The vascular volume at the distal part of the phalanges is monitored by PPG and a finger cuff is required to compensate the change in vascular volume. The instantaneous BP is represented by the finger cuff pressure that is maintaining the constant vascular volume.

Figure 3.3 Block diagram of the ambulatory system for the measurement of instantaneous arterial pressure in the finger [66]

Vascular unloading method describes the finger pressure pulse and provides the beat-to-beat arterial pressure. However, this method has some shortcomings. 1) The measurement device is generally large, complex and difficult to use. The microprocessor takes a long time to determine the reference pressure that makes the artery in unloading condition. 2) The device can be unreliable and uncomfortable if it is used for a long time because the persistent cuff pressure may occlude venous return. 3) The Mean BP and DBP obtained by vascular unloading method are acceptable. But the SBP can be widely discrepant and usually have a standard deviation in excess of 8mmHg [67].

The method is constantly improved and applied in a range of devices. CNAP™ Monitor 500 (CNSystems Medizintechnik AG) [68] and other similar devices (e.g. BMV, CnSystems) alternate measurement on two fingers so as to

alleviate the problem of venous obstruction, and make use of the brachial cuff pressure to calibrate the finger pressure [69].

3.2.3 Pulse wave velocity or pulse transit time

The Photoplethysmography (PPG) is a optical technique to detect blood volume changes in peripheral arteries [70] and provide useful information of the arterial system [71]. PPG waveform comprises consists of two parts: a pulsant ('AC') part that shows the change of blood volume in each heart beat, and a baseline ('DC') that varies slowly with respiration, sympathetic nervous system activity, etc. In recent years, the PPG technology has been widely used in clinical setting because of its noninvasive measurement, lightweight, simple-to-use and low-cost. Many medical devices based on this technology are available to measure the oxygen saturation, heart rate, BP, and cardiac output. Sometimes PPG technology is also used to find out the peripheral vascular disease or assess autonomic function. An general review on the applications of PPG in a number of physiological measurements has been provided by Allen [72].

There are similarities between the blood volume pulse measured by PPG and the blood pressure pulse. There are several approaches to measure BP non-invasively based on PPG. Vascular unloading method enables measurement of arterial pulse and beat-to-beat peripheral BP by an inflatable finger cuff and a simple PPG sensor. Another popular approach based on PPG is pulse wave velocity (PWV) or pulse transit time (PTT). The first record of detecting the change of BP using PWV dates back to 1976. Brain Gribbin's experiments showed that the PWV could reliably track the varying BP, but did not provide the absolute value of BP [73]. To find out the functional relationship between

BP and PWV, experiments were done on 11 subjects. Linear relation was found in 7 subjects and high order functional relationship appeared in the other 4 subjects [74]. The factors that may influence the linear relationship between BP and PWV were further discussed by W. M. Lu [75]. He pointed out that the variation of the functional relation between BP and PWV might result from the vascular elasticity and vasomotion which indirectly affect the PWV. It was suggested that vasomotion could be measured together with PWV to improve the accuracy of the estimated BP. Someone had established regression equations by statistics to calculate SBP and DBP based on PTT [76]. The specific method was: The time interval between the R wave of ECG and the finger pulse was considered as PTT. Two regression equations corresponded to SBP and DBP respectively. To ensure the accuracy and generality, calibration was required before the SBP and DBP could be estimated by the regression equations. However, the regression equations were insensitive to DBP. It was reported that DBP changes very small (only $\pm 2\text{mmHg}$) during 24 hours measurement [76].

Although many studies show that PWV may be linear correlated to BP, there is still no standard model. A specific model depends on the pulse detection method and measurement location on human body. The measurement of PWV may be affected by some influencing factors like temperature, heart rate, etc. These influencing factors can make the PWV measurement very unstable. Consequently, the estimated BP will include nonsystematic errors. Up to now, the PWV method is mainly used in research lab but has not been used in clinical setting. Further development is required, especially on the BP-

PWV model and the methods of reducing the nonsystematic errors caused by varying PWV.

3.3 Summary and conclusion

Continuous and noninvasive BP measurement has been a topic of study for years. Many measuring techniques and commercial devices have also been available for decades. The most commonly accepted and widely used techniques are applanation tonometry and vascular unloading method. Some devices based on the two measuring techniques, such as T-line (Tensys Medical Systems) [62] and CNAP™ Monitor 500 (CNSystems Medizintechnik AG) [68], satisfy the accuracy criteria of AAMI. TL-150 can detect the pulse waveform of radial artery based on applanation tonometry, which requires carefully determining the position of radial artery on wrist. The system in the sensor can dynamically obtain beat-to-beat maximum pulse pressure via continuous calibration [77]. These result in a sensor of complex structure, discommodious usage and extremely high manufacturing cost. Consequently, the devices based on applanation tonometry are hard to be widely applied clinically. CNAP™ Monitor 500 is a representative of finger-cuff device based on vascular unloading method. Two CNAP™ cuffs are placed over two neighboring fingers of the patient to detect finger pressure pulse, and a normal cuff controller is fixed on the patient's arm for information feedback and repeated calibration [78]. The close-loop control system is complex in structure, which results in high manufacturing cost. In addition, it is uncomfortable when the device is used for a long time since the maintaining of finger cuff pressure will occlude venous return [6]. Till now, most similar devices based on vascular

unloading are used only in clinical research and laboratory, seldom being used in operation room.

In order to avoid the complex and high-cost sensor or close-loop control system, the easy-to-use, low-cost and technically mature PPG is good choice for exploring a new method for continuous and non-invasive BP measurement [72]. The peripheral pulse obtained by PPG can provide some valuable information of the arterial system, such as pulsatile pressure, heart rate, peripheral arterial narrowing or occlusion [79]. One of the popular approaches is to make use of the relationship between BP and the parameters of PPG wave, such as PWV or PTT, to estimate BP. Though the PWV approach is still in the test phase, its prospective application has been presented.

Chapter 4

Pulse Wave Reflection and Velocity

4.1 Mathematical models

4.1.1 Models of pulse wave propagation

The left ventricular ejection causes the increase of blood volume and pressure in the arterial system, as well as the propagation of pulse wave through arterial tree. The relationship between the blood volume and pressure is approximated to that between electric quantity and voltage, as expressed in equation (4.1).

$$C = \frac{\Delta V}{\Delta P} \quad (4.1)$$

where C is the arterial compliance, ΔV is the change in blood volume and ΔP is the change in arterial pressure [80-82]. This linear model has certain physiological significance, for example, it shows that the same stroke volume may generate a higher pressure when one's arterial elastic modulus decreases due to age [83-85]. However, this model is too simple to describe the time-related changes of the pulse wave in the arterial system.

As the concept of arterial impedance with phase and modulus is introduced, some frequency-related models were developed to describe the pulse wave propagation. McDonald proposed an flow model (equation (4.2)) which expressed the pressure and flow in the frequency domain [86] [87].

$$P(\omega_i) = Z_{in}(\omega_i) \times Q(\omega_i) \quad (4.2)$$

where $i = 1, 2, 3, \dots, N$.

P , Q and Z_{in} are magnitude of the pressure pulse, flow rate, and arterial input impedance respectively, while $P(\omega_i)$, $Q(\omega_i)$ and $Z_{in}(\omega_i)$ are the sinusoidal components of these variables in the period of a cardiac cycle, where ω is the harmonic. At most the first ten harmonics ($N=10$) are used to describe the arterial pulse, as 90% of the energy is in the first five to eight harmonics [86].

Womersley's simplified the arterial system to be a closed cylindrical conduit and developed the fluid motion equations which introduced the concept of wave reflection, dimension and elasticity of the artery, as well as the viscosity and density of blood, so that the pressure pulse along the uniform tube can be calculated [88, 89]. Equation (4.3) defines the reflection coefficient (Γ) for each harmonic (ω).

$$\Gamma(\omega) = \frac{Z_T(\omega) - Z_0(\omega)}{Z_T(\omega) + Z_0(\omega)} \quad (4.3)$$

where Z_0 is the tube characteristic impedance that depends on the properties of blood as well as the arterial wall within a uniform segment of a length of L . Z_T represents the terminal impedance. [90]

The transmission of pulse in the tube is expressed using the transmission ratio that is calculated by dividing P_L (the pressure pulse at length L) by P_0 (the pressure pulse at the input).

$$\frac{P_L}{P_0} = \frac{1 + \Gamma}{e^{\gamma L} + \Gamma e^{-\gamma L}} \quad (4.4)$$

where the propagation coefficient (γ) not only depends on the properties of blood such as the density and viscosity, but also the wall properties (elastic and geometric) of the segment of a length of L . P_L , P_0 , γ , Γ are all functions of frequency (ω) [90, 91].

Although equation (4.3) is based on an ideal arterial model, it indicates that the pulse wave can be reflected anywhere in the arterial system due to the impedance mismatch. Due to the increase of the impedance along the arterial tree and the wave reflection inside the closed segment, the value of Γ is usually positive for the first two or three harmonics. From the fourth harmonic, it becomes negative. In most cases, the overall effect of the reflections is considered. The wave reflection is considered to be constructive if Γ is positive and it increases the total BP. Reversely, when Γ is negative, the wave reflection is considered to be destructive and the total BP will be decreased.

Equation (4.4) shows that the change of magnitude and phase of the pressure pulse along the arterial tree result from the change in dimension and elasticity of the arterial wall. Consequently, the wave shape and pulse pressure will be different at different locations in the arterial system. For example, the central and carotid arterial pulses have a wide and smooth incident wave crest and the reflected portion is most likely clear and high due to the 1st reflection from femoral vascular bed [6]. However, for the peripheral arterial pulse, like those at finger and toe, generally only one high peak that is the incident wave, can be observed. This is because peripheral arteries are at the distal end from heart so that they are not affected by the 1st reflection and the effect of the 2nd or higher reflections are very small [72, 79, 92]. Moreover, it is well known that

the peripheral pulse pressure is generally larger than the central pulse pressure (higher SBP and lower DBP) excluding the effect of gravitation, known as pressure amplification [93].

4.1.2 Models of blood flow and pulse wave velocity

Windkessel models describe the process that when the heart pumps blood into the arterial system, BP is generated and blood flows through the arterial tree, eventually back to heart. As shown in Figure 4.1, four components are included in Windkessel model: left ventricle, aortic valve, large arteries and peripheral arteries [94].

Figure 4.1 Schematic diagram of the Windkessel model [94]

The arterial system is considered as a system of closed type in Windkessel model. It includes a pump and a chamber filled with water. There is a pocket of air in the chamber. The operation process of this model is simple: the pressure generated by the pump makes the air in the pocket compressed, and then it presses the water to flow through the chamber and back to the pump. The arterial compliance that refers to the extensibility and elasticity of large arteries

can be simulated by the volume change of the air in the pocket. Peripheral resistance refers to the resistance blood encounters when it flows through the arterial system and finally back to the atrium of the heart. This resistance is represented by the resistance that water encounters when it flows through the chamber and return to the pump [90, 95].

This model is very useful as it expresses the changes of arterial system in hypertension. When only peripheral resistance increases, mean BP, SBP and DBP rises together. However, when the both factors changes (the peripheral resistance increases while in the arterial compliance decreases), mean BP and the pulse pressure (the difference between SBP and DBP) will increase. This results in a large increase of SBP but small increase of DBP [95].

However, two limitations have been reported for the Windkessel model. Firstly, it uses a simple chamber to represent the arterial system. Physically, the elastic modulus and diameters continuously change from the ascending aorta to the peripheral arteries which are less elastic but more muscular. This results in the corresponding changes in peripheral resistance and arterial compliance along the arterial tree. More important, PWV is assumed to be of infinite value in the Windkessel model. However, PWV is non-uniform in different arterial segments. PWV increases from the main arteries to peripheral arteries as the peripheral arteries are generally stiffer than the major arteries [93]. In healthy subjects, the PWV is about 4–6 m/s in the ascending aorta, 5–6 m/s in the thoracico-abdominal aorta, and 8–9 m/s in the femoral arteries [90].

To describe the properties of PWV, the propagative models are developed for the circulatory system. These models are based on the assumption that the

velocity of a pulse wave transiting in an artery is a finite value. The famous Moens-Korteweg equation was proposed by Frank in 1920 [96] .

$$PWV^2 = \frac{Eh}{2R\rho} \quad (4.5)$$

where E denotes the elastic modulus in the circumferential direction (which represents the intrinsic stiffness of the wall), h denotes the thickness of arterial wall, R denotes the radius, and ρ denotes blood density.

In 1922, Bramwell and Hill [97] made use of Moense-Korteweg equation to describe PWV in terms of relative change in volume and pressure during ex vivo experiments:

$$PWV^2 = \frac{V \times dP}{\rho \times dV} \quad (4.6)$$

Equation (4.6) includes the change in arterial volume (V) denoted as dV , and the corresponding change in pressure (P) denoted as dP . This equation shows the relationship between PWV and the distensibility of the artery expressed as $dV/(V \times dP)$.

The propagative models (equation (4.5) and equation (4.6)) are more realistic than the Windkessel model, and currently commonly applied in clinical studies.

4.2 Quantifying pulse wave reflections

When the heart ejects blood into the arterial system with a ventricular pressure, a forward wave is generated and it transits along the arterial system. The wave encounters a number of impedance mismatches and it is reflected at

these sites, such as the ramifications and termination points, and then transits backward to the heart. A series of reflected waves are superposed on the forward wave, which change the magnitude and shape of the pulse waveform in central body. For convenience, a single reflected wave is used to represent the summation of all reflected waves.

The characteristics of this reflected wave include its amplitude, the timing of its return or PWV of the reflected wave, the locations of the reflection points (RP) and their distance from heart [98]. From structural aspects, diffuse and continuous reflection patterns will be generated due to the impedance mismatch along the arterial system so that the pulse wave reflection (PWR) is difficult to be interpreted.

PWR is also influenced by the functional changes of arteries, such as the dilation of blood vessels, arterial stiffness and other cardiovascular diseases like hypertension. For example, PWR increases at vasoconstriction while decreases in vasodilation due to the change of arterial stiffness. Hypertension will increase the stiffness of elastic aorta, and subsequently causes the progressive change in arterial impedance. In addition, the arteries will become stiffer and stiffer with the increase of age, which make PWV increase. Younger subjects have relatively low PWV and the reflected waves can be clearly observed during late systole or diastole. Generally, PWV in old subjects is higher than young subjects. For old subjects, it seems that the reflection points in their arterial tree will move towards to heart, which results in the overlap of forward wave and reflected waves during systole. Consequently, they have higher BP, especially the SBP and pulse pressure [98]. Normally, in young subjects the

central pressure waveform looks like a C-type (Figure 4.2 (a)), and in older subjects it evolves to be an A-type wave (Figure 4.2 (b)) [99].

Figure 4.2 (a) C-type pressure waveform, with negative AP and AIx.

(b) A-type pressure waveform, with positive AP and AIx [99].

4.2.1 The timing of wave reflection

To properly investigate the timing of wave reflection, the aortic pressure and the flow wave need to be measured at the same location simultaneously. Then the measured pressure waveform is separated into the forward and reflected components [100]. The standard method for assessing the wave reflection is wave separation analysis. As it is often complicated and inconvenient to measure the pressure and flow invasively, alternative methods of analyzing wave reflection, which are more intuitive and accessible, have emerged. For instance, the timing of the return of the reflected wave can be determined by identifying the characteristic points on a single waveform.

Some parameters of wave reflection, such as the reflected wave timing and the effective length (the distance from heart to the sites where most of the

reflected waves originate) had been investigated by Segers et al [101]. They made use of two methods, which are wave separation analysis (WSA) and waveform analysis (WFA), to calculate the reflected wave timing and the reflection magnitude. Their analyses were based on the assumption that there was an effective reflection site (a theoretical reflection point) in the body [101].

Figure 4.3 Determination of the timing of reflected wave
based on WSA and WFA [101]

The results obtained by WSA and WFA are given in Figure 4.3 (A) and (B) respectively [101]. In Figure 4.3 (A), the pressure wave is split into a forward part (P_f) and backward part (P_b). ΔT_{f-b} represents the time delay between P_f and P_b . T_{f-b} is the time difference between the foot of the pulse wave and the starting of P_b . The corresponding pressure is denoted as P_{f-b} .

The critical part of WFA is to identify the arrival time of the reflected wave. Usually, the inflection point [102] and the shoulder point [103, 104] on the pulse waveform are considered as the characteristic points. In Figure 4.3 (A), both characteristic points are identified for WFA. The inflection point is found

by the second order derivative so that its timing (T_{inf}) and the corresponding pressure (P_{inf}) can be determined. The fourth order derivative is applied to find the shoulder point as well as its timing (T_{sho}) and the corresponding pressure (P_{sho}).

According to the existing reports [99, 101], different analyzing methods resulted in different reflected wave timings. WSA and WFA yielded quite different results. The change of effective lengths with age decreased in WSA but sometimes increased in WFA [101]. It was also reported by Westerhof et al [105] that timings of reflected wave based on WSA and WFA did not fully indicate the pulse transmit time between heart and the effective reflection point because the phase differences at the different reflection sites would cause extra time delays.

It has been pointed out that the reflected wave timings may not be reliable if they are determined from a single pulse waveform[106], and it is important to realize that the characteristic points identified using different methods may result in significant differences in the value of parameters [99].

4.2.2 The magnitude of wave reflection

One commonly used method to evaluate the magnitude of wave reflection is based on the forward (P_f) and backward (P_b), which can be calculated from pressure(P_{wf}), flow (Q_{wf}) and local characteristic impedance (Z_c) [107].

$$P_f = \frac{P_{wf} + Z_c \times Q_{wf}}{2} \quad (4.7)$$

$$P_b = \frac{P_{wf} - Z_c \times Q_{wf}}{2} \quad (4.8)$$

The wave reflection magnitude is calculated by dividing the amplitude of

P_b by that of P_f (P_b/P_f). Z_c is the characteristic impedance that expresses the characteristics of wave propagation inside the vessel segment. It can be obtained by taking the average of the modulus of input impedance, generally for the 3rd to 10th harmonics [107].

Another commonly used parameter to quantify the magnitude of wave reflection is augmentation index (AIx) [50], which is calculated by dividing the augmented pressure (AP) that represents the pressure increase caused by wave reflection to the pulse pressure (PP).

$$AIx = 100 \times \frac{AP}{PP} \quad (4.9)$$

AIx (usually a percentage) can be derived from the morphology of a pulse wave, as shown in Figure 4.4. P1 and P2 denote the first and second systolic peaks, while P3 is the diastolic pressure. The AP and PP are defined as P2-P1 and P1-P3. AIx is the ratio of them in percentage [93, 108].

