uOttawa

L'Université canadienne
Canada's university

FACULTÉ DES ÉTUDES SUPÉRIEURES ET POSTOCTORALES

uOttawa

L'Université canadienne
Canada's university

FACULTY OF GRADUATE AND POSDOCTORAL STUDIES

Karen Soueidan

AUTEUR DE LA THÈSE / AUTHOR OF THESIS

M.A.Sc. (Biomedical Engineering)

GRADE / DEGREE

Department of Biomedical Engineering

FACULTÉ, ÉCOLE, DÉPARTEMENT / FACULTY, SCHOOL, DEPARTMENT

Augmented Blood Pressure Measurement Through the Estimation of Physiological Blood Pressure Variability

TITRE DE LA THÈSE / TITLE OF THESIS

Hilmi Dajani

DIRECTEUR (DIRECTRICE) DE LA THÈSE / THESIS SUPERVISOR

CO-DIRECTEUR (CO-DIRECTRICE) DE LA THÈSE / THESIS CO-SUPERVISOR

Miodrag Bolic

Andy Adler

Gary W. Slater

Le Doyen de la Faculté des études supérieures et postdoctorales / Dean of the Faculty of Graduate and Postdoctoral Studies

Augmented blood pressure measurement through the estimation of physiological blood pressure variability

By

Karen Soueidan

A thesis

presented to the University of Ottawa

in partial fulfillment of the

requirements for the degree of

Master of Applied Science

in

Biomedical Engineering

Your file Votre référence
ISBN: 978-0-494-74161-0
Our file Notre référence
ISBN: 978-0-494-74161-0

Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Karen Soueidan

Abstract

Current noninvasive blood pressure (BP) measurement methods estimate the systolic and diastolic blood pressure (SBP and DBP) at two random instants in time. The BP variability and its serious consequences on the measurement are not recognized by most physicians. The standard for automated BP devices sets a maximum allowable system error of ± 5 mmHg, even though natural BP variability often exceeds these limits. This thesis characterizes the variability of SBP and DBP and proposes a new approach to augment the conventional noninvasive measurement using simultaneous recordings of the oscillometric and continuous arterial pulse waveforms by providing: 1) The mean SBP (or DBP) over the measurement interval, 2) Their respective standard deviations, and 3) An indicator as to whether or not the oscillometric reading is an outlier. Recordings with healthy subjects showed that the approach has prominent potential and does not suffer from bias relative to the conventional method.

Acknowledgements

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

I would like to express my gratitude to my supervisor Dr. Hilmi R. Dajani for his support, guidance, and assistance with the research and the writing of this thesis.

I am indebted to my fellow research team members including Professors Dr. Miodrag Bolic and Dr. Voicu Groza, expert advisors Dr. Izmail Batkin and Dr. Sreeraman Rajan and my lab mates (Silu Chen, Majid Mafi, Mohamad Forouzanfar and Dr. Saif Ahmad, Dr. Balakumar Balasingam and Dr. Soojeong Lee) for providing a fun environment to learn and grow, for their good company and generous technical help in various situations.

I owe thanks to Biosign Technologies Inc. and the Ontario Centres of Excellence (OCE) for their collaborative research support and funding.

I would also like to offer my regards to Dr. Tofy Mussivand for his valuable advice and friendly help, and my appreciation to my friends (especially Lara Kouri, Nicolas Ellaham, Marie-France Lacasse, Flora Nassrallah, Nizar Sakr, Antony Robert, Elmira Ahmady, Shelley Deeke, Seham Rabaa, Hanna Farah and Ashish Dighe) for their support and assistance during the completion of this project.

Last but not least, I am heartily thankful to my parents and lovely sisters for their encouragement, patience and understanding all along.

Table of Contents

Author's Declaration ii
Abstract iii
Acknowledgements iv
Table of Contents v
List of Figures vii
List of tables xi
List of Abbreviations xii
Chapter 1. Introduction 1
1.1 Background 1
1.2 Motivation 2
1.3 Objectives 5
1.4 Thesis overview 6
Chapter 2. Background 7
2.1 Blood pressure 7
2.2 Blood pressure measurement techniques 7
2.3 Oscillometric SBP and DBP estimations 9
2.3.1 Accuracy of oscillometric estimation of the systolic and diastolic blood pressure 11
2.4 Arterial blood pressure waveform 12
2.4.1 Calibration of the continuous arterial pulse waveform 19
2.4.2 Blood pressure fluctuation 20
2.4.3 Blood pressure differences between the two arms 21
Chapter 3. Blood pressure variability 23
3.1 Introduction 23
3.2 Methods 24
3.2.1 Subjects and measurements 24
3.2.2 Data Analysis 26
3.3 Results 30
3.3.1 Distribution characteristics 30
3.3.2 Frequency Analysis 32
3.4 Conclusions 34

Chapter 4. Augmented blood pressure measurement 36
4.1 Introduction 36
4.2 Subjects 38
4.3 Methodology 38
4.3.1 Prototype device 38
4.3.2 Reference devices 40
4.3.3 Experimental procedure 40
4.3.4 Waveform extraction 42
4.3.5 Peak Detection 46
4.3.6 SBP and DBP mapping 48
4.3.7 Calibration 49
4.4 Data Analysis 52
4.5 Partial validation 52
4.6 Overall Results 57
4.7 Selected cases 59
4.8 Extension of the proposed method: A single-cuff approach 66
4.8.1 Results 68
4.9 Assumptions and limitations 71
4.10 Conclusions 72
Chapter 5. Conclusions 74
5.1 Summary of thesis work 74
5.2 Contributions 75
5.3 Future work 76
Appendix A- Experiment Results 78
Appendix B – Validation results 80
Appendix C - Ethics approval notice 86
Appendix D – Informed Consent Form 88
References 90

List of Figures

Figure 1.1 - Stroke mortality rate in each decade of age versus systolic and diastolic blood pressure at the start of the decade. Each square has an area inversely proportional to the effective variance of the log mortality rate. The "floating absolute risk" indicates that the standard errors were not estimated in reference to a baseline group , Reported are the absolute risks on a floating scale which has no origin. The conventional interpretation chooses the relative risk of 1 to be the baseline level. (Source: Fig.2 in Lewington et al, Lancet, (2002), 360: 1903-1913)) 3

Figure 1.2 - Beat-by-beat systolic and diastolic blood pressure from a healthy subject in supine position. Each point indicates a heartbeat. The diagonal solid lines 'a' and 'b' indicate the cuff pressure readings for 2 consecutive blood pressure readings, separated by about 40 seconds. (Source: Fig.1 in Hansen et al., European Journal of Anaesthesiology, (2006)23:781-787) 5

Figure 2.1 - Auscultatory blood pressure measurement system. (Source: Wilmer W. Nichols, Michael F. O'Rourke: McDonald's Blood Flow in Arteries, 4th Edition, page 132, 1998) 8

Figure 2.2 - Cuff pressure with superimposed Korotkoff sounds (top) and amplified oscillometric cuff-pressure oscillations (bottom). (Source: Wilmer W. Nichols, Michael F. O'Rourke: McDonald's Blood Flow in Arteries, 4th Edition, page 132, 1998) 10

Figure 2.3 – Circulatory system showing the heart and its ventricles with the arrows representing the blood circulation from and into the body (Source: Global Neighbourhood (Glo10)) 13

Figure 2.4 - Arterial blood pressure waveform – a single pulse (Source: Syeda et al, American Journal of Hypertension, (2003), 16:356-362) 13

Figure 2.5 – Uncalibrated arterial blood pressure waveform (recording obtained at the output of the pressure transducer over a duration of 20 seconds) 18

Figure 2.6 - Arterial applanation tonometry calibrated using an external cuff method. SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure (Source: Fig.1 in Matthys and Pascal, Technology and Health Care, (2002) 10:65-76) 19

Figure 3.1 - A section of the raw signal of a sample from the MGH/MF database is shown on the upper figure along with the systolic and diastolic peaks. On the lower figure, the interpolated SBP (on top) and the DBP signals (below) for that same patient, over the whole duration of the recording are shown. 27

Figure 3.2 - Histograms of systolic blood pressure (SBP) values (on the left) and diastolic blood pressure (DBP) values (on the right) for an ICU patient from the Physionet Database 27

Figure 3.3 - Boxplots representing the systolic blood pressure peaks (SBP) (left plot) and the diastolic blood pressure peaks (DBP) (right plot) before removing the outliers, for an ICU patient. The rectangle represents 50 per cent of the cases and the lines protruding from the box reach out to the smallest and largest values after removal of outliers. Points are identified as outliers if they

extend more than 1.5 box-lengths from the edge of the box (shown as circles on the plot). Extreme outliers are those that extend more than 3 box-lengths and are shown as asterisks on the plot. The outliers are identified by their sample indices..... 28

Figure 3.4 - The filtered SBP peak line of an ICU patient is shown above. From top-below: (a) below VLF (low pass at 0.025 Hz and mean deducted), (b) VLF (bandpass 0.025 – 0.05 Hz), (c) LF (0.05 – 0.15 Hz) and (d) HF (0.15 – 0.5 Hz). The frequencies above 0.5Hz showed an insignificant contribution and therefore their plot was omitted. 29

Figure 3.5 - (A) Histogram of systolic blood pressure (SBP) values and (B) diastolic blood pressure (DBP) values for an ICU patient from the PhysioNet Database. The graphs show the respective histograms of the raw signal (top left), the very low frequencies (top right), low frequencies (bottom left) and high frequencies (bottom right)..... 30

Figure 3.6 - Contribution of the three frequency regions (VLF, LF, HF) to the variance of the blood pressure variations (A) ICU patients and (B) healthy subjects from the PhysioNet Database. The dark bars represent the SBP values, the white bars refer to the DBP values. VLF, 0.025-0.05 Hz; LF, 0.05-0.15 Hz; HF, 0.15-0.5 Hz. The bars show mean variance within each frequency range over all subjects ± SE. 33

Figure 4.1- Block diagram showing the steps of the proposed approach for augmented blood pressure measurement described in this chapter. 37

Figure 4.2 - Illustrative block diagram of the BP prototype developed in the laboratory..... 39

Figure 4.3 - Section of the continuous BP arterial pulse waveform 42

Figure 4.4- Cuff deflation curve (top graph) and a zoomed-in interval of that same curve showing the detected pulses (bottom graph)..... 43

Figure 4.5 - OMW obtained after highpass filtering the transducer waveform during cuff deflation 43