Figure 4.4 AIx: the ratio of augmentation pressure to pulse pressure [93, 108]

An important step in determining AIx is to identify the time of arriving of the reflected wave. For a C-type waveform as in Figure 4.2 (a), the arriving of reflected wave is in late systole so that an inflection point can be identified after the peak of the pulse wave. In these cases, Both AP and AIx are negative. Regarding the A-type waveforms in Figure 4.2 (b), the superposition of the reflected wave and the forward wave make the inflection point appear before the peak, and thus both AP and AIx are positive [99]. Generally with aging, waveform will transform from C-type to A-type. When the shape of waveform is between type A and C, the inflection point can be very near or superposed to the systolic peak. In this case, the AIx value is shown to increase from negative to positive due to the change of arterial stiffness.

The two methods (waveform analysis and AIx) are important tools to quantify the magnitude of wave reflections. However, they have some limitations. For instance, the results highly depend on the choice of characteristic points.

4.2.3 Wave reflection sites and effective reflection length

The wave reflection is non uniform along the arterial tree. For an arterial system with good elasticity, main reflections occur at the arterioles and peripheral vascular beds in lower limbs. The distance between heart and the main area of reflections is about one meter or more. These wave reflections arrive during late systole or early diastole, which create a second peak of pulse wave. Reflections from sites near the heart seem more likely to augment the central pulse wave and pressure. For a stiff arterial system, especially the

central arterial stiffness, most wave reflections arrive in early systole so that a high pressure peak appears.

To carry out study, calculation and analysis, the effective reflection site or effective reflection length is often required. The effective reflection site or length is affected by individual difference. It is commonly accepted that the stiffness of central arterial as well as the PWV will increase with age, and the effective reflection site will move towards to heart.

The effective length can be identified based on the timing of return of the reflected wave. It was reported by Mitchell et al that the effective reflection length was between 50cm and 60 cm from the heart [109], using the inflection point method introduced in Section 4.2.1. And the effective reflecting sites found by Segers et al were 40-60 cm from the heart [101] using WFA and WSA. It was suggested by Qasem and Avolio that the distal aorta is a real reflection site [110].

The calculations of effective length may be different depending on the methods and transducers for measuring the pulse wave [105]. Most analysts believe that the lower abdomen is the main area of reflections, such as the results reported by Karamanoglu et al [111]. Besides the abdominal area, wave reflections mainly occur at the aortic branches connecting to those organs requiring high blood flow like kidneys and their microvasculature [98].

Mathematically, the effective length (L_{eff}) can be estimated by equation (4.10) [101].

$$L_{eff} = \frac{PWV \times \Delta T_{f-b}}{2} \quad (4.10)$$

where ΔT_{f-b} is the time delay between the forward wave and the backward wave, which can be obtained based on the method introduced in Section 4.2.1. The measurement and calculation of PWV is discussed in Section 4.3.

4.3 Measurement of pulse wave velocity

It is commonly accepted that PWV is considered as the predictive value of aortic stiffness. The pathological changes of the aorta and its first branches, like atherosclerosis, have the most significant effect on the PWV. Therefore, the carotid-femoral PWV is considered as the gold standard of PWV measurement [93]. In contrast, PWV measured in small arteries and arteriole at the limbs (arm or leg) is not reliable to patients with end-stage renal disease (ESRD) and peripheral arterial disease (PAD) [112]. However, some investigators suggested that the brachial to ankle PWV (baPWV) might be used and as it was an independent predictor for cardiovascular deaths and events [113, 114].

The foot-to-foot PTT, which is determined from two or more pulse waves obtained simultaneously at different locations on body, is usually used to measure PWV. The end of diastole or the starting of a pulse is considered as the foot of the wave. PTT is the transmit time of the foot of a pulse over a fixed distance. The right common carotid-femoral PTT which is the time delay (Δt) between the feet of two pulse waves is shown in Figure 4.5 [93]. The pulse waves can be obtained by different methods which will be introduced later [115-117]. The distance between the two sites of measurement is considered as the pulse wave transit distance (D). Thus $PWV = D \text{ (meters)} / \Delta t \text{ (seconds)}$.

Figure 4.5 Measurement of carotid-femoral PWV by foot-to-foot method [93]

The measured PTT and transmit distance will inevitably include errors [118]. The absolute error is great in short distance between two recordings sites, and it is reduced if the transmit distance is longer. Therefore, using the complete distance between the carotid site and the femoral sites will help to improve the signal-to-noise ratio. However, the direction of blood flow from heart to carotid is opposite to that from heart to femoral sites, thus, the distance between the carotid and the sternal notch should be subtracted from that between the femoral recording site and the sternal notch so as to get the effective distance [116, 119].

Some investigators have pointed out the limitations of the carotid-femoral PWV measurement. For those patients who have diabetes, metabolic syndrome, obesity and peripheral artery disease, it may be difficult to record the femoral waveform accurately [119]. In addition, the aortic and femoral stenosis will make the waveform distorted, attenuated or delayed.

4.3.1 Methods based on pressure sensors and Doppler probes

One way to measure PWV or PTT is to obtain pulse waveforms by pressure sensors at different arterial sites simultaneously, and the time difference between each simultaneously recorded wave is determined. The time difference is considered as PTT. PWV is calculated by the distance between any two recording sites divided by the corresponding PTT. The commonly used measurement sites are neck, thigh, arm, instep, etc. The Complior Systemw (Colson, Les Lilas, France) is a device that can measure the carotid-femoral, carotid-brachial and femoral-dorsalis pedis PWV based on dedicated mechanical pressure transducers [115]. The arterial waves can also be recorded, displayed and validated.

Another method is to consider ECG as the starting, and record pressure waves simultaneously from different sites. For example, the SphygmoCor system obtains a carotid pulse, a distal pulse (radial or femoral) as well as a simultaneous ECG [116, 120]. PTT is obtained by subtracting the time between the ECG and the carotid pulse from that between ECG and distal pulse. The starting point of the pressure waveform is considered as a reference point. The PWV determined by this method is influenced little by the left ventricle isovolumic period (LVIP) and variation of heart rate [93].

PTT can also be measured from two simultaneously recorded flow pulses using the echo-tracking devices such as Doppler probes [117] , with ECG gating. Commonly used measurement sites are suprasternal notch and umbilicus area. It has been reported that the Doppler method has advantage in assessing aortic PWV in comparison with the carotid-femoral PWV.

4.3.2 Methods based on PPG

The pulse wave measured by PPG is peripheral arterial pulse and the PTT is relatively longer than the carotid-femoral PTT. In many studies, PTT is considered as the time interval between the R wave of ECG and the foot or peak of the PPG wave, as shown in Figure 4.6 [121-125] .

Figure 4.6 Identification of PTT: PTTf refers to the foot of the pulse from ECG and PTTp refers to the peak of the pulse from ECG [79]

In some researches, PTT is considered as the time interval between the ECG R wave and the point with maximum gradient [126] or 25% (Max-Min) [127] on the PPG, as illustrated in Figure 4.7 (a) and (b). The PPG signal is usually obtained from peripheral site, such as ear, finger and toe[125, 128].

Figure 4.7 (a) Pulse Arrival Time (PAT): time difference between the R peak of ECG and the maximum gradient point on the rising edge of PPG [126]. (b) PTT: time interval between the ECG R-wave and the point showing 25% (Max-Min) on the PPG [127].

It was reported by Payne et al [129] that the ECG-based PTT included the cardiac pre-ejection period that was significant in value. In order to reduce the contribution of pre-ejection, the vascular transit time (VTT) was proposed[130]. It was defined as the time interval from the heart sounds (PCG) to the foot of the PPG waveform, as shown in Figure 4.8 (a). Similarly, Foo et al [131] used

the first heart sound as the starting of VTT, but the peak of PPG was used to calculate the transmission delay, as shown in Figure 4.7 (b).

Figure 4.8 (a) Vascular transit time (VTT) is the time difference between the first heart sound of the phonocardiogram (PCG) and the foot of the finger PPG [130]. (b) VTT is the transmission delay between the first heart sound (S1) and the peak of the finger PPG [131].

Another way to remove the PEP is that the peripheral pulses (i.e. finger and toe) are recorded sequentially with a small time interval and PTT is considered as the time difference between the two recording sites, where the R peak of the ECG is used as reference [127, 132-134], as indicated in Figure 4.7 (b) [127].

This method can be early implemented using a standard vital signs recorder. However, the PTT is estimated using pulses obtained in different cardiac cycles. A more accurate way should be using two pulses in the same cardiac cycle obtained simultaneously at different arterial sites. [135-138]

It has been shown that PTT has strong correlation with BP. In some studies, beat-to-beat changes in BP can be tracked using the PTT [129, 139]. Chen *et al* [140] proposed a method to measure SBP intermittently using high frequency information in the PTT. A toilet seat prototype with housed ECG electrodes and PPG sensor was developed for monitoring SBP at home [141]. In this innovative healthcare device, the PAT was determined by an algorithm and then used to estimate BP. The PAT-based BP needed to be calibrated using a tradition cuff-based sphygmomanometer.

4.4 Summary and conclusion

There are many mathematical models expressing the arterial pressure pulse wave and its propagation in the arterial system. However, very few of them are applied to practice. In terms of PWV, Moens-Korteweg equation is the most acceptable propagative model for the circulatory system. In this equation/model, the arterial system is simplified to be a distensible tube and the peripheral resistance is considered as terminal resistance. The distributed elastic properties of this realistic model allow the pressure wave being generated and propagating along the tube.

It is suggested by O'Rourke, etc [108, 142] that waves are reflected at the end of tube with high resistance and then the retrograde waves are generated. The commonly used methods for quantifying the wave reflections are wave separation analysis (WSA), waveform analysis (WFA) and augmentation index (AIx). WSA and WFA are used to investigate the return time of the reflected wave as well as the reflection magnitude. But some researchers have shown that the timings of reflected wave obtained from WSA and WFA can be different. Another way of assessing reflected wave is AIx, which is defined as the ratio of augmented pressure (AP) to pulse pressure (PP). AP indicates the increase of pressure caused by wave reflection. Generally, AP and AIx are negative for young people whose reflected waves arrive in late systole, and positive for old people whose reflected waves arrive in early systole. Moreover, AIx can be used to indicate the stiffness of arterial system as it can be positive for young subjects who have arteriosclerosis.

Though pulse wave can be reflected anywhere along the arterial system, the arterial branches and terminal microvascular beds are thought to be the major area of wave reflections. To carry out calculation and analysis, the effective length is required although it is just a theoretical concept. How to determine the effective reflection length remains debatable. It depends on the methods and transducers for measuring the pulse wave and it is affected by individual difference. Most investigators believe that the lower abdominal area may be considered as the effective site of wave reflections.

PTT/PWV can be measured from various waveforms by the foot-to-foot method. The measuring techniques include pressure sensors, doppler probes, etc. The most commonly used PWV is carotid-femoral PWV. But its limitations

have been reported. For instance, it is difficult to record the femoral pressure waveform accurately in subjects who have diabetes, obesity and peripheral artery disease. Therefore, in some studies, PTT is measured by the low-cost and technically mature PPG from peripheral arteries. Regarding the measurement of the PPG-based PTT, a pulse wave is recorded from peripheral site (ear, finger or toe), and PTT is considered as the time difference from a simultaneously recorded ECG. The PTT measured in this way includes pre-ejection period (PEP) and therefore it is not a real transmit time of the pulse wave. In order to remove the PEP, the vascular transit time (VTT), which is the time interval from the heart sounds (PCG) to the foot of the PPG waveform, is introduced. Another way is that peripheral pulses (i.e. finger and toe) are recorded sequentially with a small time difference and PTT is considered as the time difference between the two recording sites, where the R peak of the ECG is used as reference. This method can be early implemented using a standard vital signs recorder. However, the PTT is estimated using pulses obtained in different cardiac cycles. A more accurate way should be using two pulses in the same cardiac cycle obtained simultaneously at different arterial sites.

In our project, a pair of pulse waves is acquired simultaneously at ear and toe using clip-type PPG sensors for measuring PTT. The experimental setup development will be introduced in the next section.

Chapter 5

Experimental Setup

PPG is an easy-to-use, low-cost and technically mature optical technique to obtain arterial pulse wave non-invasively at the skin surface. Hence, we make use of PPG to measure PTT and explore a new method for continuous and non-invasive BP measurement.

5.1 Brief introduction to the PPG waveform

The PPG waveform contains a pulsatile or “AC” component with the fundamental frequency of 1 Hz (This frequency is varying with heart rate), and a base line or “DC” component that depends on some physiological factors, such as tissues and blood volume. The base line varies slowly with respiration, vasomotor activity, body movement and body temperature [143-156]. The magnitudes of both AC and DC components depend on the body site [157]. They can be extracted for pulse wave analysis from suitable body sites with proper filtering and amplification.

Multiple optical processes will occur when the light passes through biological tissue, such as transmission, absorption, scattering and reflection

[158]. These optical processes have been related to PPG measurements in several studies and investigations [159-170]. It has been reported that the efficiency of the photodetector in terms of receiving light can be affected by some factors, such as blood volume and movement of arterial wall.

The PPG waveform also depends on the wavelength of the light emitted by LED [171]. Generally, the longer infrared, ultraviolet and shorter wavelengths are easy to be absorbed by human tissue. Only the visible red light and near infrared light can easily pass through the water-based tissue. Therefore, a small window of wavelengths from red to infrared is suitable for measuring blood volume and flow. That is why the red or near infrared LEDs are often used as the light source for PPG measurement [172].

5.2 Block diagram of experimental setup

Experimental setup is useful for two purposes.

- Signal detection and analysis: acquiring the pulse waves from ear and toe for studying the relationship between PWV and BP, and the algorithm of PWV identification.
- BP measurement: continuously estimating BP based on the BP-PWV model and the real-time identified PWV.

Our experimental setup is developed on the basis of an existing multi-channel data acquisition device. The existing device consists of sensors, filters and amplifiers, a dedicated computer including a 12 bit multi-channel A/D convertor and a remote control that can be used to adjust the amplifier gain. The

block diagram of the existing multi-channel data acquisition device is shown in Figure 5.1.

Figure 5.1 Block diagram of the existing multi-channel data acquisition device

The dedicated computer including the common software for data acquisition and the remote control can be used in our experimental setup. However, the sensors, filters and amplifiers in the existing device are inapplicable to our study, and thus redesign is required. A pair of PPG sensors including the infrared LEDs and matched photo detectors is developed for acquiring pulse waves at ear and toe sites. The acquired pulses are appropriately filtered and amplified and then recorded to the dedicated computer at a sample rate of 250 Hz. The block diagram of our experimental setup is shown in Figure 5.2.

Figure 5.2 Block diagram of our experimental setup

In this thesis, the existing parts such as the dedicated computer are briefly discussed. Only the self-developed parts (PPG sensors, filters, amplifiers and special program) are discussed in detail.

5.3 Hardware development

5.3.1 The existing parts

The existing parts of our experimental setup include the dedicated computer, 12 bit multi-channel A/D convertor and a remote control. The A/D convertor and dedicated computer were previously designed for ECG acquisition, and thus the standard sample rate of 250 Hz was used. The bandwidth of the filter in the PPG sensor is 0.1-26Hz as detailed in Chapter 5.3.2. According to the sampling theorem, the sample rate of 250 Hz is more than enough for arterial pulse wave. The existing parts embody most of the necessary functions for real-timely acquiring pulse wave. The remote control allows the experimenters to sit far away from the operating table so that they

will not disturb the surgeons. However, the dedicated computer designed for real-time operation has limited function for data/signal processing and analysis, and the data is stored in a special format. When off-line processing is required, format conversion must be done so that the data can be processed in a general-purpose computer with some powerful software.

5.3.2 PPG sensor design

A PPG sensor often includes two components: a red or near infrared LED and a matched photo detector. The wavelength is usually from 0.8 to 1 μm [173]. The function of LED is to convert the electrical energy to the light energy that can pass through the human tissue. The bandwidth of the light is narrow, typically 50 nm. Oppositely, the function of a photo-detector is to convert the light energy into electrical current that is easy to amplified and filtered. With advances in electronics, the technology of LED is robust and reliable. Modern LEDs are compact and operating in a constant peak-emitted wavelength over a wide temperature range. The operating life is also very long. Most of them can work more than 100 hours. The photodetector is also compact, sensitive, fast response and low cost.

The amplifying and filtering circuitry includes a high pass filter to reduce the DC component and boost the AC component. The filter should be chosen carefully to remove the higher frequency noise, such as the white noise and 50 /60Hz electrical interference. On the other hand, excessive filtering must be avoided as the pulse shape is easy to be distorted. The choice of bandwidth of the filter is always a design compromise [79, 174].

The circuit diagram of the self developed PPG sensor is given in Figure 5.3.

Figure 5.3 Circuit diagram of the PPG sensor for ear channel including the infrared LED, the matched photo detector, filter and amplifier

Basically, the PPG sensor consists of three parts: 1) infrared LED and the matched photodetector; 2) three stages of filters and amplifiers. The parameter design of the ear channel and toe channel are the same.

The infrared LED D301 and a pair of resistors R301 and R302 construct a light-emitting circuit that works as a constant light source under 5V d.c. A voltage stabilizing diode DZ304 is used to ensure the stability of the driving voltage. The light receiver circuit includes the photodetector D302 that converts optical signal to electrical signal and a low pass filter U601A that serves as an amplifier also. The cutoff frequency of the low pass filter is 44Hz and the magnification factor is 7 calculated as below.

$$f_{H1} = \frac{1}{2\pi \times R_{304} \times C_{320}} = \frac{1}{2\pi \times 360k\Omega \times 0.01\mu F} = 44.21Hz$$

$$A_1 = 360k/51k = 7.06$$

The output of U601A is connected to a high pass filter consists of a capacitor C301 and a resistor R305 which reduces the DC signal and low frequency noise. The cutoff frequency of the high pass filter is 0.07Hz.

$$f_{L1} = \frac{1}{2\pi \times R_{305} \times C_{301}} = \frac{1}{2\pi \times 680k\Omega \times 3.3\mu F} = 0.0709Hz$$

The second stage low pass filter is U604A with an amplifier whose magnification can be adjusted by an electronic switch U303. The low pass filter again removes the high frequency noises including the 50Hz or 60Hz interference and its harmonics. The cutoff frequency is designed to be 45Hz.

$$f_{H2} = \frac{1}{2\pi \times R_{332} \times C_{310}} = \frac{1}{2\pi \times 160k\Omega \times 0.022\mu F} = 45.21Hz$$

The minimum magnification factor of the amplifier is $A_{2\min}=1+160k/33k=5.85$, and the maximum magnification factor is $A_{2\max}=1+160k/1k=161$. Therefore, the range of the magnification factor A_2 is between 5.85 and 161.

The second stage high pass filter that consists of C311 and R333 is the same as the first stage high pass filter with the cutoff frequency of $f_{L2}=f_{L1}=0.07Hz$.

The third stage of filtering and amplification is achieved by the low pass filter U604D together with resistors R335, R336 and R337. The resistors are used to adjust the base line of the output signal. The cutoff frequency of U604D denoted as f_{H3} is the same as f_{H2} . The third stage magnification factor is $A_3=1+160k/(4.7k+1.8k)=25.8$.

The total cutoff frequency of the two stages of high pass filters is f_L calculated as below:

$$f_L = \sqrt{f_{L1}^2 + f_{L2}^2} = \sqrt{0.0709^2 + 0.0709^2} = 0.1Hz$$

The total cutoff frequency of the three stages of low pass filters is f_H calculated as below:

$$\frac{1}{f_H} = \sqrt{\frac{1}{f_{H1}^2} + \frac{1}{f_{H2}^2} + \frac{1}{f_{H3}^2}} = \sqrt{\frac{1}{44.21^2} + \frac{1}{45.21^2} + \frac{1}{45.21^2}} Hz$$

$$f_H = 26Hz$$

In summary, the total filter bandwidth is 0.1-26Hz, and the total range of the magnification is 1065-29325.

The material object photographs of ear and toe sensors are given in Figure 5.4.

Figure 5.4 Material objects of the ear and toe sensors

5.3.3 Discussion of the filter bandwidth

Allen had stated in his article [174] that careful filtering was needed so that characteristics of pulse wave could be reproduced faithfully. If the cut-off of the high pass filter is set too low, the DC component will dominate and some low frequency noise like body movement will come in, and consequently the shape of pulse wave is hard to be reproduced. If cut-off frequency is set too high, the shape of pulse will be distorted by over-filtering and some lower frequency characteristics of the pulse will be lost. There is always a compromise between fidelity and stability. In our study, the requirement of waveform fidelity in

measuring PTT_s (PTT related to SBP) is much higher than that in measuring PTT_d (PTT related to DBP) because some characteristics on wavecrest are easy to be lost or distorted due to filtering.

Allen [175] had suggested using the PPG amplifiers with bandwidth of 0.5-30Hz for Multi-site PPG pulse measurement and analysis. Nitzan [176] had used a PPG probe which was filtered to a bandwidth of 0.03-30Hz for PTT measurement. We had tested the above two bandwidths previously. Regarding the bandwidth of 0.5-30Hz, the obtained pulse waves were stable since the low frequency noises were removed. However, the ear pulse wave had a narrow wavecrest, and thus the difference between the measured PTT_s and PTT_d was very small which was incorrect theoretically. The methods of determining PTT_s and PTT_d are detailed in Chapter 7 and 8 respectively. This result indicated that the low frequency cut-off of 0.5 Hz was too high for the ear wave. Therefore, the bandwidth of 0.5-30Hz was suitable for measuring the foot of a pulse wave that corresponds to PTT_d as suggested by Allen [175], but unsuitable for measuring the characteristic points on pulse wavecrest which correspond to PTT_s . If the bandwidth of 0.03-30Hz was used, the ear pulse wave suffered from serious base line variation caused by the low frequency noises. Hence, the cut-off of 0.03 Hz was too low for ear pulse. But this bandwidth could be used to measure pulse waves at finger and toe as reported by Nitzan [176].

Based on the above, the bandwidth of 0.1-26Hz is determined and verified based on numerous experimental tests in our studies. The filters with this bandwidth setting can clearly remove the 50 Hz or 60 Hz power line interference and the harmonics, as well as give good fidelity of waveform which is very important in PTT measurement. The ear pulse wave measured in

this bandwidth can well reflect the important characteristics of the aortic pressure wave which correlate to central BP, such as the dichrotic notch and the high reflected peak caused by the the 1st reflection from femoral vascular bed. The toe pulse wave measured in this bandwidth also reflects the characteristics of the peripheral pulse at the distal end. For example, the toe pulse is not affected by the 1st reflection and the 2nd or higher reflections are very small. Therefore, generally, only one high peak that is the ejected wave can be observed. In a word, the pulse waves measured in this bandwidth satisfy the requirement of our study.

Regarding the low frequency physiological variation, the major sources are respiration and movement artifacts. Respiration has great effect on the electrodes placed on the chest, but has little effect on the PPG sensors placed on peripheral sites. According to our experimental results, the disturbances resulting from respiration are negligible on the ear pulse and even smaller on the toe pulse wave with this bandwidth setting. In order to reduce the movement artifacts, the PPG sensors are fixed on ear and toe using adhesive tape.

5.4 Software development

The arterial pulse wave is a periodic signal with the same period as the heart rate. The software must satisfy the requirement of the real-time measurement. The dedicated computer already has the common software for data acquisition. The functions of the common software include:

- Drive the A/D convertor to real-timely acquire and store data

- Convert the numerical data into waveform and display the waveform on the monitor graphically
- Allow remote control the experimental setup

With the hardware and the functions of the common software given above, the experimental setup can be used for the first purpose mentioned at the beginning that is pulse waves acquisition and analysis. To achieve real-time BP measurement, special application software must be developed.

The period of arterial pulse wave is a cardiac cycle which is variable. Our objective is to measure the beat-to-beat BP from the real-timely acquired pulse wave. Basically, the work done by the application software is almost the same in every cardiac cycle. In another word, the application program is cyclic, whose work cycle is limited by a cardiac cycle. Considering that the shortest cardiac cycle is about 240ms, all the identification and calculation work must be finished within this period. Notice that complex algorithm is not suitable for this real-time application program.

This application program includes two routines: 1) Interrupt routine for identification of a cardiac cycle. 2) Main cyclic routine for identification of PWV and calculation of BP.

1) Interrupt routine for identification of a cardiac cycle

The main tasks of this interrupt routine include identifying the end of a cardiac cycle from the sampled data sequence, determining the length of the cardiac cycle and giving a flag for the use of other routines. The data segment within the determined cardiac cycle represents a complete pulse

wave that will be processed by other routines immediately. This interrupt routine has a high priority. It executes in every new sampling of data, therefore, the three main tasks must be completed within the interval between two adjoining sampling. Since the sampling rate is 250Hz, the runtime of this interrupt routine must be smaller than 4ms. The algorithm of identifying a cardiac cycle from the arterial pulse wave is similar to the method of identifying a cardiac cycle from ECG, which is technically mature.

The flowchart of the interrupt routine is shown in Figure 5.5.

Figure 5.5 Flowchart of the interrupt routine for identification of a cardiac cycle

2) Main cyclic routine for identification of PWV and calculation of BP

The main results of the thesis include the methodologies of identifying PWV and calculating BP by the identified PWV, which will be discussed in

the following chapters. The program written according to the methodologies includes many tasks and thus the runtime is relatively long. Therefore, it is designed as the main cyclic routine. The basic real-time requirement of this main cyclic routine is that the runtime of a cycle must be smaller than a cardiac cycle (about 240ms). The main cyclic routine allows being interrupted frequently by the existing and self-designed interrupt programs. It runs in the time intervals between these interrupt programs. Therefore, its runtime must be much smaller than a cardiac cycle. Before the main program starts the cyclic work, initialization is required. The operator will input parameters (age, gender and height) using remote control. The main program first calculates L_{et} that is the distance of pulse wave propagation between ear and toe, and determines proper model parameters according to the age and gender for the use of the cyclic routine. After initialization, the main program will enter the loop.

The flowchart of the main cyclic program is shown in Figure 5.6.

The application program including two routines is embedded into the common software of the dedicated computer. The experimental setup is upgraded from a data acquisition device to real-time BP measurement device. Regarding the software, besides the operation system of the dedicated computer, the priorities of the application programs are list as below:

- The highest priority: Interrupt program of data sampling (a existing program of the dedicated computer)
- The second priority: Interrupt program for identification of a cardiac cycle.

- The lowest priority: Main cyclic program for identification of PWV and calculation of BP.

Figure 5.6 Flowchart of the main cyclic program for identifying PWV and calculating BP

5.5 Summary

Experimental setup are developed based on an existing multichannel data acquisition device to obtain the ear and toe pulse waves simultaneously using self-developed PPG sensors [177]. The bandwidth of amplifiers in the PPG sensors is set as 0.1Hz-26Hz. The high pass filter cut-off of 0.1 Hz has been validated by Allen and Murray [174]. The filter with this bandwidth setting can clearly remove the 50 Hz or 60 Hz power line interference and harmonics, as well as give good fidelity of waveform which is very important in PTT measurement. The gains of the two PPG amplifiers can be set individually. The pulse waves are recorded to a dedicated computer at a sample rate of 250K Hz.

The software in the dedicated computer allows storing the data in spreadsheet files and displaying the waveform on the monitor. In addition, special application software is developed for real-time BP measurement. This application program includes two main routines: 1) Interrupt routine for identification of a cardiac cycle. 2) Main cyclic routine for identification of PWV and calculation of BP.

The reason why we chose ear as a site for measuring PTT is that ears locate very near the common carotid artery so that the ear pulse wave can well reflect the important characteristics (e.g. dischrotic notch) of the aortic pressure wave which correlates to central BP [6]. Another peripheral pulse wave is obtained at toe so that the wave propagation path includes the arterial sites which are most sensitive to the change of BP, such as thoracic aortas, abdominal aortas and femoral vascular bed. The ear-to-toe PTT is the longest PTT that can be

obtained by PPG sensors. The use of the longest PTT helps reducing the proportion of random errors in the measured PTT so as to improve the signal-to-noise ratio.

Chapter 6

BP-PWV Relationship Model

The possibility of estimating beat-to-beat BP based on PTT or PWV has previously been investigated. Generally, the necessary steps include obtaining PTT or PWV, modeling BP-PTT or BP-PWV relationship, and identifying the model parameters. With real-time detected PTT/PWV, continuous BP can be estimated using a specifically established mathematical model, which can generally express the relationship between BP and PTT/PWV. The model parameters are usually identified by individual calibration [140, 178-185]. Modeling of the relationship between BP and PTT/PWV is a crucial part in the methodology.

6.1 Reviews of existing mathematical models

So far, the proposed theoretical models fall into two categories: linear models and nonlinear models. Representative examples of the linear models include the linear BP-PTT relationship model and the multiple linear regression model proposed by Chen [140] and Chua [178] respectively. Chen's model

shows that there is a linear relationship between the systolic blood pressure (SBP) and the pulse arrival time [140].

$$p_e = p_b + \Delta p = p_b - \frac{2}{\gamma T_b} \Delta T \quad (6.1)$$

In Eq. (6.1), the estimated SBP that is expressed as p_e consists of two terms: a base level BP p_b and a changing component Δp that can be estimated from the change in the pulse arrival time ΔT . The coefficient γT_b can be determined by calibration repeatedly. But the above estimation does not show how DBP should be handled. Moreover, recalibration must be done whenever the base level BP is changed.

Chua's model given in Eq. (6.2) is a recursive model consisting of two input variables: pulse arrival time (PAT) and the foot to peak amplitude of the rising edge of the photoelectric plethysmograph (PPG) [178].

$$p_{[i]} = b_0 + b_1 PPG_{[i]} + b_2 PAT_{[i]} + b_3 PPG_{[i-1]} + b_4 PAT_{[i-1]} \quad (6.2)$$

In this model, p is the estimated output pressure, $[i]$ denotes time instant i , and the unknown parameters b_0 , b_1 , b_2 , b_3 and b_4 are determined by individual calibration. This linear model can estimate short-term BP. For long term BP estimation, although recursively correction is maintained, there is still considerable bias and the average error is also large. Reproducibility of the calibration is rather low, indicating that intermittent recalibration is required [178].

Some researchers considered the nonlinearity of the elastic property of the vascular wall and established two typical non-linear models [179, 181-184].

$$p = A \ln(ptt) + B \quad (6.3)$$

And
$$p = A(1/ptt)^2 + B \quad (6.4)$$

where p is mean BP, ptt is PTT, A and B are model parameters to be identified by individual calibration using conventional cuff-based BP devices. The beat-to-beat PTT and BP are highly correlated within a short period but the correlation coefficient decreases when the number of beats increases, suggesting that the coefficients A and B are changing at a relatively fast rate and recalibration is still inevitable [183]. By going through the modeling procedures, it is noted that both nonlinear models are derived from the two equations below [140, 184]:

$$\text{Moens-Korteweg equation: } c = \sqrt{\frac{Gh}{2\rho R_0}} \quad (6.5)$$

$$\text{Hughes' equation: } G = G_0 e^{\alpha p} \quad (6.6)$$

Moens-Korteweg equation expresses PWV explicitly in terms of vessel dimensions, blood density and arterial wall elasticity, where c is pulse wave velocity, ρ is the blood density, R_0 is the vessel radius, h is the wall thickness and G is the Young elasticity modulus of the vessel wall. Hughes' equation was obtained from experiment on 12 dogs [186], where p is BP, G_0 is the elastic modulus at zero pressure and α is a coefficient ranging from 0.016 to 0.018 (mmHg^{-1}), which depends on the particular vessel. Let $ptt=L/c$, where L is pulse wave propagation length. Substituting Eq. (6.6) into Eq. (6.5) arrives at the conclusion in Eq. (6.3) [184]. On the other hand, the change of stress can be considered as the change in BP, i.e.

$$\Delta p = G \frac{2\Delta R}{R_0} \quad (6.7)$$

Substituting Eq. (6.7) into Eq. (6.5) gives Eq. (6.4) [184].

It can be seen that the G in Eq. (6.7) only depends on the changes of R and P . However, the G in Eq. (6.5) depends on other factors beside R and P , such as age and gender. This implies that the meanings of G in Eq. (6.5) and Eq. (6.7) are quite different. In addition, the variable G in Eq. (6.6) is obtained from non-living animals which might be also different from the G in Eq. (6.5). Hence it may be improper to obtain model (6.3) and (6.4) by canceling G in the intermediate steps.

In our study, a novel BP-PWV function is proposed and used as the basic model for beat-to-beat BP measurement.

6.2 Derivation of BP-PWV model

6.2.1 Wave equation in pulse wave propagation

Pulse wave propagation in arterial system is a physical and physiological process. Some fundamental laws allow us to establish mathematical model for this process. It is shown that when an ideal artery is considered as a thin wall and flexible cylinder tube, Eq. (6.8) is derived based on mass conservation law, momentum conservation law, balance of force and constitutive relation in material mechanics [187].

$$\frac{\partial^2 R}{\partial t^2} = c^2 \frac{\partial^2 R}{\partial x^2} \quad (6.8)$$

where x denotes a position on the ideal artery, t represents time, R is the instantaneous radius of artery and c is the PWV. The c is a variable with respect to t and x so that Eq. (6.8) is a non-linear partial differential equation. A relationship between PWV and BP can be derived by solving the equation.

As seen in Eq. (6.5), the change of G and R_0 will affect c . In our study, the elastic modulus G is considered as a variable related to age, gender and BP, and meets some assumptions as below.

- 1) For a particular group of people with fixed age and gender, the effects on G due to age and gender are fixed. In this case the change of G is mainly caused by the change of BP.
- 2) In fact the G for different arteries has slight discrepancy. Here we idealize the arterial system as a thin wall, straight and flexible cylinder tube, as illustrated in Figure 6.1. G can be treated as a constant with respect to x within the control volume between x and $x+dx$. In another word, G is considered to be a variable only respective to t [187].

Figure 6.1 A control volume between x and $x+dx$ of the ideal artery

6.2.2 Derivation of BP-PWV model

Eq. (6.8) lays a strong foundation in deriving the BP-PWV function. It represents the variation of arterial radius R with respect to time t and position x along axis direction. To solve this equation, the constrain conditions from practical considerations and real applications are listed as below:

- 1) The feet of pulse wave are used to calculate the PWV related to DBP.

Within a cardiovascular cycle, the moment when an aortic pulse start to raise indicates that the aortic valves just open and the heart starts to pump blood into aorta. So the foot of a pulse wave can be considered as the end of diastole as well as the starting of systole. In our study, the foot is considered as the end of diastole and related to DBP. On the other hand, when the aortic valves start to close, the pressure inside the left ventricle is almost the same as that in aorta. This moment can be considered as the end of systole as well as the starting of diastole. In our study, the moment of aortic valves closure is considered as the end of systole and related to SBP.

- 2) Variable c is changing with arterial pressure p . In our study, c is considered to be an independent variable which is obtained by measurement. In real applications, it is difficult to obtain the instantaneous PWV of a particular point inside arterial system. Usually, we use the propagation distance in a unit time to represent PWV, which is just the average velocity in a cardiac cycle. Therefore, the c here is a discrete variable with the time interval of a cardiac cycle.

- 3) The arterial pressure p in our study refers to SBP or DBP instead of continuous instantaneous pressure. The SBP and DBP are also changing discretely with the period of a cardiac cycle.

- 4) Although the PWV, SBP and DBP are all discrete, the relationship between PWV and SBP/DBP is a continuous function.