Figure 4.6 - Example of the MAA implementation (Chen, 2010). The systolic, diastolic and mean values are projected from the envelope back to the deflation pressure cuff..... 45

Figure 4.7 – Parallel recording of the waveforms obtained from one subject with the cuff placed on the two arms with one recording the oscillometric waveform and the other recording the continuous arterial pulse waveform, over a 90-second period. 46

Figure 4.8 – Zoomed-in interval of the continuous BP signal, showing the detected peaks 48

Figure 4.9 – The image on top shows the oscillometric waveform with the identified SBP and DBP peaks. The image below shows the synchronized continuous recording taken at a constant pressure and the mapped SBP and DBP peaks, from the oscillometric waveform, in time domain. 49

Figure 4.10 – Figure showing part of the uncalibrated continuous recording (on top). The middle graph represents the calibrated systolic peak line and the bottom graph, the diastolic peak line, after applying the calibration equation on the waveform in the top graph (Subject 120 T4). 51

Figure 4.11 – Graphs showing the paired t-test results; average of the INT_MEAN_{SBP} ± Std Error and the OMW_{SBP} ± Std Error (top graph) and average of the INT_MEAN_{DBP} ± Std Error and the OMW_{DBP} ± Std Error (bottom graph), across all trials and all subjects. 54

Figure 4.12 – Bland-Altman difference plot showing bias and limits of agreement between the SBP (a) and DBP (b) values estimated by the oscillometric method and the proposed method. The small bias values (bias = 0.449 (0.5%) for SBP and 0.099 (0.3%) for DBP) indicate that there is only a slight bias between the two methods. 56

Figure 4.13 – Zoomed-in portion of the continuous recording of the subject's pulse waveform (between the 40th and 90th seconds), after applying the peak detection algorithm; the DBP measured using the oscillometric method is identified by the arrow and circle at around 69 seconds (Subject 122_T6) 60

Figure 4.14 – The calibrated interpolated peak line joining the troughs of the continuous recording and the identified diastolic point (DBP) represented as a star (*) on the waveform at around 69 seconds. The horizontal line in the centre of the graph represents the INT_MEAN_{DBP} (Subject 122_T6). 60

Figure 4.15 – Histogram of the distribution of the DBP values over the 90 second duration of the recording. The star (*) locates the oscillometric DBP estimate on the histogram, far from the mean (Subject 122_T6) 61

Figure 4.16 – Zoomed-in portion of the continuous recording of the subject's pulse waveform (between the 45th and 92th seconds), after applying the peak detection algorithm; the DBP measured using the oscillometric method is identified by the arrow and circle at around 70 seconds (Subject 114_T3) 62

Figure 4.17 - The calibrated interpolated peak line joining the troughs of the continuous recording and the identified diastolic point (DBP) represented as a star (*) on the waveform. The horizontal line in the centre of the graph represents the INT_MEAN_{DBP} line (Subject 114_T3). 62

Figure 4.18– Histogram of the distribution of the DBP values over the 90 second duration of the recording. The star (*) locates the oscillometric DBP estimate on the histogram, far from the mean (Subject 114_T3) 63

Figure 4.19 – Zoomed-in portion of the continuous recording of the subject's pulse waveform (between the 15^{th} and 55^{th} seconds), after applying the peak detection algorithm; the SBP measured using the oscillometric method is identified by the arrow and circle at around 47 seconds (Subject 115_T6). 64

Figure 4.20 – The calibrated interpolated peak line joining the peaks of the continuous recording and the identified systolic point (SBP) represented as a star (*) on the waveform. The horizontal line in the centre of the graph represents the INT_MEAN_{SBP} line (Subject 115_T6). 64

Figure 4.21 – Histogram of the distribution of the SBP values over the 90 second duration of the recording. The star (*) locates the oscillometric SBP estimate on the histogram, far from the mean (Subject 115_T6)..... 65

Figure 4.22 - Oscillometric waveform (top) and constant cuff continuous recording (bottom) plotted in parallel, after peak detection..... 66

Figure 4.23 –Oscillometric peak line and its best fit curve after polynomial fitting..... 67

Figure 4.24 – Flattened oscillometric systolic peak line derived from a single cuff oscillometric measurement..... 67

Figure 4.25 – Constant pressure systolic peak line (output of the constant cuff on the second arm) 68

Figure 4.26 – Constant pressure waveform and "flattened" oscillometric systolic peak line superimposed (Correlation = 61.87%)..... 68

Figure 4.27 - Constant pressure and "flattened" oscillometric diastolic peak line superimposed (Correlation = 45.08%)..... 69

Figure 4.28 - Constant pressure waveform and "flattened" oscillometric diastolic peak line superimposed (Correlation = 1.88%)..... 70

Figure B-1- Scatter plot of the OMW_{SBP} values as a function of INT_MEAN_{SBP} 81

Figure B-2 – Histogram of Differences between the OMW_{SBP} and the INT_MEAN_{SBP} values over the mean of the difference 81

Figure B-3- Scatter plot of the OMW_{DBP} values as a function of INT_MEAN_{DBP}..... 84

Figure B-4– Histogram of Differences between the OMW_{DBP} and the INT_MEAN_{DBP} values over the mean of the difference 84

List of tables

Table 1-1 – Classification of blood pressure for adults (Source: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (2004)) 3

Table 2-1 - Factors affecting the accuracy of blood pressure measures, ... 12

Table 3-1 - Average, standard deviation, skewness and kurtosis for the (A) ICU patients and (B) the healthy individuals. Values are means over subjects ± SE 31

Table 4-1 – Sequence of experimental Steps 42

Table 4-2 – Data collected from case 1 (subject 122_T6) 61

Table 4-3 – Data collected from case 2 (subject 114_ T3) 63

Table 4-4 – Data collected from case 3 (subject 115_ T6) 65

Table B-1 - Detailed Bland Altman Agreement test for the SBP values 80

Table B-2 - Paired t-test between the mean SBP (INT_MEAN_{SBP}) values and the Oscillometric SBP values (OMW_{SBP})) 82

Table B-3 - Detailed Bland Altman Agreement test for the DBP values 83

Table B-4 - Paired t-test between the mean DBP (INT_MEAN_{DBP}) values and the Oscillometric SBP values (OMW_{DBP})) 85

List of Abbreviations

BP: Blood Pressure – Measure of the pressure exerted by the blood in the arteries during a cardiac cycle.

DBP: Diastolic Blood Pressure – Minimal pressure produced in the arteries, occurs at the end of a cardiac cycle

ECG: Electrocardiogram – Noninvasive recording of the electrical cardiac activity

HF: High Frequency – Frequency ranging from 0.15 to 0.5 Hz, associated with the breathing pattern and the intrathoracic pressure changes.

HRV: Heart Rate Variability – The natural tendency of fluctuation in the time intervals between heart-beats.

ICU: Intensive Care Unit – Hospital setting where intra-arterial measurements of blood pressure, considered as the gold standard, are made.

INT_MEAN: Mean of values over the 90-second time interval of the measurement.

INT_STD: Standard deviation of values over the 90-second time interval of the measurement.

LF: Low Frequency – Frequency ranging from 0.05 to 0.15 Hz, associated with vascular tone changes and the Mayer waves.

MAA: Maximum Amplitude Algorithm – Height based algorithm used to find blood pressure from the oscillometric waveform, based on characteristic ratios.

MAP: Mean Arterial Pressure – Average arterial blood pressure of the subject during a cardiac cycle.

OMW: Oscillometric Waveform

OPI: Oscillometric Pulse Index – waveform formed by the height of each pulse as a function of its location index.

SBP: Systolic Blood Pressure – Maximal pressure produced in the arteries, occurs at the contraction phase of the cardiac cycle.

VLF: Very Low Frequency – Frequency ranging from 0.025 to 0.05 Hz, associated with slow physiological variability of the blood pressure.

mmHg: Millimeters Mercury – Adopted unit to measure blood pressure.

Chapter 1. Introduction

1.1 Background

Blood pressure (BP) is an important vital sign and one of the most commonly measured physiological parameters in clinical practice. The measurement consists of determining the pressure exerted by the circulation of the blood on the walls of the large arteries throughout the cardiac cycle and is conventionally reported in millimeters of mercury (mmHg). The heartbeat is at the origin of the cardiac cycle which consists of two phases: the systole phase where the ventricles contract and pump blood to the arteries and the diastole phase where the heart ventricles relax and allow the heart to fill up with blood (Webster, 1998). During each cardiac cycle, the blood pressure varies between a maximum (systolic) and a minimum (diastolic) pressure resulting in two main values: the SBP (systolic blood pressure) and the DBP (diastolic blood pressure) that have been found to be indicative of the subject's state of health.

Blood pressure measurement methods can be invasive or noninvasive, and manual or automated. The Gold Standard, most accurate and trusted method is the intra-arterial line that measures the pressure invasively. This highly accurate technique requires qualified trained personnel and is accompanied by elevated risks of bleeding, reactions, infections, blood clotting, and other complications (Turner, 2000).

Noninvasive methods are more commonly used because they are safer, quicker and require less expertise. The noninvasive Gold Standard is the auscultatory method that uses the stethoscope and sphygmomanometer. A pressure cuff, connected to a mercury manometer, is inflated above SBP and then deflated slowly. The stethoscope is used, by a trained observer, to mark the Korotkoff sounds that are associated with the time of occurrence of the SBP and DBP. The SBP and DBP values are identified on the scale of the manometer.

The most popular noninvasive *automated* method, however, is the oscillometric technique known for its simplicity, speed, and relative accuracy. A deflating cuff connected to a pressure transducer, wrapped around the upper arm or the wrist, senses the pressure pulsations of the subject's blood circulation and reports it digitally to the signal processor. The waveform consists of arterial pulses superimposed onto a decreasing curve

representing the decreasing pressure. Specific algorithms are then used to estimate the SBP and DBP values from the recording (Ng and Small, 1994).

Hypertension, or elevated blood pressure, is highly prevalent in the general population, and particularly in elderly patients. During the first stages of chronic hypertension, the cardiac output is raised while the total peripheral resistance (TPR) remains normal; over time, the cardiac output drops to normal levels while the TPR increases. The cause is often the inability of the kidneys to excrete sodium which leads to the increase of the TPR, an overactive Renin-angiotensin system leading to an increase in blood volume or an overactive sympathetic nervous system (Pimenta et al., 2009). Despite overwhelming evidence that high blood pressure is a modifiable risk factor for cardiovascular disease, it remains underdiagnosed. The Canadian Heart Health Survey found that only 16% of adults aged 65 to 74, had adequate blood pressure control while the remainder of the adult population within that age group was either unaware of their diagnosis, inappropriately treated, or completely untreated for hypertension (Lau et al., 2006). This is possibly due to the lack of awareness within the population, but could also be due to erroneous readings obtained using the automated blood pressure measurement devices at home.