Now from elastic mechanics, we have

$$\frac{\partial R}{\partial x} = \varepsilon \quad (6.9)$$

where ε is the strain of arterial wall. Substituting Eq. (6.9) into Eq. (6.8), gives

$$\frac{\partial^2 R}{\partial t^2} = c^2 \frac{\partial \varepsilon}{\partial x} \quad (6.10)$$

According to the relationship of stress σ and strain ε in elastic mechanics, we have

$$\sigma = G\varepsilon \quad (6.11)$$

Based on the assumption in the Section 6.2.1, we ignore the discrepancy of G between different blood vessels and consider it to be invariant along axis direction x . Substituting Eq. (6.11) into Eq. (6.10), we have:

$$\frac{\partial^2 R}{\partial t^2} = \frac{c^2}{G} \frac{\partial \sigma}{\partial x} \quad (6.12)$$

Let M be the mass of an arbitrary particle on arterial wall. Multiply M on both sides of Eq. (6.12), yields

$$M \frac{\partial^2 R}{\partial t^2} = \frac{Mc^2}{G} \frac{\partial \sigma}{\partial x} \quad (6.13)$$

In terms of elastic stress σ , Newton's second law can be applied. Let s be the area of application of σ , then

$$M \frac{\partial^2 R}{\partial t^2} = s\sigma \quad (6.14)$$

Combining Eq. (6.13) and Eq. (6.14), we obtain

$$s\sigma = \frac{Mc^2}{G} \frac{\partial \sigma}{\partial x} \quad (6.15)$$

Suppose that the length of a thin wall and straight artery is L , the thickness of the arterial wall is h , the arterial internal and external radii are r_1 and r_2 respectively. Arterial internal pressure p_1 is balanced with external pressure p_2 ,

and σ can be decomposed into circumferential direction and axial direction. Assume that L dose not change with pressure. Then σ in the axial direction can be ignored and thus σ here only represents the stress in circumferential direction. Figure 6.2 shows an arbitrary cross section of the artery. Line segment ABCD passes central axis of the artery and the surface where it is located divides this artery section into two parts. Now we consider force equilibrium condition for the upper part. Total circumferential tension applied to the surfaces where AB and CD are located is $2h\sigma L$, which are downwards and perpendicular to the surfaces of action. The component of p_1 that is perpendicular to bottom line AOD can be expressed as $p_1 \sin \theta$. Applying curvilinear integral to the upper half of the circumference of the inner circle, we get

$$\int_0^\pi r_1 p_1 \sin \theta d\theta = r_1 p_1 [-\cos \theta]_0^\pi = 2r_1 p_1 \quad (6.16)$$

So the total internal force applied to the inside surface of the artery section is $2r_1 L p_1$ directing upwards. In a similar way, the total external force applied to the outside surface of the artery section is downwards and equal to $2r_2 L p_2$. According to the balance condition of force, Oka-Azuma equation is obtained [188].

$$2h\sigma L + 2r_2 L p_2 = 2r_1 L p_1 \quad \text{or} \quad h\sigma = p_1 r_1 - p_2 r_2 \quad (6.17)$$

Figure 6.2 Force equilibrium in the arterial wall section L

Suppose that h is very small so that it can be ignored, and let $r_1=r_2=r$, we have the Laplace equation

$$h\sigma = (p_1 - p_2)r \quad (6.18)$$

Note that $p=p_1-p_2$ is the transmural blood pressure. So Eq. (6.18) becomes

$$h\sigma = rp \quad (6.19)$$

If we consider the artery wall as a thin-wall cylindrical shell and neglect the geometrical change of arterial vessel, r can be seen as a constant with respect to x . Substituting Eq. (6.19) into Eq. (6.15), we get

$$\frac{rp}{h} = \frac{rMc^2}{shG} \frac{\partial p}{\partial x} \quad \text{or} \quad \frac{\partial p}{\partial x} = \frac{sG}{M} \frac{p}{c^2} \quad (6.20)$$

According to the second and third constrain conditions, p refers to the SBP or DBP instead of instantaneous pressure, c is the average PWV in a fixed unit time T , Then c can be expressed as the function of distance x .

$$c = \frac{x}{T} \quad (6.21)$$

Taking partial derivative of c respect to x , we get

$$\frac{\partial c}{\partial x} = \frac{1}{T} \quad (6.22)$$

Note that

$$\frac{\partial p}{\partial x} = \frac{\partial p}{\partial c} \times \frac{\partial c}{\partial x} = \frac{\partial p}{\partial c} \times \frac{1}{T} \quad (6.23)$$

Substituting Eq. (6.23) into Eq. (6.20), we have

$$\frac{\partial p}{\partial c} \times \frac{1}{T} = \frac{sG}{M} \frac{p}{c^2} \quad \text{or} \quad \frac{\partial p}{\partial c} = \frac{sGT}{M} \frac{p}{c^2} \quad (6.24)$$

Now there is only one independent variable c in Eq. (6.24), the partial derivative can be represented by the following ordinary differential equation

$$\frac{dp}{dc} = \frac{sGT}{M} \frac{p}{c^2} \quad (6.25)$$

Let $k=sGT/M$, we have

$$\frac{dp}{dc} = k \frac{p}{c^2} \quad (6.26)$$

Then

$$\int \frac{1}{p} dp = k \int \frac{1}{c^2} dc \quad (6.27)$$

We get

$$\ln p = -\frac{k}{c} + b_0 \quad (6.28)$$

$$p = be^{-\frac{k}{c}} \quad (6.29)$$

We call Eq. (6.29) as BP-PWV function for pulse wave. It is a general solution of Eq.(6.26), which can describe the relationship between BP and

PWV. The undetermined coefficient k contains elastic module G , which mostly depends on age and gender. Suppose that there are m different age groups and let i denote one particular group of them. Also using j denotes either male or female. Thus parameters k and b have $2m$ possible values expressed as:

$$\begin{aligned} k_{ij} & \quad i=1,2,\dots,m \text{ (age)} \quad j=\text{Male/Female (gender)} \\ b_{ij} & \quad i=1,2,\dots,m \text{ (age)} \quad j=\text{Male/Female (gender)} \end{aligned}$$

Once k_{ij} and b_{ij} are determined, a family of specific solutions of the general function (29) can be obtained:

$$p_{ij} = b_{ij} e^{-\frac{k_{ij}}{c_{ij}}} \quad (6.30)$$

$$i=1, 2 \dots m \text{ (age)}$$

$$j= \text{Male/Female (gender)}$$

The function family (6.30) represents the basic mathematical models which can be used to calculate the real time BP. From the mathematical point of view, Eq. (6.29) has finite number of specific solutions. From the biomedical point of view, Eq. (6.30) contains physiological information of people with different ages and genders. Determination of unknown coefficient k_{ij} and b_{ij} is a problem of parameter identification. We need some samples of p_{ij} and c_{ij} from different age and gender groups obtained from clinical trials to carry out the identification.

6.3 Algorithm of model parameters identification

The theoretical BP-PWV model (6.30) must be calibrated or the model parameters must be identified before it is applied to continuous BP measurement. In most studies, model calibration is usually done for every single subject in the process of practical measurement. In our research, in order to avoid individual calibration in practical measurement, we identify the model parameters or calibrate the model in the process of modeling.

According to the definitions in Section 6.2.2, we have m different age groups (i.e. $i=1, 2 \dots m$) for both gender (i.e. $j=1, 2$). For group ij , the algorithm of identifying parameters k_{ij} and b_{ij} is listed as follows:

- 1) N ($N \geq 5$) volunteers of the same age and gender corresponding to group ij are selected to be subjects investigated. Based on our experiments, the minimum number of N is 5.
- 2) Simultaneously record $p_{ij,n}$ and $c_{ij,n}$ data for the n^{th} ($n=1, 2 \dots N$) volunteer. $p_{ij,n}$ is the beat-to-beat BP (It is best to use the most accurate invasive BP), and $c_{ij,n}$ takes the average value of PWV in 8 cardiac cycles in order to cancel the effect of respiration. In each trial, at least 10 pairs of $p_{ij,n}$ and $c_{ij,n}$ data are recorded.
- 3) For the n^{th} volunteer, his/her $p_{ij,n}$ must have some changes. The variation range of BP must satisfy: $\Delta \text{DBP} \geq 25 \text{mmHg}$ and $\Delta \text{SBP} \geq 40 \text{mmHg}$. This is because only the $p_{ij,n}$ and $c_{ij,n}$ with large variation are reliable for model parameter identification.

- 4) For the n^{th} volunteer, a scatter diagram is plotted using his/her $p_{ij,n}$ and $c_{ij,n}$, and curve fitting is done by '*cftool*' in Matlab software based on the BP-PWV function (6.29). A pair of model parameters $k_{ij,n}$ and $b_{ij,n}$ for this individual can be obtained.
- 5) In some cases, the curve fitting may be unsuccessful. For examples, the BP variation range of a patient is too small, catheter jams resulting in irregular invasive $p_{ij,n}$, and the displacement of sensor results in irregular $c_{ij,n}$. In these cases, a new volunteer in group ij must be selected, and the 2nd, 3rd and 4th steps above must be repeated for this new volunteer.
- 6) After all the N volunteers in group ij are considered, model parameters k_{ij} and b_{ij} are obtained by taking the average of all the $k_{ij,n}$ and $b_{ij,n}$ respectively.

$$b_{ij} = \frac{1}{N} \sum_{n=1}^N b_{ij,n} \quad \text{and} \quad k_{ij} = \frac{1}{N} \sum_{n=1}^N k_{ij,n}$$

- 7) Change the age i or gender j factor and repeat the above steps until the parameter identification is finished for all the groups.

In the model parameter identification and benchmark models development, there is no restriction for pulse wave acquisition and PWV calculation method. Pulse wave acquisition includes ultrasound, plethysmograph and pressure transducers. These methods have different positions of measurement and different distances between sensors. So PWVs determined using different methods may more or less have some discrepancies. Therefore, k_{ij} and b_{ij} obtained from different c_{ij} may have some discrepancies as well. That is,

different signal acquisition methods may correspond to different BP-PWV functions. Current researches have not reached a consensus in term of the best way of PWV measurement. PPG is used in our studies to measure PWV.

6.4 Summary

In this section, a novel BP-PWV model is established based on the fundamental physics and physiology as well as some constrained conditions from practical considerations. Model parameters b and k take different values for different ages and genders. In order to avoid individual calibration of model parameters in practical measurement, we propose an algorithm of model parameters identification, in which the calibration is achieved in the modeling process through determining the model parameters of a family of BP-PWV functions by statistical method. We call the calibrated models as 'benchmark models'. These 'benchmark models' form an function base for people in different ages and genders. For a person with fixed age and gender, there always exists a suitable benchmark model that can be used to estimate BP based on the measured PWV. In this way, calibration in practical application is no longer required. This modeling idea is similar to the development of gene information base for disease diagnosis.

Chapter 7

Verification of Modeling Methodology by Diastolic Blood Pressure Measurement

In Chapter 6, we have shown that the BP-PWV model is sustainable in theory. In this Chapter, we aim to verify the feasibility of this modeling methodology by practical DBP measurement. Four benchmark models for 19 and 60 age groups (representing young and old) of both genders are developed using clinical data obtained from patients with healthy cardiovascular system. DBP is measured by PWV_d based on the benchmark models. The measurement results are compared with the accuracy criteria in AAMI SP10 in order to assess the validity of the BP-PWV model and the algorithm of model parameter identification.

7.1 Determination of PWV related to DBP

7.1.1 Identification of PTT related to DBP

Since the wave length of a pulse wave is longer than its propagation distance, PTT is obtained from the propagation of the same characteristic point

from the ear pulse to the toe pulse. As discussed in Section 4.3, the most commonly used method for estimating PTT is the foot-to-foot method. The foot of the pulse wave is defined at the end of diastole, when the steep rise of the wavefront begins [93], therefore, the foot-to-foot PTT is the PTT related to DBP (PTT_d).

The method of intersection of two tangents is commonly used to identify the foot of a pulse wave [118, 136, 189]. We illustrate this method by identifying point A on the ear pulse in Figure 7.1. Firstly, the points denoting the lowest point and the maximum gradient of the systolic rising edge of the ear pulse wave are identified. Then we determine the point showing 60% of the maximum gradient between the lowest point and maximum gradient point. Point A is considered as the intersection between the tangent line indicating 60% of the maximum gradient and the tangent line of the lowest point. Point a on toe pulse can be identified in the same way. The time interval T_a between points A and a is regarded as PTT_d .

Figure 7.1 Identification of the starting points of ear pulse and toe pulse

The criterion on 60% of the maximum gradient is determined by numerous experimental tests according to our requirement. When this percentage is used, the corresponding tangent locates at the lower portion of the rising edge. The position of the intercept point on the time axis depends on the maximum gradient as well as the curvature of the initial part of the waveform. Thus the foot identified in this way is closer to the lowest point. Consequently, the PTT_d determined based on these feet is closer to the real PTT in end diastole which is corresponding to DBP. But if there is no requirement of relating PTT_d to DBP, it is convenient to use the maximum gradient directly. The percentage of the maximum gradient may also be adjusted according to different transducers and measurement positions. But note that the identified foot should neither be too close to the unstable lowest point, nor so high as to lose the meaning of a foot.

7.1.2 Determining propagation distance and calculating PWV_d

The propagation distance with respect to PTT_d is required for calculating PWV_d . The propagation distance between ear and toe is denoted as L_{et} . In fact, the propagation direction from aortic arch to ear is opposite to that from aortic arch to toe. When we consider L_{et} , the distance between aortic arch and ear must be subtracted from that between aortic arch and toe.

Let L' be the distance between aortic arch (near presternum) and the top of head. It is estimated to be 0.3m for adults by statistics. Let L be the height of a subject obtained by measurement, and the distance between aortic arch and toe be L_t calculated by $L - L'$. L_e denotes the distance between aortic arch and ear. It is estimated to be 0.18m for adults by statistics due to small individual difference. Then

$$L_{et} = L_t - L_e = L - L' - L_e = L - 0.3m - 0.18m. \quad (7.1)$$

Then the PWV_d can be calculated as

$$PWV_d = \frac{L_{et}}{PTT_d} \quad (7.2)$$

7.2 Reference BP

In our study, the main transmission path of the pulse wave includes carotid arteries, thoracic and abdominal aorta, femoral arteries and large arteries in the legs. Hence the ear-to-toe PWV is the average velocity, which has the best correlation with the average BP of the arterial system. However, it is too difficult to measure the BP from every position and thus the calculating the average BP of the arterial system is impossible. An effective way of reference BP acquisition is to make use of the BP measured at a specific position to represent the average BP in arterial system. According to AAMI standard, brachial arterial BP and radial arterial BP are used as reference BP according to noninvasive and invasive methods respectively [26]. Although the measurement is taken in a peripheral limb, the values are generally assumed to reflect the pressure throughout the arterial tree in large conduit arteries [6]. In our study, the commonly acceptable radial arterial pressure is chosen as the reference BP. This facilitates the experimental verification according to AAMI standard.

7.3 Experimental verification

7.3.1 Experimental subjects and conditions

Experiments were conducted in operation rooms of Southwest hospital in Chongqing, China. 23 Patients with age around 19 and 60 representing the young and old were involved in the experiments. By choosing experimental subjects in this way, we were able to investigate the differences caused by age and gender factors. Study was approved by the Medical Ethics Committee of Southwest Hospital and written informed consent was obtained from every subject. Information of subjects is given in Table 7.1.

Table 7.1 Information of experimental subjects

Experimental Subjects	Male	Male	Female	Female
Age-bracket	17-23	56-64	18-24	56-65
Average age	19.2	60.4	19.8	59.7
Number of subjects	5	7	5	6
Number of data set per trial	12-28	14-62	11-43	26-59
Variation range of invasive DBP	51mmHg to 142mmHg			

In Table 7.1, each data set includes one patient's DBP and PWV_d acquired simultaneously. The experimental setup in Chapter 5 was used for real-time measuring and recording PWV. Note that the subjects are in supine positions during measurement. At the same time, patients were undergoing surgical operations in which their radial arteries were cannulated (BD 20-gauge, BD Medical Devices Co) and connected via pressure tubing and transducer (PX 260 Pressure Monitoring Kit, Edward Life sciences LLC) interfaced with a monitor (Patient Monitor Solar 8000 M, GE medical Systems Information Technologies Inc) that provided real time invasive BP. The invasive BP's were recorded by the computer in the operation room. Data acquisition continued for a few hours including the time before, during and after anaesthetic. Figure 7.2 illustrates the experiment environment.

(a)

(b)

(c)

(d)

(e)

Figure 7.2 Experimental set-up and environment

- (a) Pressure tubing and transducer for arteriopuncture
- (b) Arteriopuncture and cuff sphygmomanometer
- (c) Invasive BP monitoring
- (d) Transducer at ear
- (e) Transducer at toe

Patient's response to anesthetic agents and surgical intervention was highly variable and unpredictable, and the combination of both commonly induced significant and rapid changes in BP. In some cases, DBP went beyond 100mmHg. In certain other cases, such as brain surgery that must be done in low BP condition, DBP needed to be maintained near 50mmHg. In different situations, we had different ways of DBP recording. If BP maintained almost unchanged, data was recorded in every 5minutes. If BP changed fast, data was recorded in every 20-60 seconds.

7.3.2 Curve fitting of individual subjects

According to the algorithm of model parameter identification in Section 6.3, for each of the 23 subject, a scatter diagram is plotted using his/her DBP and PWV_d and curve fitting is done by '*cftool*' in Matlab software based on the Eq. (6.29). Figure 7.3 shows the curve fitting results of four subjects in different age or gender as examples to illustrate and explain our findings. x axis represents PWV value (meter per second) and y axis represents DBP value (mmHg).

(c)

(d)

Figure 7.3 (a) Curve fitting of a 60 years old male

(b) Curve fitting of a 58 years old female

(c) Curve fitting of an 18 years old male

(d) Curve fitting of a 19 years old female

It can be observed that for each of the four subjects, the PWV_d vs DBP distribute closely around the curve, which indicates that Eq. (6.29) fit well with the experimental data distributions. Similar results are obtained from other 19 subjects.

For comparison, Figure 7.4 illustrates the curve fitting results of the subject in Figure 7.3 (b) using some previously proposed functions and the Eq. (6.29). In these functions, p denotes estimated BP, c denotes PWV, p_o denotes a constant base level BP, b and k are model parameters. It can be observed that function 3 and 4 could not fit the experiment data well. Both function 1 and 2 fit the experiment data well within the data range.

Figure 7.4 Comparison of the curve fitting results of four different functions

To compare the fitting results of the four functions quantitatively, we compute the summed square of residuals (SSE) and the square of the correlation between the response values and the predicted response values (R-Square) for each subject using '*cftool*' in Matlab. The mean SSE and R-Square (across all 23 subjects in Chapter 7.3.1) for each fitting function are reported in the Table 7.2.

Table 7.2. Quantitatively comparison of the mean SSE and R-Square for
four different functions

	$p=b*\exp(-k/c)$	$p=k*\ln(c)-p_0$	$p=k*c*c+p_0$	$p=k*c-p_0$
SSE	219.56	220.53	368.17	267.42
R-Square	0.897	0.900	0.774	0.859

Table 7.2 shows that the fitting results of Eq. (6.29) and the logarithmic function are better than the other two functions, which lead to the same conclusion as that in Figure 7.4. But there is no significant difference between the exponential function and the logarithmic function.

$$\lim_{c \rightarrow +\infty} (k \ln(c) + p_0) = -\infty \quad (7.3)$$

$$\lim_{c \rightarrow +\infty} (k \ln(c) + p_0) = +\infty \quad (7.4)$$

$$\lim_{c \rightarrow 0} (be^{-\frac{k}{c}}) = 0 \quad (7.5)$$

$$\lim_{c \rightarrow +\infty} (be^{-\frac{k}{c}}) = b \quad (7.6)$$

For the logarithmic function, p approaches negative infinity when c approaches zero. It indicates that it has a problem to express BP-PWV relationship within low BP range. For Eq. (6.29), the limit of p is zero when c approaches zero, and p converges to a limit when c approaches plus infinity. It means that our model is a bounded function and always maintains positive, which makes sense in the real condition that BP varies in a positive and limited range.

7.3.3 Model Parameter identification and benchmark model development

According to the algorithm of model parameter identification introduced in the in Section 6.3, the model parameters b and k of the age groups 19 and 60 for both genders can be identified and four benchmark models can be obtained using the experimental data of patients in Chapter 7.3.1. The four calibrated benchmark models are illustrated in Figure 7.5. As the values of parameters b and k are obtained by statistical method, they depend on the transducers and other factors such as the race of experimental subjects. To avoid misleading the investigators, the values of model parameters b and k are not given in this thesis.

The effects of age and gender can be observed from Figure 7.5. The M-19.2 and M-60.4 represent male groups of average age 19.2 and 60.4 respectively, while F-19.8 and F-59.7 represent female groups of average age 19.8 and 59.7 respectively. It can be seen that under the same DBP condition PWV of M-60.4 is much faster than M-19.2. And the same conclusion can be drawn for F-59.7 and F-19.8. This is because the elastic modulus of arterial wall increases

with age which causes the increase of PWV. The effect of gender can be investigated by comparing PWV of M-19.2 and F-19.8 in the same DBP condition. Obviously, PWV of M-19.2 is faster since the elastic modulus of arterial wall of male is usually larger than that of female at the same age.