More accurate blood pressure readings accompanied with confidence parameters could potentially improve the diagnosis and control of hypertension.

1.2 Motivation

The table below (Table 1-1) shows the classification of blood pressure status for adults taken from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (2004). The prehypertension category is designated to identify individuals at high risk of developing hypertension and who require clinical assistance for prevention. According to this report, the relationship between BP and risk of cardiovascular disease events is continuous, consistent, and independent of other risk factors. High blood pressure leads to higher risk of heart attack, stroke and kidney disease. Fig. 1.1 shows the relationship between stroke mortality rate in each decade of age and the blood pressure.

Table 1-1 – Classification of blood pressure for adults (Source: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (2004))

Blood Pressure Classification	SBP mmHg	DBP mmHg
Normal	<120	and <80
Prehypertension	120–139	or 80–89
Stage 1 Hypertension	140–159	or 90–99
Stage 2 Hypertension	≥160	or ≥100

SBP, systolic blood pressure; DBP, diastolic blood pressure

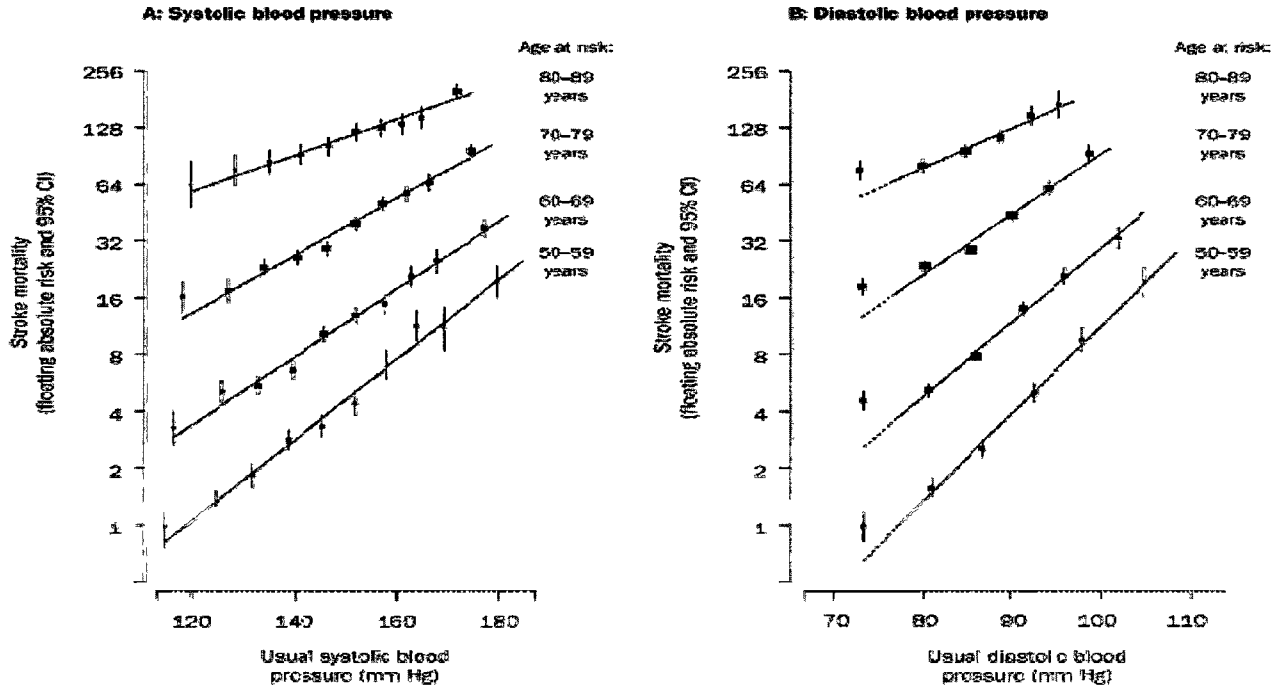


Figure 1.1 - Stroke mortality rate in each decade of age versus systolic and diastolic blood pressure at the start of the decade. Each square has an area inversely proportional to the effective variance of the log mortality rate. The "floating absolute risk" indicates that the standard errors were not estimated in reference to a baseline group , Reported are the absolute risks on a floating scale which has no origin. The conventional interpretation chooses the relative risk of 1 to be the baseline level. (Source: Fig.2 in Lewington et al, Lancet, (2002), 360: 1903-1913))

However, a recent editorial in the journal Hypertension of the American Heart Association asserts that "few measurements in medicine are done as poorly and

inconsistently as blood pressure measurement. Methods used today in clinical practice and in clinical trials are little changed from the earliest days of measurement. Though there is a clear recognition of biological variability, we continue to make decisions largely upon measurements taken at random times under poorly controlled conditions" (Jones and Hall, 2008).

The BP signal of a normal individual is characterized by continuous fluctuations; some are fast and happen within seconds, while others are more prolonged, lasting minutes to hours. Fig. 1.2 shows the variations in the systolic and diastolic pressures (SBP and DBP) over two minutes. This variability can be viewed as introducing uncertainty to the conventional noninvasive measurements of SBP and DBP which are taken at two random instants of time, compared to the gold standard intra-arterial measurement, which continuously monitors the BP over time, and may report a running average of SBP and DBP. By not taking into account ongoing variability in blood pressure, conventional noninvasive readings, taken at a given instant in time, may fail to represent the person's blood pressure very well. For example, in Fig. 1.2, which shows the beat-by-beat systolic and diastolic blood pressure values, the diagonal solid lines indicate how the measured SBP and DBP might vary between two blood pressure measurements using a deflation rate of 3 mmHg/s. Line 'a' would give a blood pressure reading of 156/71 mmHg for the SBP and DBP, respectively, while line 'b' would indicate 169/63 mmHg, only a few seconds later (Hansen and Staber, 2006).

The question remains as to whether an imprecise blood pressure estimate poses a problem for diagnosing and treating hypertension. The editorial in Hypertension answers that "although some might argue that a 3- to 4- mmHg increase in blood pressure is not clinically significant, clinical trials and population studies remind us of the importance of these seemingly small changes" (Jones and Hall, 2008). A recent 1-million-patient meta-analysis suggests that a 3- to 4- mmHg systolic increase in blood pressure would translate into 20% higher stroke mortality and a 12% higher mortality from ischemic heart disease (Lewington et al., 2002).

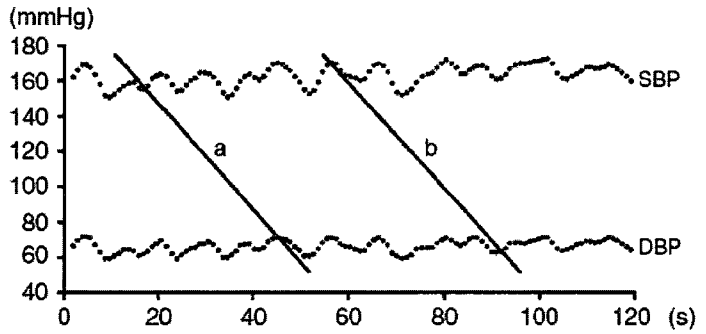


Figure 1.2 - Beat-by-beat systolic and diastolic blood pressure from a healthy subject in supine position. Each point indicates a heartbeat. The diagonal solid lines 'a' and 'b' indicate the cuff pressure readings for 2 consecutive blood pressure readings, separated by about 40 seconds. (Source: Fig.1 in Hansen et al., European Journal of Anaesthesiology, (2006)23:781-787)

According to the standards, commercial blood pressure measurement devices are required to be within ±5 mmHg of auscultatory readings, taken by trained observers, with a standard deviation of 8 mmHg or less (AAMI/ANSI-SP10, 2002). However, it has been demonstrated that the BP waveform varies by up to 20 mmHg within seconds, in normal healthy humans, due to intrinsic physiological variability. Therefore, the uncertainty in the BP readings, generated by the combined effect of device uncertainty and physiological variability, could lead to incorrect diagnosis and poor patient management.

Consequently, the detection of the overall variability, as the waveform oscillates with the so-called Mayer wave, respiration, etc. could be of great importance. The assessment of variability can be obtained by the analysis of a continuous, beat-to-beat, blood pressure recording.

1.3 Objectives

The one or two blood pressure readings taken at the doctor's office do not represent the time varying nature of the blood pressure very well.

The first part of this study involves an investigation of the characteristics of SBP and DBP variability, using available databases of continuous arterial pulse waveforms, and data collected in new measurements. A new approach is then proposed to minimize the uncertainty caused by this variability, with the following three specific objectives:

1) Provide SBP and DBP estimates that are more representative of the variable blood pressure levels than those taken at arbitrary instances of time.

2) Provide a measure of the uncertainty of the readings.
3) Determine whether a given SBP or DBP estimate is unusually high or low, which could be used to issue an alert (e.g. to repeat the measurement).

The proposed approach will enhance the potential of existing commercial home monitoring devices by using information from the beat-to-beat waveform to augment the conventional single number output for systolic and diastolic pressure.

1.4 Thesis overview

A detailed study of the statistics of the variability and a focus on the main frequency components using continuous recordings of the arterial pulse waveform in healthy subject and intensive care unit (ICU) patients appears in *Chapter 3* of the thesis. A frequency analysis of the physiological fluctuation follows, identifying the contribution of the various frequency ranges in the variability. The naturally introduced uncertainty is then compared to the maximum uncertainty allowed by the hardware and the processing errors of the oscillometric device. These results were published in two papers presented at the Canadian Medical and Biological Engineering Conference (Soueidan, K.; Dajani, D. R.; Bolic, M.; Groza, V.; Chen, S., 2010), and at the International Workshop on Medical Measurements and Applications (Soueidan, K.; Dajani, H. R.; Bolic, M.; Groza, V.; Chen, S., 2010).

Chapter 4 describes an approach to augment the standard oscillometric method through estimation of the variability in BP. This approach relies on the measurement of the continuous arterial pulse waveform using a second sensor. Results from experiments with healthy subjects are presented. This chapter also discusses an attempt to simplify this approach by relying solely on the oscillometric waveform measured in one pressure cuff. Chapter 5 summarizes the main conclusions, discusses the main contributions of the work, and proposes some avenues for future work.

Chapter 2. Background

2.1 Blood pressure

Blood pressure is the force exerted by the blood against the walls of the blood vessels. Arterial blood pressure changes continuously during the course of the cardiac cycle. The highest pressure reached throughout a cycle is the Systolic Blood Pressure (SBP) (during systole), while the lowest is the Diastolic Blood Pressure (DBP), which is the level corresponding to the resting phase of the heart between two beats (during diastole). Both pressure readings are clinically used to evaluate the status of a patient's blood pressure (Webster, 1998).

The measured blood pressure is widely used in clinical assessment, representing a significant vital sign. However, many factors such as physical activity, anxiety, stress, or the time of the day could influence the measured entity. Blood pressure is known to be lower in the morning than throughout the rest of the day, it is also lower in the summer and higher in the winter, but more importantly, it is also subject to continuous variability causing it to fluctuate over a short period of time (ranging from a few seconds to a few minutes).

2.2 Blood pressure measurement techniques

Arterial blood pressure is most accurately measured **invasively** using an arterial line. A thin catheter inserted into the artery is connected to an electronic pressure transducer (Webster, 1998). This Gold Standard technique involves the direct measurement of the arterial pressure and is often used in the intensive care units at hospitals. The accuracy of the measurement is accompanied by a high risk of complications such as thrombosis, infections and internal bleeding. Therefore, it requires the close supervision of licensed medical personnel (such as a doctor, a nurse or a therapist) and is not well-suited for home monitoring or measurement in the doctor's clinic.

Consequently, many **noninvasive** techniques have been developed over the years, aiming to obtain accurate readings of the arterial blood pressure with a reduced risk level. These indirect measurement methods are mainly based on the quantification of counter-

pressure though peripheral blood flow occlusion. Particular care is needed in order to ensure reproducibility and accuracy of the recordings using these methods.

The noninvasive gold standard is the **auscultatory method.** Published in the MD thesis of Nikolai Korotkoff (Russia, 1905), this technique uses a stethoscope and a sphygmomanometer, which is a blood pressure meter comprising an inflatable cuff to restrict blood flow and a manometer (mercury or mechanical pressure gauge) to measure the pressure (Fig. 2.1). The procedure consists of quickly raising the cuff pressure to a pressure above the systolic blood pressure of the patient, i.e. until the blood circulation on the distal side of the cuff is stopped. At this point, no sound will be heard. Pressure in the cuff is slowly released and the operator listens for audible sounds through the stethoscope placed on the skin, at a distal arterial point (wrist or elbow) (Sorvoja, 2006). When the pressure in the cuff drops just below the maximum pressure in the artery produced by the heart, some blood will start flowing through the obstructed vessel producing the first sound, and the pressure read at this moment will correspond to the systolic blood pressure of the subject. As the pressure in the cuff decreases, other sounds are heard until they become muted. The pressure at that specific moment corresponds to the diastolic blood pressure value. This measurement technique is highly dependent on having a trained observer with good hearing. It is often unreliable and not practical in a home setting and in the absence of the medical personnel.

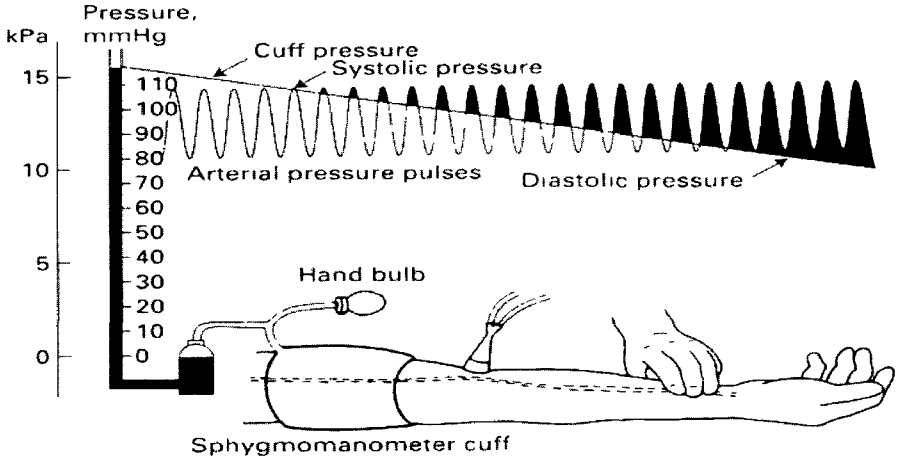


Figure 2.1 - Auscultatory blood pressure measurement system. (Source: Wilmer W. Nichols, Michael F. O'Rourke: McDonald's Blood Flow in Arteries, 4th Edition, page 132, 1998)

Automatic blood pressure measurement devices, used in home settings, usually employ another noninvasive technique known as the **oscillometric method.** This method was first invented by Marey in 1876, who detected the pressure oscillations generated by the blood pulsation on the cuff around the arm (Marey, 1876). An inflatable cuff, similar to the one used for the auscultatory method, is wrapped around the upper arm or wrist occluding the peripheral blood flow to the arm. A pressure transducer is mounted on the device and is used to record the pressure oscillations within the cuff resulting from the blood pressure pulses in the vessels. The output is a deflation pressure curve with superimposed beat-to-beat pressure pulsations. A variety of existing algorithms can be applied in order to estimate the SBP and DBP values.

2.3 Oscillometric SBP and DBP estimations

For the first few decades after its discovery, it was believed that the maximum oscillation amplitude corresponded to the diastolic blood pressure. It was not until Posey and Geddes' findings were verified with adults (Yelderman and Ream, 1979) and with newborn infants (Kimble et al., 1981) that the maximum amplitude point was actually demonstrated to refer to the mean arterial pressure (MAP), and that the systolic and diastolic blood pressures could be determined using characteristic ratios of the MAP (see Fig.2.2).

Several approaches that seek to improve the **oscillometric algorithms** for the estimation of SBP and DBP have been reported in the literature. Different procedures have been investigated to extract the oscillometric waveform and its envelope from the deflation curve, remove existing artifacts and interference, locate the SBP and DBP points on the envelope, and evaluate the corresponding pressure levels on the deflation curve (e.g. Moraes et al., 1999; Amoore, 2006; Baker et al., 1997; Lee et al., 2002). However, what they all share is the drawback that they estimate SBP and DBP at two arbitrary instants in time, and so do not reflect well the variation of BP over a measurement period. Therefore, the differences found between these techniques were not relevant to this study as the method proposed in this thesis is applied after identifying the SBP and DBP points using the oscillometric algorithm and is independent of the approach used to do so.

The blood pressure estimates obtained using the oscillometric method can be directly related to the gold standard noninvasive approach, the auscultatory method. In the oscillometric method, the pulsatile blood flow through the artery produces oscillations at the vessel wall that are transmitted to the cuff surrounding the arm. When the cuff is inflated to a pressure level higher than the systolic pressure, only small-amplitude oscillations are transmitted to the cuff (Nichols and O'Rourke, 1998). As the cuff pressure decreases, the amplitude of the pressure oscillations increases to reach its maximum when the cuff pressure corresponds to the mean arterial pressure (MAP). After this specific point, the amplitude starts decreasing until it stabilizes, indicating the end of the oscillometric waveform. Unlike the auscultatory method, the first oscillometric pulse does not correspond to the systolic blood pressure value, but rather to the beginning of the oscillometric waveform that will be used to generate the SBP and DBP estimations.

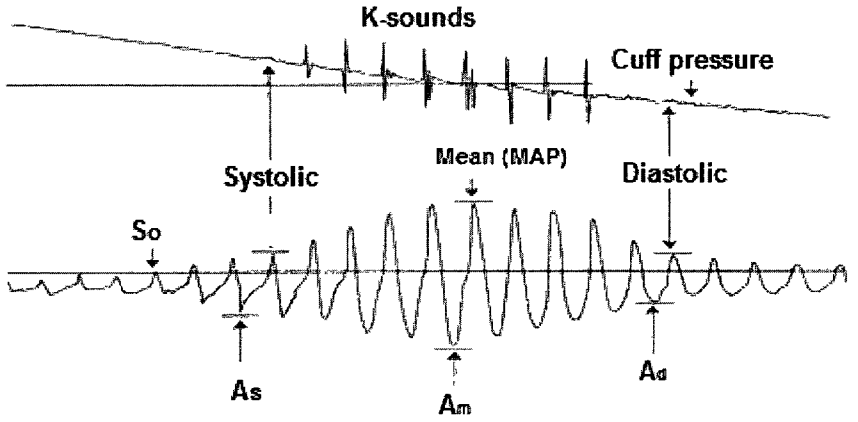


Figure 2.2 - Cuff pressure with superimposed Korotkoff sounds (top) and amplified oscillometric cuff-pressure oscillations (bottom). (Source: Wilmer W. Nichols, Michael F. O'Rourke: McDonald's Blood Flow in Arteries, 4th Edition, page 132, 1998)

In Fig. 2.2, the oscillometric cuff pressure curve is shown in parallel with the Korotkoff sounds. In the auscultatory method, the first Korotkoff sound detected indicates the point that corresponds to systolic pressure. The systolic blood pressure value can then be read from the cuff pressure curve. Similarly, the transition from muffling to silence indicates the point that corresponds to diastolic pressure, and again the diastolic blood pressure value can be read from the cuff pressure curve. In the oscillometric method, the systolic and diastolic pressures are typically located using empirically determined characteristic ratios between the pulse wave amplitudes (A_s and A_d) relative to the maximum amplitude (A_m).

These locations are then projected onto the cuff-pressure curve to determine the calibrated systolic and diastolic pressure values. The correspondence in time between the systolic and diastolic pressures determined by both methods forms the basis for the estimation method proposed in this work, as will be described in *Chapter 4*.

2.3.1 Accuracy of oscillometric estimation of the systolic and diastolic blood pressure

Recent studies have shown that oscillometric devices often give unreliable readings for BP, ranging from 15 % to nearly 40 %, depending on the measurement and the tolerance accepted. In a study on 755 patients using a validated professional oscillometric BP measurement device, unreliable readings (defined as > 10 mmHg difference relative to reference value) were found in 15 % of systolic and 6.4 % of diastolic BP measurements (Stergiou et al., 2009). In another study, with validated automatic BP monitors, measurements in 20 – 38% of individuals were inaccurate (by more than 5 mmHg) (Gerin et al., 2002).