The developed benchmark models can be used to estimate BP for the 19 and 60 age groups of both genders. For instance, the benchmark model M-60.4 can be used to estimate the DBP of a male near 60 without individual calibration.

Figure 7.5 Four benchmark models for the 19 and 60 age groups of both genders

7.3.4 Clinical measurement of DBP by benchmark models

To validate the developed benchmark models, they are practically used to measure DBP continuously and non-invasively for subjects whose ages are near 19 and 60. Based on the benchmark models and the method of calculating

PWV_d, program was written and integrated into the previously developed experimental setup. The work cycle of the program was limited by a cardiac cycle.

Conditions of clinical verification are listed below:

- 1) Subjects chosen for clinical verification are different from those samples chosen for benchmark models development
- 2) Invasive DBP of subjects are measured under the same conditions in Chapter 7.3.1, and used as the criterion. The noninvasive DBP measured by PWV method and cuff sphygmomanometer are simultaneous with the reference invasive DBP.
- 3) Clinical verification must meet the test standard for electronic sphygmomanometer in ANSI/AAMI SP10, as given in Table 7.3 [26]. According to the test standard, at least 5 set of BP data must be measured in each trial. If the measured data extend 10 sets, the first 10 sets are used. The time interval between two consecutive records ranges from 1 to 10 minutes.

20 subjects of age round 19 (5 male and 5 female) and 60 (5 male and 5 female) were chosen for clinical verification. According to AAMI standard [26], their invasive and noninvasive DBP are recorded at 5-minute intervals. The sample size for each trail was 10 sets. Each set of data includes one invasive DBP value and two noninvasive DBP values. The range of invasive DBP is from 40mmHg to 128mmHg. The mean deviation and standard deviation are

calculated because the error distributions of noninvasive DBP are normal distributions [26]. Detail error calculation method is strictly based on the test standard in AAMI SP10. The measurement results are summarized in Table 7.3. It can be seen that DBP measurement results by PWV method have met the AAMI test standard, and they are better than that obtained by cuff sphygmomanometer. But the results in our study are only suitable for people who have healthy cardiovascular systems. For those who have pathological angiosclerosis, their PWV should be faster than normal healthy people so that the benchmark model may overestimate their BP. In these cases, individual calibration is required.

Table 7.3 DBP measurement results of two noninvasive methods

AAMI Standard	DBP measured by PWV method	DBP measured by cuff method
 mean deviation 	 mean deviation 	 mean deviation
$\leq 5\text{mmHg}$	$= 1.4\text{mmHg}$	$= 1.6\text{mmHg}$
Standard deviation	Standard deviation	Standard deviation
$\leq 8\text{mmHg}$	$= 7.5\text{mmHg}$	$= 7.9\text{mmHg}$
NO. of data sets	NO. of data sets	NO. of data sets
≥ 150	$= 200$	$= 200$
NO. of subjects ≥ 15	NO. of subjects $= 20$	NO. of subjects $= 20$

Figure 7.6 illustrates the error distribution of the two noninvasive methods for the 200 sets of data. The two methods give quite different error distribution compared to the invasive one, and both of them have few number of errors

going beyond the range of 16mmHg (two standard deviations), but corresponding to different subjects. In fact, no matter what noninvasive method is used, it is ineluctable that a small quantity of subjects has large error. But their different error distributions are very useful for doctors in clinical condition. For instance, in certain BP measurement, the two noninvasive methods are applied together and the measurement results are compared. If both methods give similar results, it indicates that the noninvasive measurement error for this subject is relatively small and both methods are feasible. But if the measurement results are quite different, it means that one of them has large measurement error. Although it is difficult to determine which method is more accurate in this case, the results may call attention to the doctor to use invasive method in order to improve accuracy.

(a)

(b)

Figure 7.6 (a) Error distributions of DBP measured by PWV method compared to invasive method. (b) Error distributions of DBP measured by cuff sphygmomanometer comparing to invasive method.

For the purpose of allowing readers to get a good sense of long-term DBP measurement, Figure 7.7 gives the time courses of the reference invasive DBP and two noninvasive DBP of a 60 years' old man. x axis shows the number of records with maximum of 50. The time interval between two records is 5 minutes so that the entire time of BP measurement is 4 hours and 10 minutes. In fact, beat-to-beat DBP could be measured by PWV method, but since cuff sphygmomanometer only provided DBP value per 5minutes, we record the three DBP values simultaneously at 5-minute intervals for better comparison. The time course line of PWV method verges on the line of cuff method in the first 50 minutes, and locates between the lines of cuff method and invasive method in the next 150 minutes. In the last 50 minutes, it approaches to the line

of invasive method. This indicates the accuracy of DBP measurement by PWV method falls in between the cuff method and invasive method.

Figure 7.7 Time courses of the reference invasive DBP and two noninvasive DBP for a 60 years' old man

7.4 Summary

To verify the feasibility of the BP-PWV model and the algorithm of model parameter identification in Chapter 6, we identify the model parameters b and k by statistical method using the invasive DBP's and their corresponding PWV_d's obtained from 23 study subjects who have healthy cardiovascular systems and in 19 and 60 age groups of both genders. The PWV_d is determined by the commonly used foot-to-foot method. The calibrated models serve as benchmark models for the four age-and-gender groups. The DBP of other 20 test subjects

with healthy cardiovascular system and whose ages are around 19 and 60 are measured by the four benchmark models without individual calibration. The measurement results ($DBP \leq 125 \text{ mmHg}$) meet the accuracy criteria in AAMI SP10. Based on the results of clinical validation, we can conclude that the proposed BP-PWV model correctly expresses the dynamic relationship between BP and PWV, and the algorithm of model parameter identification is valid.

Chapter 8

Determination of PWV_s and Measurement of Systolic Blood Pressure

We have developed benchmark models for 19 and 60 age groups of both genders and verified them with DBP measurements. PWV_d is determined by the commonly used foot-to-foot method. However, it is difficult to determine proper PWV related to SBP (PWV_s) because the shape of the pulse wavecrest changed unpredictably due to various influencing factors. The influencing factors made PWV_s include large non-systematic errors, which cannot be reduced utilizing the existing noise filtering techniques. In this chapter, a method is proposed to reduce non-systematic errors and obtain PWV_s that is stable for estimating SBP. To verify the method, SBP and DBP are measured from a small population of subjects with no evidence of cardiovascular disease using PWV_s and PWV_d based on the previously proposed BP-PWV model.

8.1 Methodology of Determining Suitable PWV_s for SBP Estimation

In this section, different PTT's with respect to SBP (PTT_s) are selected for comparison. Methods of identifying PTT_s in low, normal and high SBP conditions are proposed. A criterion is obtained from a validated BP-PWV model so as to determine proper PTT_s for estimating SBP. PWV_s is calculated using the propagation distance divided by PTT_s and used to estimate SBP.

8.1.1 Different PTT_s on pulse wavecrest

Figure 8.1 shows a pair of ear and toe pulse waves obtained simultaneously from a 20-year old man with healthy cardiovascular system (height =172cm, SBP=108mmHg, DBP=65mmHg). We use this case as an example to illustrates different PTT_s 's on the ear and toe pulses.

A pulse wave can be considered as the superposition of more than two independent waves: the incident wave propagating from heart to the peripheral arteries, and the reflected waves propagating from the peripheral arteries and reflection points to heart [142, 190, 191]. Regarding a pulse wave obtained from a healthy subject with no evidence of cardiovascular disease and in normal or low BP condition, the first wavecrest locating before the dichrotic notch is generally considered as incident portion, and the second wavecrest locating after dichrotic notch is considered as reflected portion [192], as shown in Figure 8.1 (a). Since the ear pulse is similar to central (carotid) arterial pulse that is greatly affected by the 1st reflection from femoral vascular bed, the reflected portion is most likely clear and high [6]. But toe is the distal end from heart so that it is not affected by the 1st reflection and the 2nd or higher reflections are very small. Therefore, generally, only one high peak that is the incident wave can be observed [72, 79, 92].

Figure 8.1 PTT_d and five different PTT_s 's

The incident portion of a pulse wave can be divided into three parts: peak, rising-edge and falling-edge. PTT_d and five different PTT_s 's are illustrated in Figure 8.1. Their definitions are summarized in Table 8.1. T_{pp-1} , T_{rr} and T_{ff} in Figure 1 (b), (d), (e) are considered as the propagation time of incident wave from ear to toe. T_{pp-2} and T_{rp} in Figure 1 (c) and (f) are considered as the propagation time of reflected wave from toe to ear.

Table 8.1 Definitions of PTT_d and five different PTT_s 's

PTT_s	Definition
PTT_d	PTT_d between the feet of the ear and toe pulses
T_{pp_1}	PTT_s between the peak of the incident portion of the ear pulse and that of the toe pulse
T_{pp_2}	PTT_s between the peaks of the toe incident portion and the ear reflected portion
T_{rr}	PTT_s between the upper rising-edge of the incident portion of the ear pulse and that of the toe pulse
T_{ff}	PTT_s between the upper falling-edge of the incident portion of the ear pulse and that of the toe pulse
T_{rp}	PTT_s between the upper rising-edge of the toe incident portion and the peak of the ear reflected portion

8.1.2 Method of identifying PTT_s in low and normal SBP conditions

Regarding the pulse waves obtained from subjects with no evidence of cardiovascular disease and in low or normal BP condition, T_{pp_1} and T_{pp_2} are easy to identify since the peaks can be found by the method of local maximum or first derivative. T_{rr} , T_{ff} and T_{rp} can be identified by the method of intersection of two tangents, which is commonly used to identify the foot of a pulse wave for determining PTT_d [118, 136, 189]. We illustrate this method by identifying T_{rr} in Figure 8.2. Firstly, the points denoting the peak and the maximum gradient of the systolic rising-edge of the ear pulse wave are identified. Then

we determine the point showing 60% of the maximum gradient between the peak and maximum gradient point. Characteristic point R is considered as the intersection between the tangent line indicating 60% of the maximum gradient and the tangent line of the peak point. Characteristic point r on the toe pulse can be identified in the same way. T_{rr} is the time difference between characteristic points R and r. The criterion on 60% of the maximum gradient is determined by numerous experimental tests. We have tried different percentages of the maximum gradient to adjust the positions of characteristic points R and r. If the percentage is too large (e.g. 80%), the characteristic point is far from wavecrest and thus the determined T_{rr} loses the meaning of PTT related to SBP. If the percentage is too small (e.g. 40%), the characteristic point locates too close to the peak (peaks are used to determine T_{pp_1} and T_{pp_2}). When 60% is used, the corresponding tangent locates on the upper portion of the rising edge, while the position of characteristic point is near wavecrest but not too close to the peak.

Figure 8.2 Identification of T_{rr} by the method of intersection of two tangents

T_{ff} and T_{rp} can be identified in the same way. For T_{ff} , the tangent line indicating 65% of the maximum down gradient is used to identify the characteristic points on the upper falling-edges of ear and toe incident waves. This is because the maximum gradient of the falling edge is generally smaller than that of the rising edge for both ear and toe incident waves.

We have also adjusted the amplifier gain to test if the percentages of the maximum gradient are suitable for different amplitudes of pulse wave. The results show that the amplification of pulse wave has very little effect on the value of identified PTT_s on time axis. However, the percentages may be adjusted according to different types of sensors, measurement positions and specific conditions. The percentages used in this article just provide a reference to readers.

8.1.3 Method of identifying T_{rp} and T_{pp_2} in high SBP condition

During surgical operations, BP may rise rapidly from normal to high due to surgical intervention (SBP may exceed 200mmHg). Different method is used to identify T_{rp} and T_{pp_2} in high BP condition since the feature of the ear reflected portion changes greatly. We use Figure 8.3 to illustrate the feature change of ear pulse when BP increases from normal to high.

(a)

(b)

(c)

Figure 8.3 Ear pulses obtained from a 61 years old man under three different BP conditions. (a) SBP=112mmHg and DBP=65mmHg (b) SBP=148mmHg and DBP=87mmHg (c) SBP=197mmHg and DBP=109mmHg

It can be seen that the reflected portion moves to left along time axis and then overlaps itself on incident portion. In Figure 8.3, the characteristic point indicated by dot is considered as 'peak' of the reflected wave in our study; t_0 denotes the time of the starting of ear wave; t_1 denotes the time of the characteristic point on the upper falling-edge of incident wave that is used to find T_{ff} in Figure 8.1 (e), which can be identified by the method introduced in Chapter 8.1.2. Based on our observation, the position of t_1 on time axis is less affected by the shape variation of pulse wave, comparing to the peak. The time interval between t_0 and t_1 is from 260ms to 280ms for adults, which is similar to the left ventricular ejection time (LVET) that is 270ms. t_2 is determined by $t_2 - t_1 = t_1 - t_0$, therefore, $t_2 - t_0$ is about twice of LVET and thus includes the main

features of the incident and reflected wavecrests. The gradient is either negative or zero between t_1 and t_2 and its change in this interval is indicated under the ear pulse. Figure 8.3 (a) show the ear pulse in normal BP condition. Although there is no raised reflected peak, an inflection point can be identified by the method of first derivative as there is a sharp change of gradient from zero to negative. Figure 8.3 (b) shows the condition that the characteristic point of reflected wave just shifts to overlap on the incident wave, while a small inflection point can still be identified by the method of first derivative. But in Figure 8.3 (c) BP continuously increases and the characteristic point is unidentifiable. Hence another feature that is the area under the ear pulse is used to identify T_{rp} and T_{pp_2} in high BP condition. Figure 8.4 (a), (b) and (c) show the effective areas (a section of waveform between t_0 and t_2) of the three ear waves in Figure 8.3 (a), (b) and (c) respectively.

(b)

(c)

Figure 8.4 Effective areas between t_0 and t_2 of the three ear waves in Figure 8.3 under different BP conditions. (a) SBP=112mmHg and DBP=65mmHg (b) SBP=148mmHg and DBP=87mmHg (c) SBP=197mmHg and DBP=109mmHg

Here we use T_{rp} as an example to explain the identification method. The basic idea is that the T_{rp} in normal BP condition together with the change of effective area are used to estimate T_{rp} in high BP condition. Since the gain of the amplifier in the sensor is adjusted at any time in real-time pulse wave detection, it is difficult to compare the effective areas detected at different time. We use a reference area denoted as S to normalize the amplitudes of pulse waves.

$$S = h_{max} (t_2 - t_0) \quad (8.1)$$

where h_{max} denotes the maximum height of the ear pulse (from starting point to the highest peak).

Let Z be the ratio of an effective area to a reference area S as given in Eq. (8.2) and h denotes the instantaneous amplitude of ear pulse.

$$Z = \frac{1}{S} \int_{t_0}^{t_2} h dt \quad (8.2)$$

Z is not affected by the variable amplifier gain. Through analyzing the continuously varying Z from different subjects, it is found that Z decreases with the increase of BP. For example, Z equals 0.82, 0.68 and 0.43 in Figure 8.4 (a), (b) and (c) respectively. It is well known that PTT also decreases if BP increases. This indicates that the changing trends of Z and PTT with respect to BP are roughly the same. Based on this finding, we assume that Z is approximately a linear function of T_{rp} . This assumption will be verified by the experimental data in Chapter 8.3. The gradient R of the linear graph Z versus T_{rp} is given in Eq. (8.3)

$$R = \frac{T_{rp-1} - T_{rp-0}}{Z_1 - Z_0} \quad (8.3)$$

where Z_0 denotes the value of Z when the characteristic point of reflected wave just shifts to overlap on the incident wave, while a small inflection point can be identified by the method of first derivative, such as the case in Figure 8.3 (b). Z_I denotes the value of Z when the characteristic point of reflected wave can easily be identified by the method of local maximum or first derivative, such as the case in Figure 8.1 (f) or Figure 8.3 (a). T_{rp_0} and T_{rp_1} are values of T_{rp} corresponding to Z_0 and Z_I respectively, which can be identified by the method introduced in Chapter 8.1.2. Typically, a patient is maintained in normal BP condition before surgery. If a patient has very high BP at the beginning, a physician will act to decrease his/her BP to normal condition. Therefore, the values of Z_0 , Z_I , T_{rp_0} and T_{rp_1} can always be obtained. When BP increases to certain level, T_{rp} in the high BP condition is estimated using Eq. (8.4).

$$T_{rp} = R(Z - Z_0) + T_{rp_0} \quad (8.4)$$

In the same way, we obtain the linear function of Z and T_{pp_2} , and then the T_{pp_2} in the high BP condition can be estimated by Z .

8.1.4 Criterion and method of determining suitable PTT_s for

SBP estimation

It is commonly accepted that the foot-to-foot PTT is related to DBP. But there is still no criterion to determine PTT_s . The BP-PWV model in Eq. (6.29) is derived from the classical wave equation and applicable for any BP and PWV. SBP and DBP are just two specific values of the BP variable within a cardiovascular cycle. In Chapter 7, we have validated that the BP-PWV model

can well estimate the DBP ($\leq 125\text{mmHg}$) of people with healthy cardiovascular systems and in 19 and 60 age groups of both genders. Now we assume that both SBP and DBP can be estimated by the calibrated models but using different PWV's. The validity of this assumption will be verified later. Under this assumption, PTT_s can be calculated by the inverse model in Eq. (8.5).

$$T_s = \frac{L_{et} \ln(b / SBP)}{k} \quad (8.5)$$

where T_s denotes the calculated PTT_s and L_{et} is the propagation distance between ear and toe as detailed in Chapter 8.1.5. T_s is considered as a criterion to determine suitable PTT_s for estimating SBP. The method is presented as follows.

25 subjects with no evidence of cardiovascular disease and belong to 19 and 60 age groups are selected for study from previous obtained data in Chapter 7[177], as indicated in Table 8.2 (G1 and G2). Those who were diagnosed or suspected with angiocardopathy, hypertension or other vascular diseases have been ruled out in order to avoid the effect of pathogenic factors on the pulses and PTT. Their T_s 's are calculated by Eq. (8.5) with the calibrated model parameters b and k . 20 pairs of ear and toe pulses are selected from each subject. The features of these pulse waves are not distorted by transfusion, surgical intervention, etc. For every pair of pulses, five different PTT_s 's (T_{pp_1} , T_{pp_2} , T_{rr} , T_{ff} and T_{rp}) are identified by the method introduced in Chapter 8.1.2 and 8.1.3. Although the PTT_s 's obtained from different subjects change with their height, age and BP, the ratio of PTT_s/T_s for different subjects can be compared and analyzed statistically. Then five kinds of PTT_s/T_s are calculated for each pair of pulses. In total there are 500 sets of data in each kind of PTT_s/T_s . The mean of

each kind of PTT_s/T_s is calculated and denoted as $(PTT_s/T_s)_{mean}$. For instance, $(T_{ff}/T_s)_{mean}$ denotes the mean of all T_{ff}/T_s obtained from the 25 subjects.