The accuracy of the oscillometric devices is of critical importance. Measurement inaccuracies (5 to 10 mmHg) can commonly occur as a result of the use of improper blood pressure techniques. Table 2-1 lists a few common factors that can affect the accuracy of the BP measurements (Handler, 2009). The American National Standard for Manual, electronic, or automated sphygmomanometers recommends a maximum allowable device-related measurement error of ±3 mmHg and an overall system error of ±5 mmHg (AAMI/ANSI-SP10, 2002). While the standards for measurement accuracy require measurements not to vary by more than a few mmHg compared to a reading done by a qualified health professional, the actual physiological variability is often ignored, even though it can reach up to 20 mmHg making it greater than the margin of error allowed by the standards.

Table 2-1 - Factors affecting the accuracy of blood pressure measures,
(Source: Handler, Permanente Journal (2009) 13:3)

Table 2.1- Factors affecting accuracy of blood pressure measure	
Factor	**Magnitude of systolic/diastolic blood pressure discrepancy (mmHg)**
Talking or active listening	10/10
Distended bladder	15/10
Cuff over clothing	5-50/
Cuff too small	10/2-8
Smoking within 30 minutes of measurement	6-20/
Paralyzed arm	2-5/
Back unsupported	6-10/
Arm unsupported, sitting	1-7/5-11
Arm unsupported, standing	6-8/

2.4 Arterial blood pressure waveform

The arterial tree starts with the aorta and the major branches of this vessel. The aorta and its branches stretch in order to receive blood from the contracting left ventricle of the heart, and then recoil to distribute the blood and maintain a sufficient level of arterial pressure throughout the body. The blood pressure in the aorta during systole is the indicator of the pressure that the left ventricle must overcome to eject blood to the body (Fig. 2.3). The diastolic pressure is affected by other factors such as blood viscosity, arterial elasticity, and cardiac cycle length. The mean arterial pressure (MAP) represents the mean perfusion pressure throughout the cardiac cycle, while the pulse pressure represents the difference between the systolic and diastolic pressure. A normal pulse pressure is in the range of 40 mmHg (McGhee and Bridges, 2002). The dicrotic notch, represented by a transient increase in aortic pressure, is the marker of the end of the ejection period. Just as the ventricles enter diastole, the brief reversal of flow from the aorta back into the left ventricle causes the aortic valves to shut (Klabunde, 2007). Looking at one single arterial pulse (Fig. 2.4), the peak and trough represent the systolic and diastolic blood pressures (SBP and DBP), respectively.

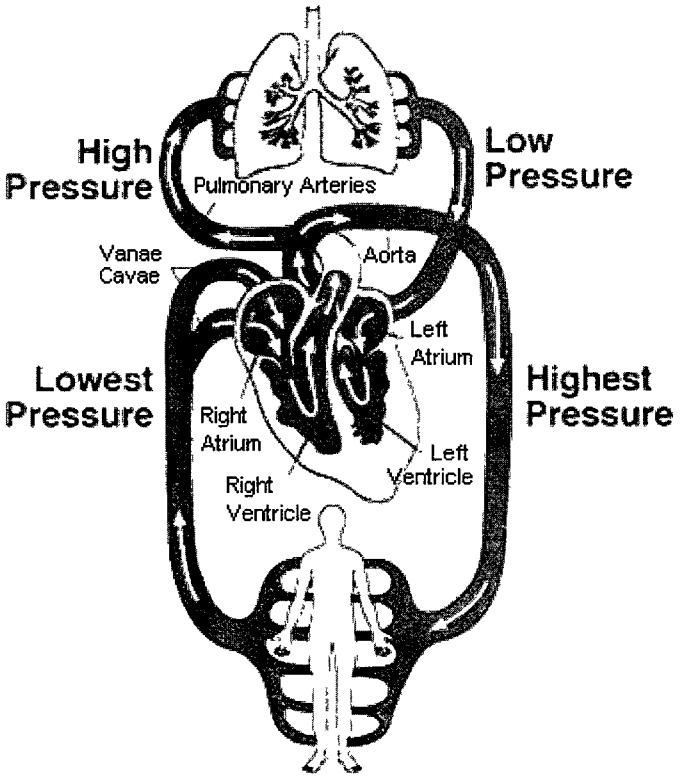


Figure 2.3 – Circulatory system showing the heart and its ventricles with the arrows representing the blood circulation from and into the body (Source: Global Neighbourhood (Glo10)).

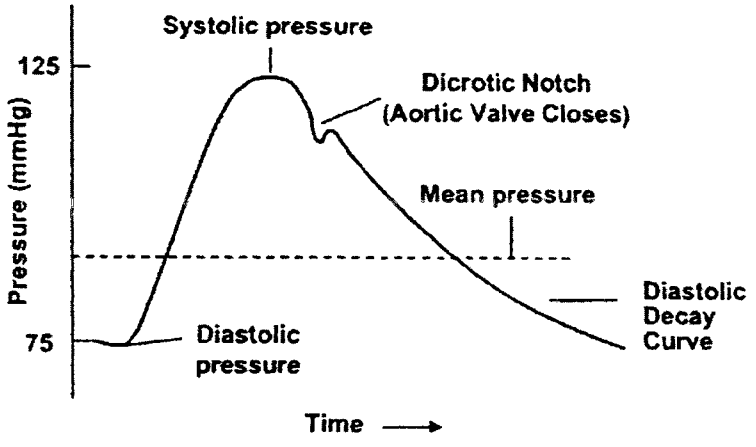


Figure 2.4 - Arterial blood pressure waveform – a single pulse (Source: Syeda et al, American Journal of Hypertension, (2003), 16:356-362)

Throughout the years, noninvasive blood pressure monitoring has been mostly limited to the measurement of systolic and diastolic blood pressure at random instances in time. Efforts have been ongoing to improve the measurement of blood pressure, and to achieve continuous noninvasive monitoring of the arterial pulse waveform. Various techniques

have been investigated for the purpose of extracting the arterial pulse waveform in a noninvasive and accurate way.

Plethysmography is a noninvasive technique used to measure changes in blood flow in different parts of the body. It may be used to detect blood clots or simply derive the blood pressure from the flow data. The photoplethysmogram is the optically obtained plethysmogram, similar, in appearance, to the arterial blood pressure waveform (Reisner et al., 2008). With this method, a light source illuminates the skin and derives the volumetric measurement by measuring the changes in light absorption throughout the different layers of the organ (Shelley and Shelley, 2001).

In 2002, a cuffless solution for the continuous measurement of the blood pressure was suggested (Yang et al., 2002). The system consisted of two photoplethysmographs, shaped as rings, placed on the patient's finger, displaced by a predetermined distance. An electrical impedance plethysmograph in contact with the finger measures the change in the electrical impedance between the two rings. The system also measures the change of diameter of the two segments in order to derive, through a mathematical model, the flow and the volume changes as a function of time, allowing the calculation of the instantaneous BP values of the subject. The arterial vessel is considered to be a rectilinear, deformable, thick shell of isotropic, incompressible material. The blood is an incompressible Newtonian fluid flowing in a longitudinal movement through the circular section of the vessel. Two-dimensional Navier-Stokes equations and the continuity equation for an incompressible Newtonian fluid in cylindrical coordinates are used to derive the parameters.

A similar technique was patented in 2008 offering a method for BP monitoring that does not involve the oscillometric cuff either. The device consisted of two plethysmographic elements. The first is positioned on the wrist of the subject, capturing the signal of the blood volume in the ulnar or radial artery and the second plethysmographic signal generated from the finger of the subject. Knowing the distance that separates the two transducers and using the information gathered by the two signals, one can calculate the transit time of a circulatory pressure wave and the wave speed. A

pulse waveform can then be reconstructed and used as a reference for blood pressure measurement (McCombie et al., 2008).

In 2004, an alternative device was patented for monitoring vital signs including blood pressure. The idea was, once again, to suppress the cuff and measure BP using a cuffless, low cost approach. The system was equipped with various sensors, one of which monitors BP. This sensor comprises a light source and photodetector in communication with a pulse-oximetry circuit. A microprocessor analyzes the data on board and sends it wirelessly to a server. The analysis of the red and infrared radiation measured by the photodetector allows the determination of the patient's blood oxygen saturation level and the generation of the photoplethysmograph. The innovation of the patent focused on the transmission of the data wirelessly in order to allow measurements outside of a medical facility (Banet and Visser, 2007). The simplicity and safety of the procedure made it a good candidate for noninvasive generation of the blood pressure waveform in hospitals; however, many covariates can affect the appearance of the photoplethysmogram, including minor movement of the limb or minor changes in the probe's pressure on the skin. These factors put the reliability and reproducibility of the method in question (Reisner et al., 2008). More importantly perhaps, a photoplethysmograph does not provide a calibrated blood pressure waveform.

The ongoing desire to eliminate the use of the cuff directed other groups towards **cuffless arterial tonometry** methods in an attempt to extract a reliable arterial pulse waveform.

Arterial tonometry is a pressure measurement method that allows noninvasive and continuous recordings of the arterial pressure waveform, by applying a force causing applanation (flattening) of a superficial artery below the sensor. The chosen artery has to be supported by a bone structure. The concept was first introduced in ophthalmology as "ocular tonometry". It is a direct application of a physics principle first discovered by Hans Goldmann (1899 – 1991), known as the *Imbert-Fick Law* (1960) stating that "the internal pressure in a spherical body with an infinitely thin, dry and perfectly flexible membrane wall, equals the force exerted on this body, divided by the applanation surface" (Weiss, et

al., 1996, Matthys and Pascal, 2002). However, the potential of long-term continuous noninvasive monitoring of blood pressure using this method is not yet fully explored (Matthys et al., 2008).

The pressure transducer (in the form of a piezo-electric sensor array or flexible diaphragm) is placed on the surface of the skin above the pulsating artery. When the sensor is pushed towards the vessel with the appropriate level of pressure, the vessel flattens but is not occluded. If the applanation is properly applied, the intra-arterial forces exerted by the blood circulation will be sensed by the external transducer firmly attached on the skin surface. These forces will then be translated into arterial pressure waveforms.

Several studies attempted to improve the robustness of the continuous recording of the pulse waveform and focused on obtaining the signals by placing piezo-electric sensors on the skin surface.

Matthys et al. placed a single-element tonometric pressure transducer (model SSD-936, Millar Instruments, Houston, TX, USA) over the right radial artery of their subjects and immobilized it using a Tegaderm patch (3M Health Care, Borken, Germany). A custom made bracelet with a screw was used to apply hold-down pressure on the sensor. This setup allowed the acquisition of the pulse waveform. The study suggests that, once calibrated, the tonometric blood pressure (TBP) mirrors the intra-arterial blood pressure in all steady state conditions and performs fairly well in reporting the variations of the signal, over a short period of time. However, due to the many sources of artifact such as the movement of the sensor at the skin surface, the arterial tonometry remained misrepresentative of the true BP variations. The study admits to the presence of a degree of unpredictability in the method when used for long-term recordings (Matthys et al., 2008).

The Phoenix group from the University of Minnesota also worked on the constant monitoring of the blood pressure waveform using piezo-electric sensors. Two SDT1-028K (Measurement Specialties, Inc.) film piezo-electric sensors were applied on the skin; one on the wrist and one on the mid-arm section, using cloth athletic tape. Both output analog signals were amplified and highpass filtered (with a cutoff frequency of 1.6Hz). The technique worked in theory but the results of the experiments were declared "poor"

because of the sensors' weak coupling to the skin, the high sensitivity to movement and the non-repeatability of the procedure mainly due to the low intensity of the applied pressure. Therefore, the method needed major improvements before it could be used in the future (Peterson et al., 2005).

The technique of placing piezo-electric sensors on the skin struggles with many sources of errors and artifacts that prevent it from obtaining accurate results. Even though the theory seems to find a solution for continuous arterial pulse recording, the practical design encounters many drawbacks and hence, fails to properly fulfill the objective of the concept. The generated continuous waveforms were not very reliable. Positioning the sensor is one important problem. If the sensor is not well positioned above the artery, the signal captured by the sensor is not strong enough and the pulses are not easily identified. Automatic positioning is challenging but could be done if the device is mounted with an array of sensors surrounding the artery. However, even with the sensor array, the stable segments of the recording were limited in time; unexpected and involuntary movements of the subject happened often and caused major artifacts in the output signal (Matthys and Pascal, 2002).

Hence, previous work confirms that cuffless tonometry using piezo-electric sensors positioned on the skin surface, without cuff pressure, did not seem to be a reliable solution for continuous noninvasive arterial waveform recordings (Weiss et al., 1996; Matthys and Pascal, 2002; Matthys et al., 2008; Ng et al., 2004). A method that is less sensitive to movement of the layers separating the artery from the sensor was needed.

A variation of tonometry can be performed by inflating a cuff that incorporates a pressure transducer to a constant pressure; the pressure exerted by the blood on the artery walls is transmitted to the transducer through the air in the hose linking the cuff to the transducer. This procedure is much less sensitive to positioning (the cuff surrounds the artery from all sides) and to movement (the air in the cuff and the air hose are not affected by the movement of the skin surface as would be the case with piezo-electric sensor placed on the skin surface). Therefore, the technique generates a more robust continuous pulse pressure waveform (Fig.2.5).

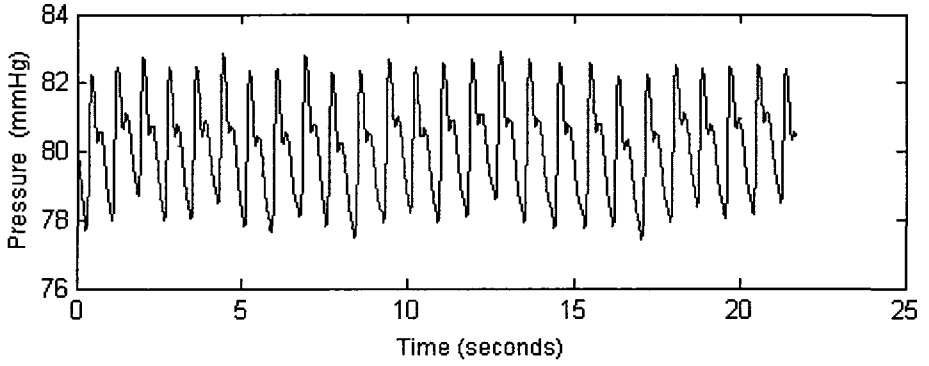


Figure 2.5 – Uncalibrated arterial blood pressure waveform (recording obtained at the output of the pressure transducer over a duration of 20 seconds)

In this context, Ding et al. recently presented an approach that allows the acquisition of the continuous pulse from the radial artery using a **low cuff pressure approach** that consisted of two consecutive parts. The oscillometric method was applied first in order to obtain reference blood pressure parameters (SBP, DBP and MAP). The low cuff process followed in order to acquire the pulse waveform in the radial artery. A relation was derived, relating the blood pressure parameters to the pulse waveform. The goal of the study was to compare the average errors and standard deviation of SBP/DBP between the conventional oscillometric technique and the low cuff continuous method. The cuff was applied at different low pressure values (20, 30, 40 and 50 mmHg) and the statistics, such as means, average errors, and standard deviations for five subjects, were calculated for each of the pressure levels. The study showed feasibility of continuous blood pressure measurement at low cuff pressure with the possibility of a high accuracy and good variability tracking (Ding et al., 2007).

A similar setup and approach to that of Ding, et al. are used in this thesis to acquire the oscillometric and continuous arterial pulse waveform. However, in this work the two procedures are done simultaneously and the goal was to use the additional information gathered from the continuous waveform (i.e. variability) to improve the oscillometric measurement as opposed to simply compare the results of both methods, separately. While the previous studies focused on producing continuous estimates of BP or calibrating the tonometric signal using the conventional methods, the approach proposed in the thesis does the inverse. It uses tonometry to get an estimate of the BP variability during the measurement period in order to augment the conventional oscillometric readings (i.e. the

SBP and DBP estimates). The justification for this comes from the observation that physicians commonly rely on these two single numbers to make clinical decisions, rather than rely on a calibrated continuous arterial pulse waveform.

The goal of the proposed method is to augment the oscillometric SBP and DBP points using information about BP variability parameters obtained from the continuous arterial pulse waveform for the purpose of reporting a more representative estimation of the blood pressure readings (SBP and DBP) over time. The proposed method will also report a measure of the variability and identify whether the oscillometric measurement is an outlier.

2.4.1 Calibration of the continuous arterial pulse waveform

Attempts have been made to calibrate the generated continuous tonometric BP waveform using the oscillometric technique. Oscillometry could provide the maximum and minimum values of the blood pressure and help rescale the waveform to its proper offset and amplitude (Matthy and Pascal, 2002).

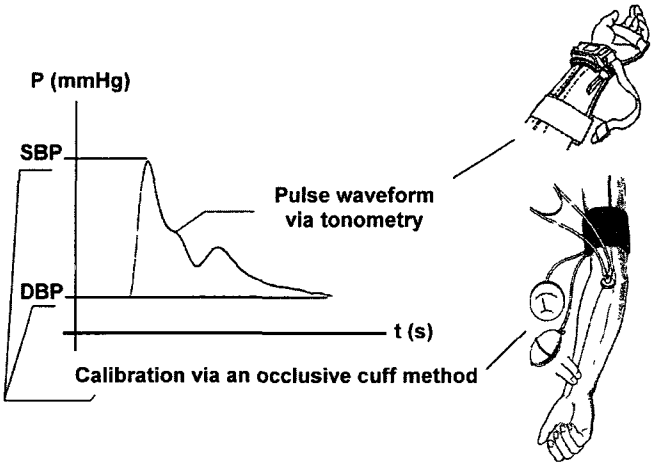


Figure 2.6 - Arterial applanation tonometry calibrated using an external cuff method. SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure (Source: Fig.1 in Matthys and Pascal, Technology and Health Care, (2002) 10:65-76)

Studies showed that using the conventional external method to calibrate the continuous arterial waveform generated introduces its own error component that is added to the error of the arterial tonometry (Hansen and Staber, 2006). A valid calibration could

be performed using invasive intra-arterial recordings, but this is not always possible and certainly not recommended as a routine procedure.

One of the most used commercial noninvasive calibrated arterial blood pressure, beat-by-beat, monitors has been the Finapres device (Ohmeda, Louisville, CO, USA), now replaced by the Finometer, a plethysmography device manufactured by FMS (Finapres Medical Systems BV, Arnhem, The Netherlands) (Maestri et al., 2005). The device is based on the volume-clamp method previously studied by Penaz (1967) to measure the arterial blood pressure at the finger tip. The method consists of a photoelectric plethysmograph (transmitter and detector) and uses a finger cuff and an inflatable bladder in order to reconstruct the brachial artery waveform. A frequency dependent filter is applied to compensate for the delay, amplitude difference, and distortion caused by the reflections and pressure gradients that exist between the finger blood pressure and the brachial pulsations. The Finapres device allows the continuous estimation of the blood pressure and provides reliable measurements of the BP and its relative changes. However, the device is not widely used in the clinic in part because of its prohibitive cost, and because of questions regarding the accuracy of the calibrated values that it provides (Ristuccia et al., 1997). Furthermore, it is known to be inaccurate in specific cases (when used on pregnant women, for example).

2.4.2 Blood pressure fluctuation

Blood pressure (BP) is a highly variable signal characterized by continuous fluctuations. These fluctuations include fast changes that can reach up to 20 mmHg over a few heartbeats and larger, more prolonged variations over durations of minutes or hours (Parati et al., 2003). As an example of slow variations over a long period of time in normal subjects, blood pressure drops significantly at night, when the body is at rest, and climbs back to its higher level when the individual wakes up. A reduced nocturnal dip can be an important indicator of cardiovascular problems (Dajani and Leung, 2008).

Many physiological factors affect the blood pressure at a rapid pace and can result in significant fluctuations over a short period of time. The respiratory cycle induces some of the arterial pulse pressure variations first noted by Hales (1733); subjects breathing at a

normal rate exhibit a variation of 3 to 6 mmHg in SBP, while subjects breathing deeply showed a much larger variation of 15 to 20 mmHg (Ramsey, 1991). Similarly, Mayer waves represent fluctuations in arterial pressure possibly caused by a delay in the blood pressure control system and occur at approximately 10 second cycles (Ando et al., 1997).

This variability and its serious consequences on the measurement of BP are not recognized by most physicians. Clinical decisions are still typically made based on one instantaneous measurement taken at a non-specific time (Pickering et al., 2005). The variability and the associated high short-term perturbations vary from one person to another, which also increases the uncertainty of BP readings.