We compare the five kinds of $(PTT_s/T_s)_{mean}$ by histogram in Figure 8.5 for the purpose of choosing PTT_s whose value approximates T_s . It is clear that T_{pp_1} , T_{rr} and T_{pp_2} are different from T_s because $(T_{pp_1}/T_s)_{mean}=1.762$, $(T_{pp_2}/T_s)_{mean}=0.696$ and $(T_{rr}/T_s)_{mean}=1.859$. But T_{ff} and T_{rp} are similar to T_s since $(T_{ff}/T_s)_{mean}=0.873$ and $(T_{rp}/T_s)_{mean}=1.129$. Therefore, T_{ff} and T_{rp} (representing PTT_s of incident wave and that of reflected wave) are used in PWV_s calculation and will be further assessed by experimental data in Chapter 8.2.1 and 8.3.1.

Figure 8.5 Comparison of five kinds of $(PTT_s/T_s)_{mean}$

8.1.5 Determining propagation distance and calculating PWV_s

The propagation distance with respect to PTT_s is required for calculating PWV_s . The propagation distance of incident wave between ear and toe is denoted as L_{et} , which can be calculated by Eq. (7.1) as introduced in Chapter 7.1.2.

The propagation distance for reflected wave is relatively difficult to determine. Actually, the reflected wave of ear pulse does not only result from the reflection at toe. It is composed of reflections from a number of ramification points and termination points in the arterial system, such as the femoral vascular bed, the arterioles in thighs, crura and soles. It is very difficult to distinguish the roles of different reflection points [105]. To carry out analysis and calculation, we need a point that gives the equivalent effects of all these reflection points. Considering that the femoral vascular bed and the arterioles in legs are the main areas of reflection, the location of the equivalent reflection point in body is assumed in the middle of the leg. By statistics, the distance between this point and toe is about $2L_e$ so that the reflected wave propagation distance from the equivalent reflection point to ear should be $L_t + L_e - 2L_e = L_t - L_e = L_{et}$, which is approximately the same as the incident wave propagation distance. Then the PWV_s can be calculated as

$$PWV_s = \frac{L_{et}}{PTT_s} \quad (8.6)$$

8.1.6 Estimating SBP and DBP by one mathematical model with the same model parameters

SBP and DBP are estimated using the validated model in Chapter 7 and separate PWV's, as shown in Eq. (8.7) and (8.8). The identified model parameters b_{ij} and k_{ij} ($i=19$ or 60 and $j=\text{male or female}$) in Figure 7.5 [177] are used.

$$SBP = b_{ij} e^{-\frac{k_{ij}}{PWV_s}} \quad (8.7)$$

$$DBP = b_{ij} e^{-\frac{k_{ij}}{PWV_d}} \quad (8.8)$$

8.2 Experimental validation

Experiments were conducted in operation rooms of Southwest Hospital in Chongqing, China. Only subjects with no evidence of cardiovascular disease and in two age groups (19 and 60) of both genders are involved in this study. Ethical approval was given for all clinical experiments by the Medical Ethics Committee of Southwest Hospital. Written informed consents of anaesthesia were obtained from all the participants before the operations, which included invasive BP measurement (Patient Monitor Solar 8000 M, GE medical Systems Information Technologies Inc) according to the requirement of surgeries. All subjects were in supine position during measurements.

To allow readers have an overall picture of the experimental studies, table 8.2 summarizes all the experimental groups involved in Chapter 7 and 8.

Table 8.2 Summary of experimental groups involved in Chapter 7 and 8

Experimental group	Number of subjects	Age	Experimental purposes
Group 1 (G1) in Chapter 7	23 (12 men and 11 women)	19 $\pm$ 2 and 60 $\pm$ 2	(1) Identify model parameters b and k by statistical method. [177] (2) 15 subjects are selected from G1 to determine five kinds of $(PTT_s/T_s)_{\text{mean}}$ [193]
Group 2 (G2) in Chapter 7	20 (10 men and 10 women)	19 $\pm$ 1 and 60 $\pm$ 2	(1) Validate the calibrated models by DBP measurement [177] (2) 10 subjects are selected from G2 to determine five kinds of $(PTT_s/T_s)_{\text{mean}}$ [193]
Group 3 (G3) in Chapter 8	9 (5 men and 4 women)	19 $\pm$ 2 and 60 $\pm$ 2	Assess PWV_s (PWV_{ff} , PWV_{rp} and PWV_{mean}) by experimental data [193]
Group 4 (G4) in Chapter 8	26 (15 men and 11 women)	19 $\pm$ 1 and 60 $\pm$ 1	Measure SBP and DBP by the calibrated models with the same model parameters and separate PWV 's (PWV_s and PWV_d) [193]

8.2.1 Experiment for assessing PWV_s

As indicated in G3 (Table 8.2), 9 subjects were involved in this experiment.

Their invasive BP's were recorded by the computer in the operation room. At

the same time, their ear and toe pulse waves were acquired and three PTT's (PTT_d , T_{ff} and T_{rp}) were recorded by a self-developed experimental setup [177, 193, 194]. A data set included SBP, DBP, PTT_d , T_{ff} and T_{rp} obtained simultaneously from a subject. The number of data sets per subject ranged from 27 to 51. If BP maintained almost unchanged, data was recorded in every 5 minutes. If BP changed fast, data was recorded in every 20-60 seconds. Data acquisition continued for a few hours including the time before, during and after anaesthetic. The variation range of invasive SBP was from 79mmHg to 187mmHg, and that of invasive DBP was from 45mmHg to 99mmHg.

8.2.2 Experiment for continuously measuring BP

Based on the results of PWV_s assessment as detailed in Chapter 8.3.1, PWV_{mean} in Eq. (8.9) was used to estimate SBP. Program was written and combined with the one for calculating PWV_d [177]. The program was integrated into the self-developed experimental setup [177, 193, 194] for acquiring ear and toe pulses as well as estimating BP by PWV based on the calibrated models. The work cycle of the program was set as 200ms which was shorter than a cardiac cycle.

Subjects and conditions were given in G4 (Table 8.2). This experiment was conducted strictly according to the experiment specifications of AAMI SP10 [26]. Invasive BP's of subjects were recorded as references, while their noninvasive BP's were measured by PWV using our experimental setup. A data set included an invasive BP and a noninvasive BP recorded simultaneously and manually. Data acquisition continued for a few hours including the time before, during and after anaesthetic. The time interval between two adjacent records

ranged from 1 to 10 minutes, depending on whether the BP changed. The BP's measured by cuff method were also recorded in every 5 minutes for comparison. The number of data sets per subject ranged from 20 to 45. The variation range of invasive SBP was from 62mmHg to 221mmHg, and that of invasive DBP was from 33mmHg to 110mmHg.

8.3 Results

8.3.1 Assessment of PWV_s by experimental data

Four types of PWV_s are calculated as follows for each set of data according to Chapter 8.2.1.

$$PWV_d = \frac{L_{et}}{PTT_d}; \quad PWV_{ff} = \frac{L_{et}}{T_{ff}}; \quad PWV_{rp} = \frac{L_{et}}{T_{rp}}; \quad PWV_{mean} = \frac{L_{et}}{T_{mean}} \quad (8.9)$$

$$\text{Where } T_{mean} = \frac{T_{ff} + T_{rp}}{2}$$

For every one of the 9 subjects in G3 (Table 8.2), three scatter diagrams are plotted using each PWV_s (PWV_{ff} , PWV_{rp} and PWV_{mean}) vs SBP and PWV_d vs DBP. Curve fitting is done by the 'cftool' in Matlab software based on the Eq. (6.29). The results of curve fitting are compared to assess the feasibility of the three PWV_s 's for estimating SBP.

A case (60-year-old man; 42 sets of data) in Figure 8.6 is used to illustrate and explain our findings.

Figure 8.6 Curve fittings of 42 sets of data obtained from a 60-year-old man.

(a) PWV_{ff} vs SBP and PWV_d vs DBP (b) PWV_{rp} vs SBP and PWV_d vs DBP

(c) PWV_{mean} vs SBP and PWV_d vs DBP

As shown in Figure 8.6 (a), the dispersion degree of PWV_{ff} vs SBP (dots) are higher than that of PWV_d vs DBP (triangles). At the same BP level, the coordinates of two dots locating farthest from each other are (20.2, 150) and (27.7, 152). So the largest variation range of PWV_{ff} is 7.5 meter/sec. The largest variation range of PWV_d is 2.4 meter/sec, which is calculated from the two triangles locating farthest from each other with the coordinates of (11.4, 95) and (13.8, 96). The largest variation range of PWV_{ff} is about three times of that of PWV_d , which indicates that the random error in PWV_{ff} is much larger than that in PWV_d . According to the results in Table 7.3, DBP estimated by PWV_d

gave a standard deviation of 7.5 mmHg which just satisfied the accuracy criterion of AAMI (standard deviation ≤ 8 mmHg). It can be expected that the SBP estimated by PWV_{ff} based on the BP-PWV model Eq. (6.29) cannot satisfy the accuracy criterion of AAMI.

Similarly in Figure 8.6 (b), the dispersion degree of PWV_{rp} vs SBP are much higher than that of PWV_d vs DBP. For the same reason, PWV_{rp} is not suitable being used to estimate SBP. In addition, the PWV_{rp} data can be used to verify the assumption of the linear relationship between T_{rp} and Z. For this case, when $SBP > 140$ mmHg, PWV_{rp} is determined based on Eq. (8.4). It can be observed that the PWV_{rp} obtained from Z is able to follow very high SBP, and the dispersion degree of PWV_{rp} when $SBP > 140$ mmHg is slightly higher than that of PWV_{rp} when $SBP < 140$ mmHg. This phenomenon can also be seen in Figure 8.6 (a) that the dispersion degree of PWV_{ff} increases with the increase of SBP. Around $SBP = 140$ mmHg, there is no sudden change of the dispersion degree.

Although the PWV_{ff} and PWV_{rp} cannot be used directly in estimating SBP, their average PWV_{mean} has better performance. In Figure 8.6 (c), the PWV_{mean} vs SBP distribute closely around the curve. The largest variation range of PWV_{mean} is 2.3 meter/sec, which is very close to that of PWV_d (2.4 meter/sec). This indicates that the dispersion degree of PWV_{mean} vs SBP is similar to that of PWV_d vs DBP. Consequently, PWV_{mean} is the most suitable choice for SBP estimation.

In addition, PWV_{mean} can estimate SBP exceeding 150 mmHg, which indicates that the method of identifying PTT_s in high SBP condition in Chapter 8.1.3 is feasible. Moreover, the dots and triangles are overlapped in the BP

range of 86 mmHg-96 mmHg, which means that PWV_{mean} equals PWV_d when SBP equals DBP. This finding verifies that SBP and DBP can be estimated using one BP-PWV model with the same model parameters and separate PWV's. Similar results are obtained from other 8 subjects.

8.3.2 BP measurement results

In G4 (Table 8.2), the number of data sets per subject exceeds 10 sets. According to the test standard of AAMI, the first 10 sets of data are used in statistical analysis so that the overall sample size is 260 sets.

Bland-Altman plots are displayed for SBP measured by invasive method vs SBP estimated by PWV method in Figure 8.7 (a) and for DBP measured by invasive method vs DBP estimated by PWV method in Figure 8.7 (b). For comparison, invasive BP vs BP measured by cuff sphygmomanometer are also displayed in the same way in Figure 8.7 (c) and (d). The average of the invasive BP and the BP either estimated by PWV method or measured by cuff sphygmomanometer is plotted on the x-axis with the difference between the readings plotted on y-axis. Upper and lower limits of 2 standard deviations (95% confidence level) around the mean difference (solid line) are indicated as dashed lines on each graph. In considering SBP, there is a positive bias (95% confidence interval) of 2.16 (-10.0 – 14.4) for PWV method in Figure 8.7 (a) and a similar bias but wider confidence interval of 2.20 (-13.1 – 17.5) for cuff method in Figure 8.7 (c). For DBP, the plot for PWV method in Figure 8.7 (b) shows smaller bias with mean values being -1.49 (-14.2 – 11.3) compared to -4.30 (-18.6 – 10.0) for cuff method in Figure 8.7(d).

From the statistical results, it can be concluded that the two non-invasive methods give similar SBP estimation, but the cuff method tends to underestimate DBP compared to the PWV method. Regarding the PWV method, our benchmark models slightly overestimate SBP by PWV_{mean} and underestimate DBP by PWV_d .

(a)

Bland-Altman of SBP by PWV: Difference vs Average

(b)

Bland-Altman of DBP by PWV: Difference vs Average

(c)

Bland-Altman of SBP by Cuff:Difference vs Average

(d)

Bland-Altman of DBP by Cuff:Difference vs Average

Figure 8.7 Bland-Altman plots: Upper and lower limits of 2 standard deviations (95% confidence level) around the mean difference (solid line) are indicated as dashed lines. (a) SBP measured by PWV compared to the invasive SBP. (b) DBP measured by PWV compared to the invasive DBP (c) SBP measured by cuff sphygmomanometer compared to the invasive SBP (d) DBP measured by cuff sphygmomanometer compared to the invasive DBP.

Figure 8.8 Scatter plots of the noninvasive BP vs the invasive BP. (a) the SBP measured by PWV and Cuff vs the invasive SBP (b) the DBP measured by PWV and Cuff vs the invasive DBP

The 260 sets of invasive BP and noninvasive BP (obtained by PWV method and cuff method) are also illustrated in scatter plots (Figure 8.8). The linear fits of PWV vs invasive and cuff vs invasive are indicated in each plot. It can be seen from the gradients of the linear fits that the cuff method generally underestimates the invasive BP, especially for DBP. In comparison, the PWV method has a better performance. But the PWV method sometimes may also underestimate BP compared to the invasive method. This may be because the pulse wave measured in our study is volume wave instead of pressure wave. The shape of the volume wave is slightly different from the pressure wave measured by invasive method, especially when the BP is high and the pressure wave becomes sharp. The high cusp of the pressure wave may not appear on the volume wave. In these cases, our PWV method will underestimate BP.

Table 8.3 Errors of BP measured by PWV method comparing to AAMI

Standard		
AAMI Standard	DBP measured by PWV method	SBP measured by PWV method
 Mean Deviation 	 Mean Deviation 	 Mean Deviation
$\leq 5\text{mmHg}$	$= 1.49\text{mmHg}$	$= 2.16\text{mmHg}$
Standard Deviation	Standard Deviation	Standard Deviation
$\leq 8\text{mmHg}$	$= 6.4\text{mmHg}$	$= 6.1\text{mmHg}$
NO. of data sets ≥ 150	NO. of data sets = 260	NO. of data sets = 260
NO. of subjects ≥ 15	NO. of subjects = 26	NO. of subjects = 26

Table 8.3 summarizes the errors of SBP and DBP measured by PWV_{mean} and PWV_d comparing to the accuracy criteria of AAMI. The mean deviations (2.16mmHg for SBP and 1.49mmHg for DBP) and standard deviations (6.23mmHg for SBP and 6.51mmHg for DBP) satisfy the criteria of AAMI, which verify that 1) The methods of identifying PTT_s in low, normal and high SBP conditions are valid. 2) For people with no evidence of cardiovascular disease and whose ages are around 19 and 60, the calibrated models in Eq (8.7) and (8.8) are valid for measuring their SBP and DBP in large variation range without intermittent recalibration of model parameters.

Generally, the measurement errors may result from identification of PTT_s , estimation of L_{et} , identification of model parameters b and k by statistical method, and influences of physiological and environmental conditions. The results in Table 8.3 indicate that the errors from a variety of sources mentioned above are within acceptable range.

Table 8.4 Errors of BP measured by cuff method comparing to AAMI Standard

AAMI Standard	DBP measured by cuff method	SBP measured by cuff method
 Mean Deviation 	 Mean Deviation 	 Mean Deviation
$\leq 5\text{mmHg}$	$= 4.3\text{mmHg}$	$= 2.2\text{mmHg}$
Standard Deviation	Standard Deviation	Standard Deviation
$\leq 8\text{mmHg}$	$= 7.15\text{mmHg}$	$= 7.65\text{mmHg}$
NO. of data sets ≥ 150	NO. of data sets = 260	NO. of data sets = 260
NO. of subjects ≥ 15	NO. of subjects = 26	NO. of subjects = 26

For comparison, Table 8.4 shows the errors of SBP and DBP measured by cuff sphygmomanometer comparing to the accuracy criteria of AAMI. The same conclusion can be drawn that the PWV method performs better than the cuff method in DBP measurement. The error of SBP measured by PWV method is also slightly smaller than that measured by cuff method.

Figure 8.9 Tracking the invasive SBP and DBP by PWV method and cuff method. The x axis shows the number of records with maximum of 41. The y axis is BP value (mmHg). The time interval between two records is 5 minutes so that whole recording period is 3.5 hours.

For the purpose of allowing readers to get a good sense of long-term BP measurement, Figure 8.9 illustrates the time courses of the reference invasive BP and two noninvasive BP measured by PWV method and measured by cuff method from a 60 years' old man. In fact, beat-to-beat BP could be measured by PWV method, but since cuff sphygmomanometer only provided BP value per 5minutes, we recorded the three BP values simultaneously at 5-minute intervals for better comparison. This figure shows the results of tracking invasive BP by two methods. In this trial, the BP measured by PWV well tracks the invasive BP. It is easy to observe that the SBP measured by cuff method shows large error from number 7 to 20, thus PWV method gives better results than cuff method in this case.

Figure 8.10 Beat-to-beat recording of BP during anesthesia by PWV method in 1minute and 30 seconds.

An example of beat-to-beat recording of BP during anesthesia by PWV method is provided in Figure 8.10. The BP data were obtained from a 47 years old woman. The total number of records is 102 and the period of recording is 1 minute and 30 seconds. Due to the effect of narcotic, BP continuously drops within a short time (SBP drops from 126mmHg to 87mmHg and DBP drops from 78mmHg to 51mmHg). The fluctuation results from respiration.

8.4 Discussions

8.4.1 Measuring SBP and DBP by the same BP-PWV model but separate PWV's

In nature, SBP and DBP are two special pressure states in arterial system, which correspond to different PTT's denoted as PTT_s and PTT_d [195, 196]. It has been shown that PWV in systole is faster than that in diastole [197]. Hence, within the same cardiac circle, there are $SBP > DBP$ and $PTT_s < PTT_d$. However, in many available results, a single PTT and a model with different model parameters are used to estimate SBP and DBP [121, 181, 183]. In this way, the model parameters are changing at a fast rate when BP changes significantly and rapidly. Consequently, intermittent recalibration using external device is inevitable. Intermittent recalibration is difficult to response to the urgencies in operation room. In order to achieve the aim of fast-response and easy-to-use, we try to find a way in which intermittent recalibration can be avoided.