Recently, there has been increasing recognition of the problem introduced by this variability in terms of producing consistent and meaningful BP readings (Jones and Hall, 2008); however, it remains unaddressed. Very little effort has been made to deal with the effect of this variability on the measurement.

2.4.3 Blood pressure differences between the two arms

Some studies have shown that there can be blood pressure differences between the right and left arms. If the difference is consistent, the guidelines suggest using the arm with the higher pressure for decision making (O'Brien et al., 1986). Sequential and simultaneous BP measurement techniques were tried but the prevalence and prognostic value of this difference is not well explored. Slome et al. found a tendency toward a preponderance of pressure in the right arm in normotensive persons and in the left arm for hypertensive subjects (study covered 319 subjects) (Slome et al., 1959). Gould et al. found no substantial blood pressure differences between the two arms; they reported an average of about 1 mmHg for both systolic and diastolic pressures, in 91 subjects (Gould et al., 1985). Others claim that a significant inter-arm difference could indicate increased risk of morbidity and mortality (Clark and Powell, 2002). Shock and Ogden suggest that the major cause of the differences is functional rather than anatomical. The differences could be an indication of pressure drop along the aorta or could be due to physical changes in the tissue properties (Shock and Ogden, 1939). This is contradicted by a more recent publication, stating that there is a small but consistent BP difference between the 2 arms, and that any larger

differences in the range of 5 to 10 mmHg are due to random variations or anatomical abnormalities (Eguchi et al., 2007). The results of the various studies suggest that measurements be done on both arms before diagnosing and treating hypertension. Following his rigorous clinical study, Gosse recommends carrying out a bilateral measurement on first consultation in all patients and then, in the event of a significant difference, checking the BP in the two arms, simultaneously (Gosse, 2002).

In contrast to the work on BP levels, there does not appear to be any information found in the literature comparing BP variability in the two arms. In order to address this issue, we collected continuous arterial pulse waveforms from the two arms simultaneously and examined the level of correlation between the two signals. The results are presented in Chapter 4.

Chapter 3. Blood pressure variability

3.1 Introduction

Blood pressure variability is primarily determined by sympathovagal balance of cardiovascular regulation (Laitinen et al., 1999). Unlike heart rate variability (HRV), the beat-to-beat BP variability has been much less investigated (Uusitalo et al., 2004) even though it could strongly affect the uncertainty of BP measurements and impact clinical management. BP variability can be studied over various time scales ranging from seconds to years (e.g. Ando et al., 1997, Hansen et al., 2006). It can be investigated using intermittent SBP and DBP measurements or be extracted from continuous recordings of the arterial pulse waveform.

When the arterial pulse waveform is available, the oscillations in BP can be divided into three main frequency ranges using spectral analysis: the very low frequency (VLF) ranging from 0.025 to 0.05 Hz, the low frequency (LF) ranging between 0.05 and 0.15 Hz associated with vascular tone changes and so called Mayer waves, and the high frequency (HF) ranging from 0.15 to 0.5 Hz associated with the respiratory pattern and intrathoracic pressure changes (Omboni et al., 1993; Ando et al., 1997). The first aim of this study is to quantify the statistical characteristics of SBP and DBP variability, and estimate the contributions of the different frequency ranges (VLF, LF, HF) to this variability.

Intermittent noninvasive automatic measurement of systolic and diastolic blood pressure (SBP and DBP) is widely used in a broad variety of clinical settings and in home health monitoring. As part of the blood pressure waveform, the systolic and diastolic blood pressures are also subject to significant continuous changes over different time scales. Generally, SBP and DBP are estimated at two instances that do not take into account the significant variability of BP over time.

According to the ANSI/AAMI SP10 standard, the maximum accepted error of an automated sphygmomanometer is limited to ±5 mmHg relative to reference readings taken simultaneously by at least two trained operators with a calibrated manometer (Manual, Electronic or Automated Sphygmomanometers(AAMI/ANSI-SP10, 2002)), although the measurements with the automated sphygmomanometer and the trained operators need

not be simultaneous. However, intrinsic physiological oscillations can lead to shifts of up to 20 mmHg in both the SBP and DBP within a few heartbeats. Therefore, the estimation of blood pressure is subject to two sources of uncertainty, the first due to measurement inaccuracy, and the second due to physiological variability. Blood pressure measurement standards, such as the ANSI/AAMI SP10, limit the uncertainty introduced by measurement error, but do not say anything about the contribution of physiological variability to the estimation (Jones and Hall, 2008).

How should uncertainty introduced by BP variability be characterized? Although statistical measures such as the variance are useful, they do not allow a direct comparison between the uncertainty introduced by measurement inaccuracy and the uncertainty introduced by biological variability. Therefore, the percentage of SBP and DBP beats that exceeds ±5 mmHg relative to the mean value, in the analyzed interval of the continuous recordings of arterial pulses, was calculated. This analysis is not meant to imply that biological variability contributes to measurement inaccuracy or device error. Rather, it is meant to assess the relative contribution of biological variability to BP estimation uncertainty. As part of the analysis, we also seek to identify the percentage of beats that would lead to 'outlier' readings of SBP and DBP, in a given time interval.

The appropriate interval over which the mean should be taken is not known; however, a duration in the range 1 to 2 minutes is expected to include the major short-term physiological oscillations ranging from the VLF to the HF range.

3.2 Methods

3.2.1 Subjects and measurements

The analysis was done on data obtained from the PhysioNet online database (Phy10). Twenty recordings were studied; ten recordings were calibrated intra-arterial BP recordings taken from patients in intensive care units (MGH/MF Waveform Database), and ten recordings were photoplythesmographic recordings of BP waveforms in young healthy subjects (Fantasia Database) measured using Finometer® PRO (Finapres Medical System, FMS©, Amsterdam, The Netherlands). The waveforms obtained from healthy subjects in the Fantasia database are uncalibrated. In order to allow comparison with data from the

MGH/MF database, a mean SBP of 120 mmHg and a mean DBP of 80 mmHg were assumed for all samples in this database. Although this calibration can introduce some errors in the analysis, the main interest of this study is to characterize relative changes and variability, the analysis of which is in some cases independent of absolute levels. Eight out of ten signals of the MGH/MF recordings had a length of 160 ± 15.1 seconds (means±SD) whereas the other two were much shorter (58 ± 3.5 seconds). Seven out of ten signals from healthy subjects were 236±7.2 seconds long and three were 108±2.8 seconds. All waveforms were analyzed using MATLAB and its statistical toolbox (The MathWorks Inc, Natick, MA, USA).

In addition, the study included preliminary testing on five healthy subjects (4 men, 1 woman; age range 18 to 65 years) using a prototype device developed by the team in our laboratory. Blood pressure (BP) and electrocardiogram (ECG) were recorded for 40 seconds to 1 minute. The instrument uses an inflatable cuff that was modified by stitching a strip of conductive fabric on its inner side. The conductive fabric, connected to external hardware, acts as the dry electrode for the ECG measurement. The second electrode is stitched to a wristband worn on the opposite wrist to continue the ECG circuit and allow the recording of a clear ECG signal (Ahmad et al., 2010). The BP data is obtained through an analog pre-processing sub-system which consists of a Vernier pressure transducer (SenSym SDX05D4) connected to a National Instruments™ (NI) (Austin, TX, USA) data acquisition system and controlled by a virtual instrument developed in LabVIEW NI. The output of the sub-system is an analog voltage signal corresponding to the pressure exerted by the vessels against the cuff. The signal is sampled at 1613 Hz (minimum requirement of the hardware) with a 24-bit resolution, after passing through an in-built anti-aliasing filter in the data acquisition board. The digitized waveform is filtered using a 3rd order FIR lowpass filter with a cutoff frequency of 30Hz to minimize the effects of 60Hz noise and other noise components, and then analyzed, off-line, using Matlab (The MathWorks Inc., Natick, MA, USA) and its statistical toolbox.

For each subject, the BP arterial pulse waveform was obtained by applying a constant pressure that was 20 mmHg above the subject's DBP determined at the beginning of the measurement, using an OMRON automated BP device (HEM-790IT). The measurement with healthy subjects gave uncalibrated BP, so a mean SBP of 120 mmHg and

a mean DBP of 80 mmHg were assumed for calibration and the pulse waveforms were scaled accordingly.

3.2.2 Data Analysis

The first step of the analysis was to estimate the systolic (SBP) and diastolic (DBP) variability that results from BP fluctuations and to investigate the sources of this variability based on the frequency content of the waveform. A peak detection algorithm allowed the identification of the peaks and troughs of the BP waveform, which correspond to the SBPs and DBPs respectively (details of the peak detection method are presented in *Chapter 4, section 4.3.5*). After defining the pulses by zero crossings, a peak was determined as being the maximum point (maximum height) in a single pulse and the troughs as the minimum point. The detection of the peaks was done in a semi-automatic manner; the identified peaks were confirmed visually. Histograms (with a bin width of 0.8) of these values were constructed to characterize the distribution of the SBP and DBP, and the mean, standard deviation, skewness, and kurtosis were determined. In the analysis of heart rate variability, short duration signals of < 5 min are assumed to be stationary (Task force of the European Society of Cardiology the North American Society of pacing electrophysiology, 1996). As a result, we also assumed that the signals we analyzed were statistically stationary, since all are considerably shorter than 5 min.

The peaks and troughs extracted from the raw signal were linearly interpolated (with a new sampling rate of 100Hz) to form evenly sampled waveforms at 1613 Hz. Example of an arterial waveform, the interpolated SBP and DBP signals and the respective histograms of a subject (acquired over an interval of 151 seconds) are shown in Fig. 3.1 and Fig. 3.2.

The next step was to identify the uncertainty in the SBP and DBP estimates that result from BP variability, and to classify outlier values. After data pre-processing, statistical analysis was performed using SPSS (SPSS Inc., IBM, NY, USA). The normality of the signals was assessed using the Kolmogorov-Smirnov test of normality, after removal of the outliers identified by the test (see figure 3.3). To characterize the measurement uncertainty, the percentage of SBP and DBP samples in a specific time interval located beyond ±5 mmHg from the mean values was calculated.