Our mathematical model in Eq (6.29) expresses the relationship between PWV and BP (including both SBP and DBP) in low, normal and high

conditions. As shown in Figure 8.6 (c), the relationship between PWV_{mean} and SBP is the same as that between PWV_d and DBP. Therefore, in our methodology, SBP and DBP are estimated using a single mathematical model with calibrated model parameters but different PWV's (PWV_s and PWV_d). In another word, the change of BP is reflected by variable PWV instead of variable model parameters. Especially when BP changes rapidly in a wide range, our method can follow the variation of BP using PWV without intermittent recalibration of model parameters.

8.4.2 Reducing non-systematic error by taking average of T_{ff} and T_{rp}

The variation of PTT not only results from BP but also various influencing factors, such as temperature, blood volume in the arterial system, heart rate, surgical intervention, etc. BP as well as these physiological and environmental factors can change the features of pulse waves and the positions of characteristic points, and thus affect PTT. The variation of PTT resulting from BP is what we need. But the variation of PTT caused by influencing factors is considered as non-systematic error. Unfortunately, it is very difficult to distinguish what cause the variation of PTT. Therefore, it is hard to utilize a specific noise filtering technique to cater for non-systematic errors. A special method is required.

T_{ff} and T_{rp} represent PTT's of the incident wave and reflected wave respectively. If we only use one of them, the problem of non-systematic error is inevitable. As indicated in Figures 8.6 (a) and (b), PWV_{ff} and PWV_{rp} include

non-systematic errors from the influencing factors. However, the dispersion degree of PWV_{mean} in Figures 8.6 (c) is much lower than that of PWV_{ff} and PWV_{rp} . This might be because some non-systematic errors in T_{ff} and T_{rp} cancel out each other, so that the errors included in T_{mean} are reduced. Based on our observation, if only BP changes, T_{ff} and T_{rp} usually increase or decrease together; while if feature of the peripheral pulse changes due to influencing factors such as temperature and heart rate, T_{ff} and T_{rp} mainly change oppositely (i.e. one increases while the other decreases).

Here we use temperature as an example to illustrate its effect on T_{ff} and T_{rp} and how the random error in T_{mean} is reduced. The temperature of the distal ends of body such as finger and toe may change constantly. Even in the operation room that is kept at a uniform temperature, the temperature of toe may still change due to large amounts of intravenous infusion. But ear locates near the central body that maintains an invariable temperature, thus the temperature change of ear is much smaller than that of toe. Here we assume that the effect of temperature on ear is negligible and focus on its effect on toe. Based on our observation, the temperature change has little effect on the shape of toe pulse, but it will make the wavecrest of toe pulse tilt to left or right which lead to the shifting of T_{ff} and T_{rp} along the time axis.

Figure 8.11 shows the case that the wavecrest of toe pulse tilts to left due to the decrease of toe temperature when SBP remains unchanged. T_{ff} and T_{rp} indicate the state when the toe wavecrest remains not tilting, and the T_{ff}' and T_{rp}' indicate the state when the toe wavecrest tilts to left. T_o is the overlap of T_{ff} and T_{rp} , which is actually the width of the toe wavecrest. Since the shape change of toe wavecrest due to temperature change is negligible, T_o is considered as

invariant. Let e be the absolute value of random error. The temperature change makes the toe wavecrest tilt to left by e , thus the right-end of T_{ff} and the left-end of T_{rp} shift to left by e . The left-end of T_{ff} and the right-end of T_{rp} remain unchanged because the effect of temperature on ear pulse is very small. Then we have $T_{ff}' = T_{ff} - e$ and $T_{rp}' = T_{rp} + e$. In this case, T_{mean} is calculated by taking the average of T_{ff}' and T_{rp}' so that the error is balanced out.

$$T_{mean} = \frac{T_{ff}' + T_{rp}'}{2} = \frac{T_{ff} - e + T_{rp} + e}{2} = \frac{T_{ff} + T_{rp}}{2} \quad (8.10)$$

Therefore, using the average of T_{ff} and T_{rp} is helpful to reduce the non-systematic errors. Practically, the non-systematic errors cannot be fully balanced out. Nevertheless, they are reduced significantly. The error analyses in Table 8.3 verify that PWV_{mean} is feasible to estimate SBP.

Figure 8.11 Schematic diagram of the toe wavecrest tilting to left due to the decrease of toe temperature

8.5 Summary and conclusion

Based on the theoretical derivation in Chapter 6, SBP and DBP can be estimated by one mathematical model with the same model parameters but different PWV's. We first assume that this methodology is feasible, and then verify the methodology by experimental data. This is a commonly used research method in the area of bioengineering and biomedical engineering. In this Chapter, the study is achieved in three steps:

- 1) Propose five different PTT_s's (T_{pp_1} , T_{pp_2} , T_{rr} , T_{ff} and T_{rp}). Then calculate T_s by the inverse model and use it as a criterion to determine proper PTT_s. Only two of the five PTT_s's (T_{ff} and T_{rp}) are carried on to the next step of investigation by experimental data.
- 2) The T_{ff} , T_{rp} and PTT_d are measured from a small population of humans whose BP's vary in a large range during operations. The method of curve fitting is used to evaluate the correlation between SBP and the practically obtained PWV_{ff} and PWV_{rp}. The findings reveal that the dispersion degrees of PWV_{ff} and PWV_{rp} are very high, so that they are difficult to be used for SBP estimation. However, their average that is PWV_{mean} is very promising for SBP estimation because the non-systematic errors are reduced significantly.
- 3) Lastly, PWV_{mean} and PWV_d are used to measure SBP and DBP of the test subjects using the developed benchmark models without recalibration of model parameters. The measurement results satisfy the accuracy criteria of AAMI, which validate that SBP and DBP can be estimated by one mathematical model with the same model parameters and two separate PWV's.

Chapter 9

Statistical Analysis of Blood Pressure

Measurement Error by Oscillometry during Surgical Operations

Indirect cuff-based sphygmomanometers are commonly used for operative and postoperative monitoring, as well as diagnosis of hypertension. During the last 10 years, sphygmomanometers for semiautomatic recordings nearly all use oscillometry as the measuring principle [16, 26-28, 35]. A number of them are recommended by professional societies such as Association for the Advancement of Medical Instrumentation (AAMI) [26] or British Hypertension Society (BHS) [27, 28]. However, the measuring accuracy of oscillometric devices in clinical wards has always been concerned [6, 16, 31, 35]. Shahriari M et al [16] had tested five different oscillometric manometers against auscultatory measurement. None of them fulfilled the criteria set by the BHS.

It is worth notice that according to the test standard set up by AAMI, only the first 5-10 sets of BP data measured per trial are used as the sample data for evaluating the devices. However, the BP data measured during surgical operations and intensive care are far more than 10 sets. Although a device has

been validated that it satisfied the accuracy criteria of AAMI, it may not perform well in long-term operative and postoperative monitoring. In addition, the occurrence of abnormal large errors and clinically meaningful errors which may cause misdiagnosis and delayed-diagnosis has yet to attract enough attention.

In this chapter, oscillometry readings are compared with the invasive readings obtained simultaneously by the same patient monitor. The mean deviation and standard deviation (oscillometry vs invasive method) throughout the surgical operations are investigated and compared with the accuracy criteria of AAMI. In addition, the probabilities of occurrence of the abnormal large errors and clinically meaningful errors are assessed. These results may help physicians to make a better judgment of the BP measurement results in clinical conditions and formulate a better treatment scheme.

9.1 Methods

9.1.1 Study subjects

Investigations were conducted in the operation rooms of Southwest Hospital in Chongqing, China, between December 2008 and May 2010. The study populations were selected from those who already had both oscillometric BP and invasive radial arterial BP (A-line) monitored according to the indication of the surgeries (cardiac surgeries were excluded). Since the oscillometry measurement required the upper arm of the patient being on the same level as

his/her heart, only patients in supine position were selected. The general characteristic of the study population were summarized in Table 9.1.

Table 9.1 General characteristic of participants

Number of study populations	270 Chinese patients (139 men and 131 women)
Range of age	1-85
Number of minors (age< 18)	73
Number of adults (age≥18)	198
Range of invasive BP	SBP: 53mmHg-247mmHg; DBP: 30mmHg-157mmHg
Number of abdominal (liver, spleen, pancreas, gallbladder, intestines or abdominal tumor) surgeries	146
Number of thoracic but non-cardiac (lung, esophagus, trachea and thoracic tumor) surgeries	105
Number of cranial (Intracranial tumors) surgeries	19
Populations who are not involved in this study	patients with peripheral vascular diseases, severe arrhythmia and obesity

Ethical approval was given by the Medical Ethics Committee of Southwest Hospital Chongqing China. Written informed consents of anaesthesia were obtained from all the participants, which included the invasive BP measurement according to the requirement of surgeries (e.g. blood gas analysis). Before the operations, we let the patients fully understand the safety of the clinical study and promised them that their personal information would never be disclosed. After obtaining their verbal informed consents, we added content that "The blood pressure measurement data recorded during this operation may be used for research purposes." in the written informed consents of anaesthesia.

9.1.2 Experimental procedures

Patients were undergoing surgical operations in which their radial arteries were cannulated (BD 20-gauge, BD Medical Devices Co) and connected via pressure tubing and transducer (PX 260 Pressure Monitoring Kit, Edward Life sciences LLC) interfaced with a monitor (Patient Monitor Solar 8000 M, GE medical Systems Information Technologies Inc) which provided the invasive BP. At the same time, the brachial BP's of the patients were measured on the same arm in every 5 minutes by the same monitor (Solar 8000 M) whose oscillometric measurement satisfied the AAMI accuracy standard ($|\text{Mean Deviation}| \leq 5\text{mmHg}$ and $\text{Standard Deviation} \leq 8\text{mmHg}$) [26]. This type of monitors was special devices for surgical operations, which had been guaranteed by Food and Drug Administration (FDA) in the UAS and validated by FDA in China. The cuff size was chosen according to the patient's age and the size of his/her upper arm. Basically, three types of cuffs were available for newborns, children and adults. The blood pressure cuff made by Critikon was

used in adults, which was applicable to the perimeter of upper arm between 23cm and 33cm.

A data set included one invasive BP data and one noninvasive BP data recorded simultaneously. The invasive BP at the time of oscillometric measurement was considered to be the average of the A-line readings just before and after the oscillometric measurement. In the 30 seconds before the oscillometric measurement, the monitor counted down. The first A-line reading was the one obtained within 10 seconds before the oscillometric measurement. However, in a 10 second period just after the oscillometric measurement, the A-line reading was sharp due to inflating, and generally stabilized after 10 seconds. Therefore, the second useful A-line reading was obtained between 10 and 20 seconds after the oscillometric measurement. The invasive BP was the average of the two A-line readings. In addition, it was known that kinks in the tubing, clots etc could influence A-line readings. If an obvious change of A-line waveform was observed, the invasive BP was considered as invalid and not recorded. After correcting the kinks in the tubing and cleaning the clots, fast flush test [198] was used to test the frequency response of the measuring channel. If the frequency response became normal, the A-line transducer was used again in invasive measurement.

The number of records depended on the duration of surgical operations. It was different from case to case. Generally, more than 15 sets of data were recorded in each trial. A total of 6640 sets of data were obtained from 270 patients. Please note that these data were obtained from several monitors of the same type. Therefore, the bias of a single device can be excluded. During our experiments, the clinical safety and performance of the monitors were examined

many times by FDA in China. Thus the error caused by the malfunction and the device-based inaccuracy can also be excluded.

9.1.3 Statistical analysis

1) *Error analysis according to AAMI standard*

Considering the invasive BP as reference, mean deviation and standard deviation (oscillometry vs invasive method) were calculated for the 6640 sets of data and compared with the accuracy criteria of AAMI. Bland Altman Plots of SBP and DBP were also provided.

2) *Probability distributions of the abnormal large errors*

In order to assess the probability of occurrence of abnormal large errors, the average, best case and worst case of each subject were investigated. For each single patient, his/her BP errors ($| \text{oscillometric SBP} - \text{invasive SBP} |$) were averaged and denoted as $\text{error}_{\text{mean}}$. His/her largest and smallest errors (absolute values) were selected out and denoted as $\text{error}_{\text{max}}$ and $\text{error}_{\text{min}}$. The $\text{error}_{\text{mean}}$, $\text{error}_{\text{max}}$ and $\text{error}_{\text{min}}$ from 270 patients formed three special groups of data. According to AAMI standard, 8mmHg was considered as one standard deviation denoted as σ . The percentages of data within σ , between σ and 2σ , ..., between 4σ and 5σ were calculated for $\text{error}_{\text{mean}}$. In the same way, the percentages of data within σ , between σ and 2σ , ..., between 7σ and 8σ were calculated for $\text{error}_{\text{max}}$, and the percentages of data within σ , between σ and 2σ , ..., between 3σ and 4σ were calculated for $\text{error}_{\text{min}}$, respectively. The probability distributions of $\text{error}_{\text{mean}}$, $\text{error}_{\text{max}}$ and $\text{error}_{\text{min}}$ were plotted using histograms (percentage vs standard deviation). The probabilities of $\text{error}_{\text{mean}} > 3\sigma$ (24mmHg), of $\text{error}_{\text{max}} > 5\sigma$

(40mmHg) and of $\text{error}_{\min} > 3\sigma$ (24mmHg) were considered as the probabilities of occurrence of abnormal large errors.

3) *Clinically meaningful error*

Typically, a physician would act if SBP was below 90 mmHg in an adult during operations. A clinically meaningful error, which was $|\text{oscillometric SBP} - \text{invasive SBP}| \geq 10\text{mmHg}$ when SBP was around 90mmHg, was devised as an outcome variable. The 198 adult patients were investigated. We chose the simultaneously measured invasive SBP and oscillometric SBP which located on opposite sides of 90mmHg (invasive SBP > 90mmHg and oscillometric SBP < 90mmHg as well as invasive SBP < 90mmHg and oscillometric SBP > 90mmHg) and also their absolute difference $\geq 10\text{mmHg}$. The percentages of adults who had such clinically meaningful differences were calculated.

9.2 Results

The absolute values of the mean and standard deviations are compared with the accuracy criteria of AAMI [26] as given in Table 9.2 [33]. The mean deviations are smaller than the criterion of 5mmHg for both SBP and DBP, but the standard deviation is about 1.86 and 1.40 times of the criterion of 8mmHg for SBP and DBP respectively [33].

Table 9.2 Mean deviation and the standard deviation (oscillometry vs invasive method) compared with AAMI accuracy criteria

AAMI accuracy criteria	SBP	DBP
 Mean Deviation 	 Mean Deviation 	 Mean Deviation
$\leq 5\text{mmHg}$	$= 1.98\text{mmHg}$	$= 4.31\text{mmHg}$
Standard Deviation	Standard Deviation =	Standard Deviation =
$\leq 8\text{mmHg}$	14.87mmHg	11.21mmHg
NO. of data sets	NO. of data sets	NO. of data sets
≥ 150	$= 6640$	$= 6640$
NO. of subjects ≥ 15	NO. of subjects = 270	NO. of subjects = 270

The mean deviations as well as the upper and lower limits of two standard deviations are indicated in the Bland Altman Plots (Figure. 9.1). The negative mean deviations (SBP = -1.98 and DBP = -4.31) imply that our oscillometric devices slightly underestimate BP. The mean deviation of SBP is smaller than that of DBP but the standard deviation of SBP is larger than that of DBP. This indicates that the dispersion degree of SBP is higher than that of DBP, and thus large errors appear more frequently in SBP measurement.

Figure 9.1 Vertical axis indicates the differences between the two BP values. The mean as well as the upper and lower limits of two standard deviations are indicated. (a) Bland Altman Plot (oscillometric vs invasive) for 6640 sets of SBP data. (b) Bland Altman Plot (oscillometric vs invasive) for 6640 sets of DBP data. Horizontal axis represents the average values of invasive BP and oscillometric BP.

The probability distributions of $\text{error}_{\text{mean}}$ for SBP and DBP are plotted in Figure 9.2 (a) and (b) respectively. The probability distributions of $\text{error}_{\text{mean}}$ can be treated as normal distributions approximately. For majority of patients, their $\text{error}_{\text{mean}}$ are within one σ (8mmHg). The probability of $\text{error}_{\text{mean}}$ greater than 3σ (24mmHg) is considered as the probability of occurrence of abnormal large errors (4.07% for SBP and 1.48% for DBP), which is much greater than 0.26% (the probability of normal random variable with absolute value greater than or equal to 3σ).

(a)

(b)

Figure 9.2 Horizontal axis indicates the number of standard deviations and vertical axis indicates the percentage of data. (a) Probability distributions of SBP $\text{error}_{\text{mean}}$ in 270 patients. (b) Probability distributions of DBP $\text{error}_{\text{mean}}$ in 270 patients.

The probability distributions of $\text{error}_{\text{max}}$ for SBP and DBP are plotted in Figure 9.3 (a) and (b) respectively, which represent the worst cases in 270 patients. The value of $\text{error}_{\text{max}}$ varies greatly with the individual and the range of variation is rather large. It can be observed that the probability of $\text{error}_{\text{max}}$ within one σ (8mmHg) is only 3.69% for SBP and 6.62% for DBP. Majority of $\text{error}_{\text{max}}$ distribute between σ and 5σ (8-40mmHg). The probability of $\text{error}_{\text{max}}$ in excess of 5σ (40mmHg) is 14% for SBP and 6%for DBP, which are considered as the probability of occurrence of the abnormal large error.

(a)

(b)

Figure 9.3 (a) Probability distributions of SBP error_{max} in 270 patients.

(b) Probability distributions of DBP error_{max} in 270 patients.

The probability distributions of error_{min} for SBP and DBP are plotted in Figure 9.4 (a) and (b) respectively, which represent the best cases in 270 patients. The probability distributions of error_{min} can also be treated as normal

distribution approximately. It can be observed that for most patients their $\text{error}_{\min}$ are within one σ (8mmHg). The probability of $\text{error}_{\min}$ greater than 3σ (24mmHg) is also considered as the probability of occurrence of abnormal large errors (0.37% for SBP and 0.37% for DBP), which exceeds 0.26%.

(a)

(b)

Figure 9.4 (a) Probability distributions SBP $\text{error}_{\min}$ in 270 patients.

(b) Probability distributions of DBP $\text{error}_{\min}$ in 270 patients.

The clinically meaningful SBP differences ($| \text{oscillometric SBP} - \text{invasive SBP} | \geq 10\text{mmHg}$) around 90mmHg is presented in Figure 9.5. The limits of 10mmHg and -10mmHg are indicated. The data above 10mmHg means that the oscillometric SBP is at least 10mmHg higher than the invasive SBP, and the data below -10mmHg means that the oscillometric SBP is at least 10mmHg lower than the invasive SBP. A total of 193 sets of large differences around SBP = 90mmHg are found in 57 adult patients, which indicates that 28.78% of the adult patients ($57/198=28.78\%$) have such clinically meaningful differences.

Figure 9.5 Bland Altman Plot for 193 sets of clinically meaningful SBP data. Horizontal axis represents the average values of invasive SBP and oscillometric SBP. Vertical axis indicates that $| \text{invasive SBP} - \text{oscillometric SBP} | \geq 10\text{mmHg}$.

9.3 Discussion

9.3.1 Long-term BP measurement error during surgeries

One of the key findings of our study is that, for an oscillometric device that satisfies AAMI accuracy standard, its mean deviation and standard deviation of long-term BP monitoring during surgical operations may be quite different from that recommended by AAMI. This may be because the conditions of BP monitoring in operation room and ICU are much more complex and unpredictable than the conditions stipulated by AAMI for device validation. It is important for users to note that the accuracy criteria of AAMI cannot represent the error range of practical BP measurement in clinical conditions since the accuracy criteria is just to facilitate the evaluation of a new device.

9.3.2 Undesirable effects of abnormal large error and clinically meaningful error

For a few individuals, abnormal large errors may occur when cuff-oscillometric devices are used to measure their BP. This type of error is noteworthy because it may result in mistake in diagnosis and treatment. Especially during operations, the error in excess of 40mmHg will cause serious consequence when doctors are not aware of the real BP condition of patients and fail to take correct actions. According to our statistical results of the worst cases ($\text{error}_{\max}$), the probability of $\text{error}_{\max} > 40\text{mmHg}$ is rather high (14% for SBP and 6% for DBP) and thus must be paid attention to. Some patients have

$\text{error}_{\text{mean}} > 24\text{mmHg}$, which indicates that large errors may appear very frequently in their BP measurements. For those patients with $\text{error}_{\text{min}} > 24\text{mmHg}$, they may invariably have very big measurement errors which cannot be avoided by repeated measurements if cuff-oscillometric device is used.

According to our results, large errors ($\geq 10\text{mmHg}$) are found in 28.78% of the adult patients when their SBP's are around 90mmHg. In these cases, if oscillometric measurement underestimates the real BP around the critical value (90mmHg), the physician may make a wrong treatment. If the oscillometric measurement overestimates the real BP around 90mmHg, the error may lead to an under-diagnosis and a delayed treatment response to perioperative hypotension and significantly increases the risk of dying.

9.3.3 A possible cause of errors

It is well known that cuff-oscillometric devices may not be reliable for patients with peripheral vascular diseases, severe arrhythmia and obesity (large body mass index). These types of patients are not involved in our study. We focus on the patients whom the cuff-oscillometric devices are adequate for. We find that the shape change of arterial pressure wave, especially the wavecrest, is very likely to be a cause of measurement errors by oscillometry. Basically, arterial pulse wave transmits through arterial wall, muscle, etc, to the skin surface and then cause vibration inside the airbag of the cuff that can be measured by oscillometry. The vibration wave inside airbag is quite different from the real arterial pressure wave measured by invasive method. The association is dependent on the transduction process, whose fidelity cannot be readily determined [6].

Generally, when the arterial pressure wavecrest is narrow and sharp, the energy transmit time during wavecrest is short and a small quantity of energy is transmitted to the skin surface. Consequently, the amplitude of the enveloping line of the vibration wave inside airbag is lower than that when the wavecrest is wide. In this case, usually, oscillometric BP is $<$ invasive BP. In high BP condition, narrow and sharp wavecrest can be observed in many patients. It can be seen in Figure. 9.1 (a) that most of errors are negative (oscillometric minus invasive) when SBP is $> 150\text{mmHg}$. Similar results can be found in other articles [31, 32, 199]. In low and normal BP conditions, narrow and sharp wavecrest can also be observed in some patients.

When the arterial pressure wavecrest is wide, the energy transmit time during wavecrest is long and more energy is transmitted to the skin surface. Comparatively speaking, the amplitude of the enveloping line of the vibration wave inside airbag is high. In this case, oscillometric BP is $>$ invasive BP for most patients. Wide wavecrest mainly appears in low and normal BP conditions.

In fact, different devices have different ways to identify SBP and DBP, and thus there are various causes of errors. Based on our observation, the shape change of the arterial pressure wavecrest is a possible cause of errors. It can be deduced that this type of error is commonly found in various cuff-oscillometric devices.

9.3.4 A possible method to identify large errors

The measuring accuracy of any non-invasive sphygmomanometer in a single patient is unpredictable and the measurement error is inevitable [6, 26]. However, for two independent measuring principles, the sources of

measurement errors are quite different, and thus large errors should distribute in different populations. Measuring BP in a single patient based on two different non-invasive principles may be a way to identify large errors. For instance, in certain BP measurement, two independent non-invasive methods are applied together and their measurement results are compared. If the results are similar, it indicates that the errors of both methods should be small and the measurement results are reliable. If the results are quite different, it means that one of them has large measurement error. Although it is difficult to determine which method is accurate in this case, the results at least can alert doctors so that certain misdiagnosis can be avoided.

To date, auscultatory measurement is considered as the touchstone in judging the accuracy of an oscillometric device [26, 35, 200]. However, strictly speaking, oscillometry and auscultation are based on very similar measuring principles since the oscillogram and K-sounds are closely associated with specific levels of cuff pressure which are related to intra-arterial pressure [6, 201, 202]. Consequently, they should have some common errors and the problem of large errors may still remain. Unfortunately, there is still no reliable measuring principle that is completely independent of cuff technique. Recently, the arterial pulse wave velocity, pulse augmentation index and some other characteristics of waveform have been shown correlating to BP[177, 193, 203, 204]. These are promising approaches and may become independent measuring principles from cuff technique in future.

9.3.5 Limitation of this study and future work

The limitation of the study is that the data used for research is obtained from one type of oscillometric devices. Nevertheless, the possible cause of errors applies to various cuff-oscillometric devices. It is hoped that the results and discussions presented in our article are found useful by doctors or others working in related research areas.

So far, except for the peripheral vascular diseases, severe arrhythmia and obesity, we have not found the relationship between the measurement errors and other characteristic of population. It is research area worthy of further investigation.

9.4 Summary

In this chapter, we aim to 1) compare the error range throughout surgical operations with the accuracy criteria of AAMI, and 2) investigate the probabilities of occurrence of abnormal large errors and clinically meaningful errors.

BP's were measured from 270 participants using oscillometry and arterial cannulation (invasive method) in the same BP monitor throughout surgeries. Mean deviation and standard deviation (oscillometry vs invasive method) were calculated from 6640 sets of data and presented in Bland Altman Plots. Also the average, largest and smallest measurement errors ($\text{error}_{\text{mean}}$, $\text{error}_{\text{max}}$ and $\text{error}_{\text{min}}$) per patient were obtained respectively. The probability distributions of the three types of errors were shown using histograms (percentage vs standard

deviation). In addition, the clinically meaningful large errors ($\geq 10\text{mmHg}$) of the adult patients when their SBP's were around 90mmHg were investigated.

The mean deviation (1.98mmHg for SBP and 4.31mmHg for DBP) satisfies the AAMI criterion ($\leq 5\text{mmHg}$), but the standard deviation (14.87mmHg for SBP and 11.21mmHg for DBP) exceeds the AAMI criterion ($\leq 8\text{mmHg}$). The probability of $\text{error}_{\text{max}} > 40\text{mmHg}$ is 14% for SBP and 6% for DBP. The probability of $\text{error}_{\text{mean}} > 24\text{mmHg}$ (4.07% for SBP and 1.48% for DBP) and that of $\text{error}_{\text{min}} > 24\text{mmHg}$ (0.37% for SBP and 0.37% for DBP) are all greater than the criterion of 0.26%. The clinically meaningful errors are found in 28.78% of the adult patients.

According to our results, the mean deviations of long-term BP measurement by our oscillometric method during surgical operations meet the AAMI criterion. However, the standard deviations exceed the AAMI criterion. The probabilities of abnormal large error and clinically meaningful error are quite high, which are worthy of attention so as to avoid misdiagnosis and wrong/delayed treatment. By analyzing the possible cause of errors, it is deduced that similar results may be found in other cuff-oscillometric devices due to the limitation of measuring principle. Measuring BP in a single patient based on two different non-invasive principles may be a way to find out the large errors.

Chapter 10

Conclusion and Recommendations

This chapter brings the thesis to conclusion. It begins by summarizing the work completed and reported herein. Future developments of the methodology and extension of the technique are enumerated and preliminary suggestions as to their execution are made.

10.1 Conclusion

In this thesis, we propose a new and systematic methodology of estimating beat-to-beat BP by PWV, in which individual calibration can be avoided in practical measurement for people who have healthy cardiovascular systems. To verify this methodology, experiments are conducted in clinical environment for measuring BP continuously and noninvasively in 19 and 60 age groups of both genders. Our experimental results meet the accuracy criteria in AAMI.

In our measurement methodology, biomedical signal is acquired in a low-cost way. Necessary calibration is achieved by developing a novel mathematical model and a data base of model parameters. In terms of engineering realization,

software replaces hardware, which much simplifies the mechanical structure and reduces the difficulty of manufacturing. Our methodology compensates for the major shortcoming (complex mechanical structure) of the applanation tonometry and vascular unloading method. Although the measuring method is still far from commercialization and clinical application, it is indeed a direction worth exploring. The method will be continuously studied and improved in order to provide people a better BP management and comprehensive surgery safety.

To conclude, it is hoped that the methodology and results presented in this thesis are found useful by others working in continuous and noninvasive BP measurement by PWV or PTT, as well as other related research areas.

10.2 Recommendations for further research

As noted throughout the thesis, a number of pieces of future work remain and are described below. The further pursuit of each item is desirable in order to build upon the foundations laid herein.

10.2.1 Improvement of experimental setup

As introduced in Chapter 5, a dedicated computer was used in our experimental setup for data/signal processing, storage and analysis. However, most powerful data processing software, such as NI LabVIEW, cannot be run in the dedicated computer. Hence, the data acquired by the existing experimental setup needs pattern format conversion so as to be processed in a general-

purpose computer with software. If experimental data bulk is very great, it is inconvenient to use this experimental setup.

The idea of virtual instrument is commonly used in the design of measuring instrument and the development of experimental setup. Basically, the virtual instrument includes three parts: transducer, data acquisition card and a general-purpose computer with software installed for data visualization, storage and retrieval. In our future study, the existing experimental setup will be replaced by a virtual instrument. The self-developed sensors can still be used. Data acquisition will be achieved using NI DAQ device which allows easy sensor connectivity with integrated signal conditioning. Data/ signal visualization, processing, storage and retrieval can be done in general-purpose computer with NI LabVIEW (a powerful software allowing real-time measurement and control).

10.2.2Improvement of model

In this study, a methodology of measuring BP continuously and noninvasively by PWV is proposed. Due to the constraint of cost and time, we only conducted experiments on a small population (19 and 60 age groups of both genders) for the purpose of verifying the measuring methodology. By choosing experimental subjects whose ages are very different, we are able to investigate the differences caused by age and gender factors. Calibration and validation of models for all the other age-and-gender groups can be carried out in the same way, but needs large amount of work to collect clinical data from many patients. More subjects will be included in further studies to improve the reliability of model parameters and specificity of the measurements.

Our benchmark models are only applicable to people who have healthy cardiovascular systems. The model may be improved so as to be applied to people who have arterial pathological changes. Moreover, for children and people of different race, the feasibility of this measuring method still requires more verification.

10.2.3 Individual calibration for people with arterial pathological changes

For those who have arterial pathological changes, their pulse waves may be abnormal, and the identified PTT will include error. How to identify the PTT on abnormal pulse waves have not been studied fully. In these cases, individual calibration is required. Our calibration method is to modify the PWV of a person with arterial pathological changes in percentage so that the modified PWV is suitable to the benchmark models of people with healthy cardiovascular systems. The calibration can be done under the condition that the deformation of pulse wave shows regularity to a certain degree and thus the error in PWV can be considered as a constant. But regarding the BP measurements in thesis, we did not meet a case requiring calibration. To test the PWV calibration program, we artificially made the PWV of a man deviate from the normal value. For example, we simulated arteriosclerosis by changing his body position from lying to standing, and simulated peripheral artery embolism by supine leg raise. The results showed that the calibration method was effective. But whether intermittent recalibration is required for real patients with arterial pathological changes is unclear at the moment, and is an area

worthy for further investigation. This calibration method will be verified by more clinical experiments and modified in our future study.

Our experiments were conducted in operation rooms. Since the operation rooms are kept at a uniform temperature, the effect of temperature on peripheral pulse is very small in our experimental validation. However, the effect of temperature must be considered if our measuring method is used in routine clinical practice. We have not done enough experiments on the effect of temperature change. Future study is required on this issue.

Our approach may fail if the pulse waves cannot be detected from a person due to angionecrosis or other unknown reasons. In these cases, the experimental setup can give an alarm.

10.2.4 Quantitative and multi-aspect assessment of arterial stiffness based on PWV

The pathological changes of arteries may result in primary organ damage or undercurrent diseases. However till date, some structural and functional changes of aortas, such as atherosclerosis, are not yet fully understood. In addition, most pathological changes of arteries, such as arterial stiffness, are non-communicable diseases and thus the knowing rate is rather low. Early recognition and quantificational identification of the structural and functional changes of arteries are useful in that it enables physicians to intervene with proper therapy so as to avoid undercurrent diseases and optimize the cardiovascular-disease management.

There are two ways to assess the structural and functional changes of arteries: the invasive method and non-invasive method. In terms of the non-invasive method, PWV is a commonly accepted indicator of the elasticity of arterial wall. Carotid-femoral PWV is considered as the ‘gold-standard’ measurement of arterial stiffness. PWV is affected by many influencing factors, such as age, gender, BP, et al. It is difficult to differentiate these influencing factors. Hence, currently, PWV is only used for qualitatively determining arterial stiffness.

In addition, PWV is usually measured using the foot-to-foot velocity method, which represent PWV_d . However, PWV_d only provides limited psychophysiology and pathological information, and thus the assessment of arterial stiffness based on PWV_d is incomplete or imperfect. PWV_s can provide more useful information. Making use of both PWV_d and PWV_s may achieve multi-aspect assessment of arterial stiffness which allows doctors early recognizing and better treating.

In previous study, we had derived and validated a mathematical model that related BP to PWV for measuring BP. The age and gender factors were included in the model parameters. The PWV was obtained from peripheral arteries (ear and toe). Although the ear-toe PWV is not suitable for assessing the arterial stiffness, the BP-PWV model can be utilized. In this study, the age and BP will be considered as variables, and the BP-PWV model is applied reversely to obtain a calibrated PWV that is considered as criterion for determining the arterial stiffness. However, re-determination of model parameters is required since the carotid-femoral PWV is used instead of the ear-toe PWV. According to the proposed algorithm, the model parameters will be

calibrated according to different age and gender groups based on the BP and PWV obtained from subjects who have healthy cardiovascular systems. The calibrated models serve as benchmark models that can be used to calculate the PWV in any BP state for a person with healthy cardiovascular systems. The inverse benchmark models are useful for two purposes.

- A benchmark PWV can be calculated, which is used as criterion for assess the randomly measured PWV.
- The changes of PWV may result from 1) the increase of age and change of BP, or 2) pathological factors. The two causes can be differentiated using the inverse benchmark model.

Basically, there are two methodologies for quantitatively assessing arterial stiffness based on PWV

Method (1): Assessment based on calibration of PWV

In medical application, a normalized PWV will facilitate comparison and analysis. A benchmark PWV in a fixed BP and age condition is selected as a criterion. A measured PWV will be normalized to the PWV in this fixed BP and age condition, and compared with the benchmark PWV. The difference between the normalized PWV and benchmark PWV indicate the degree of arterial stiffness. This process is called calibration of PWV.

Method (2): Assessment based on the equivalent increase of age

The increasing of arterial stiffness with age is a normal physiological phenomenon. However, for the patients who have pathological arterial stiffness, their PWV will be faster than those who are in the same age and gender and have healthy cardiovascular systems. In this case, their PWV can be considered

as the PWV of people older than them. The increase of PWV due to pathological arterial stiffness can be converted in to the equivalent increase of age which is easily-understood. This achieves quantitative assessment of the pathological arterial stiffness by the way of aging.

This study may achieve quantitative determination of arterial stiffness, which allows doctors understand the degree of pathological changes of the arteries even when symptoms are minor. This is very helpful in recognizing the individuals who have a high risk of undercurrent diseases.

In summary, this study has two advantages.

- The arterial stiffness in two different states (SBP and DBP) can be understood. The original method that only determines the arterial stiffness in DBP state has now been rounded out with additional information. Especially when SBP is high, our method will help understand the pathological stiffness of the elastic fiber and collagen fiber respectively. In this way, a proper and individual treatment scheme will be formulated for every single patient.
- The arterial stiffness is assessed by an easily-understood way that is the equivalent increase of age. It offers convenience to the doctors for diagnosis and treatment based on their knowledge of patients in different age groups.

Author's Publications

Journal Papers

1. **Yan Chen**, Changyun Wen, Guocai Tao, Min Bi and Guoqi Li. Continuous and noninvasive blood pressure measurement: a novel modeling methodology of the relationship between blood pressure and pulse wave velocity. *Annals of Biomedical Engineering*. **37**: 2222-33, 2009
2. **Yan Chen**, Changyun Wen, Guocai Tao and Min Bi. Continuous and Noninvasive Measurement of SBP and DBP by One Mathematical Model with the Same Model Parameters and Two Separate PWV's. *Annals of Biomedical Engineering*. **40**(4): 871-882, 2011
3. Guocai Tao, **Yan Chen**, Changyun Wen and Min Bi. Blood pressure measurement error by oscillometry throughout surgical operations compared with invasive readings. *Blood Pressure Monitoring*. **16** (6): 285–290, 2011
4. Guoqi Li, Changyun Wen, Guang-Bin Huang, **Yan Chen**. Error tolerance based support vector machine for regression. *Neurocomputing*. **74**: 771-78, 2011
5. Guoqi Li, Changyun Wen, Weixing Zheng, **Yan Chen**. (2011) Identification of a class of nonlinear autoregressive with exogenous inputs models based on kernel machines. *The IEEE Transactions on Signal Processing*. **59**(5): 2146-2159, 2011

Conference Papers

1. **Yan Chen**, Changyun Wen, Haitao Tang, Linda Xiuzhen Teng. The relationship between different pulse wave velocity and systolic/diastolic pressure. *The 3rd IEEE Conference on Industrial Electronics and Applications*, Singapore, 2009
2. **Yan Chen** and Changyun Wen. Performance analysis of pulse transducers for continuous blood pressure measurement. *The 7th IEEE International Conference on Control & Automation*, Christchurch, 2010
3. **Yan Chen**, Changyun Wen, Guocai Tao and Min Bi. A new methodology of continuous and noninvasive blood pressure measurement by pulse wave velocity. *The 11th International Conference on Control, Automation, Robotics and Vision*, Singapore, 2010

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