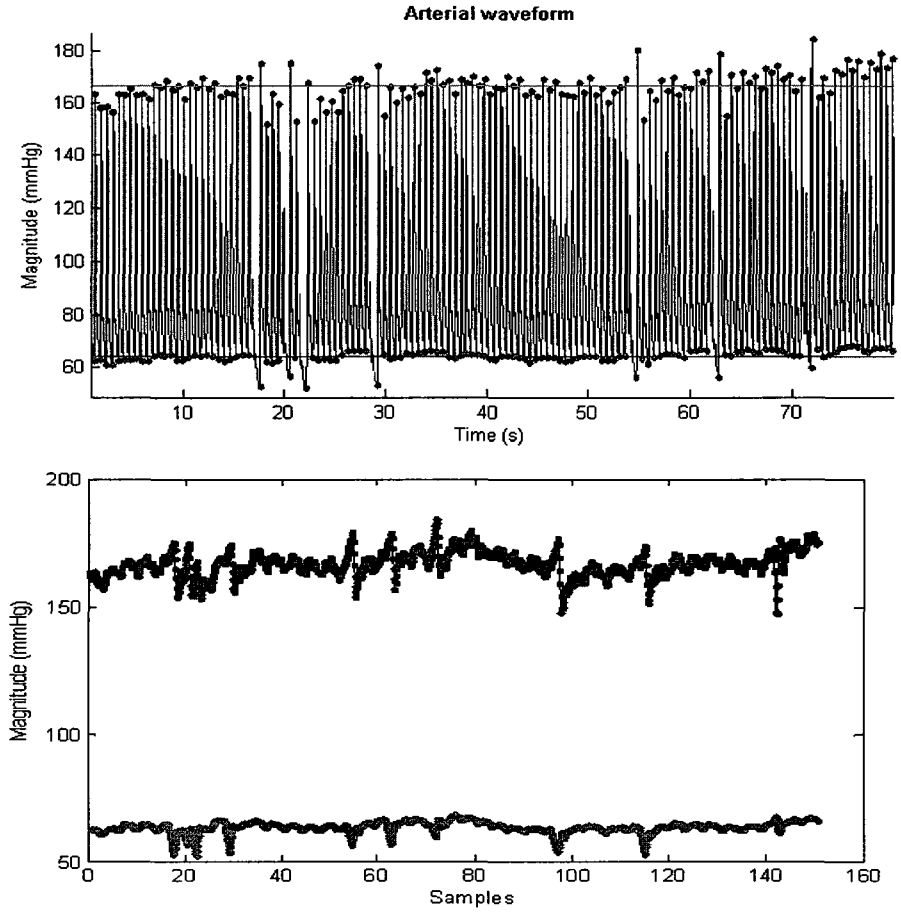


Figure 3.1 - A section of the raw signal of a sample from the MGH/MF database is shown on the upper figure along with the systolic and diastolic peaks. On the lower figure, the interpolated SBP (on top) and the DBP signals (below) for that same patient, over the whole duration of the recording are shown.

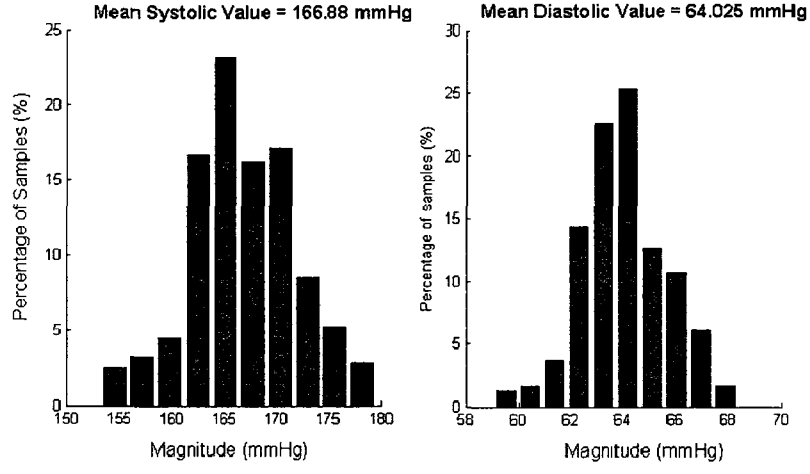


Figure 3.2 - Histograms of systolic blood pressure (SBP) values (on the left) and diastolic blood pressure (DBP) values (on the right) for an ICU patient from the PhysioNet Database.

Statistically, an outlier is an observation that is numerically distant from the rest of the data (Weisstein, 2010), but there is no agreed single definition for it. To identify the outliers, we used the approach in SPSS which estimates the central 50% of cases (shown within the rectangle in the boxplot of Fig.3.3) and defines points as outliers if they extend more than 1.5 box-lengths from the edge of the box. The percentage of occurrence of the outliers was calculated over the analyzed time interval.

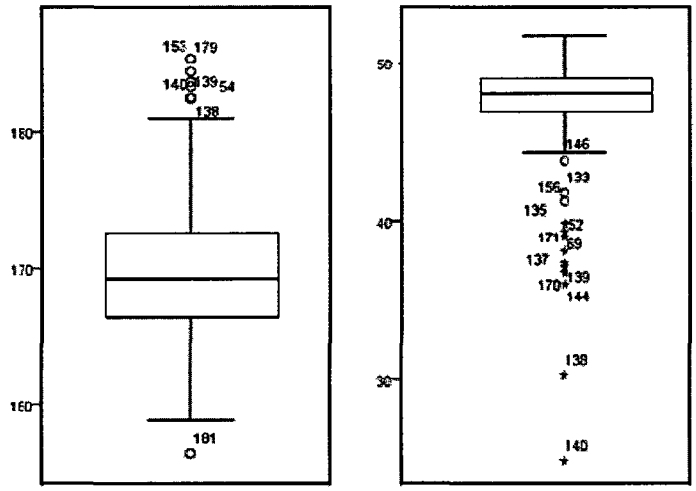


Figure 3.3 - Boxplots representing the systolic blood pressure peaks (SBP) (left plot) and the diastolic blood pressure peaks (DBP) (right plot) before removing the outliers, for an ICU patient. The rectangle represents 50 per cent of the cases and the lines protruding from the box reach out to the smallest and largest values after removal of outliers. Points are identified as outliers if they extend more than 1.5 box-lengths from the edge of the box (shown as circles on the plot). Extreme outliers are those that extend more than 3 box-lengths and are shown as asterisks on the plot. The outliers are identified by their sample indices.

Most of the power in autonomic variability is thought to be concentrated below 1 Hz. Therefore, in order to study the contribution of the different frequency ranges to SBP and DBP variability and their effect on the percentage of peaks beyond ±5 mmHg from the mean, bandpass FIR filters (500 taps) were used to isolate components of the interpolated waveform in each frequency range, VLF (0.025 - 0.05 Hz), LF (0.05 - 0.15 Hz), HF (0.15 - 0.5 Hz) (Fig. 3.4 - b, c, d). The histogram, mean, and standard deviation of each filtered waveform were then determined (Fig. 3.5). To determine the contribution of frequencies below the VLF, the signal was filtered with a 500 tap lowpass FIR filter at a cutoff frequency of 0.025 Hz and then the mean was deducted to remove the d.c. level (Fig. 3.4 - a).

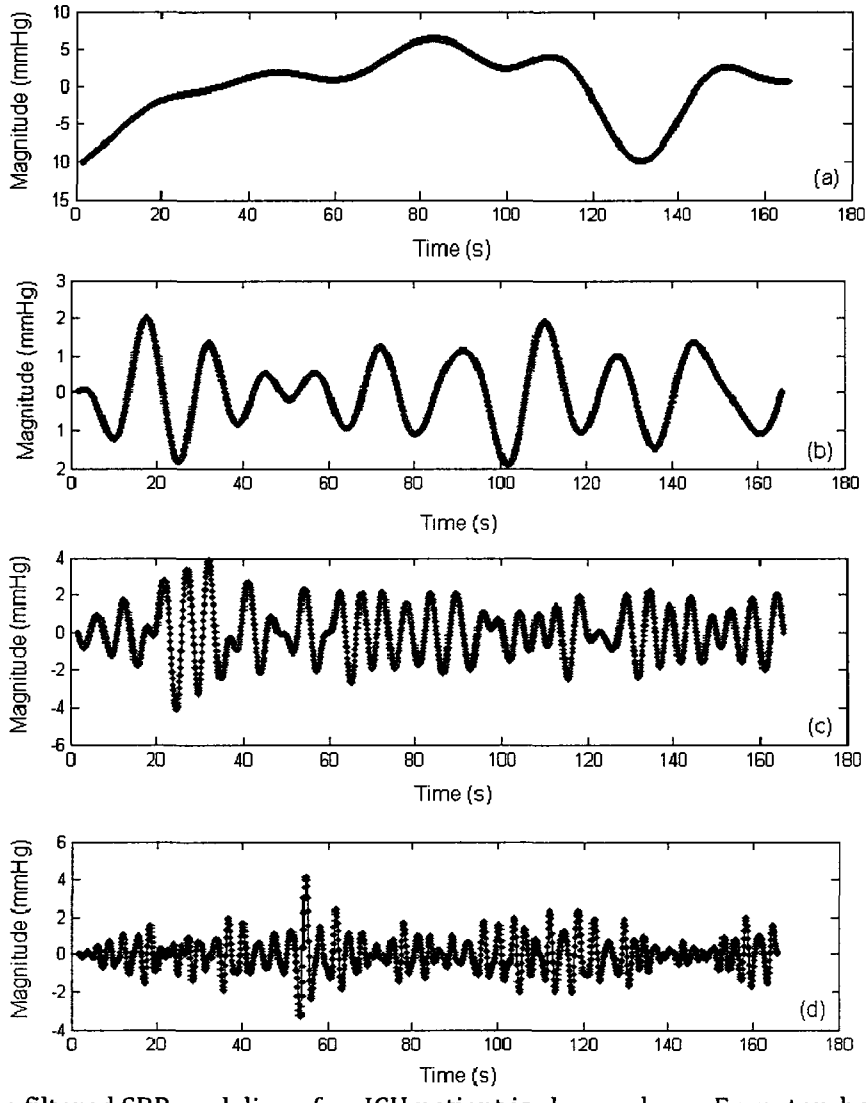


Figure 3.4 - The filtered SBP peak line of an ICU patient is shown above. From top-below: (a) below VLF (low pass at 0.025 Hz and mean deducted), (b) VLF (bandpass 0.025 – 0.05 Hz), (c) LF (0.05 – 0.15 Hz) and (d) HF (0.15 – 0.5 Hz). The frequencies above 0.5Hz showed an insignificant contribution and therefore their plot was omitted.

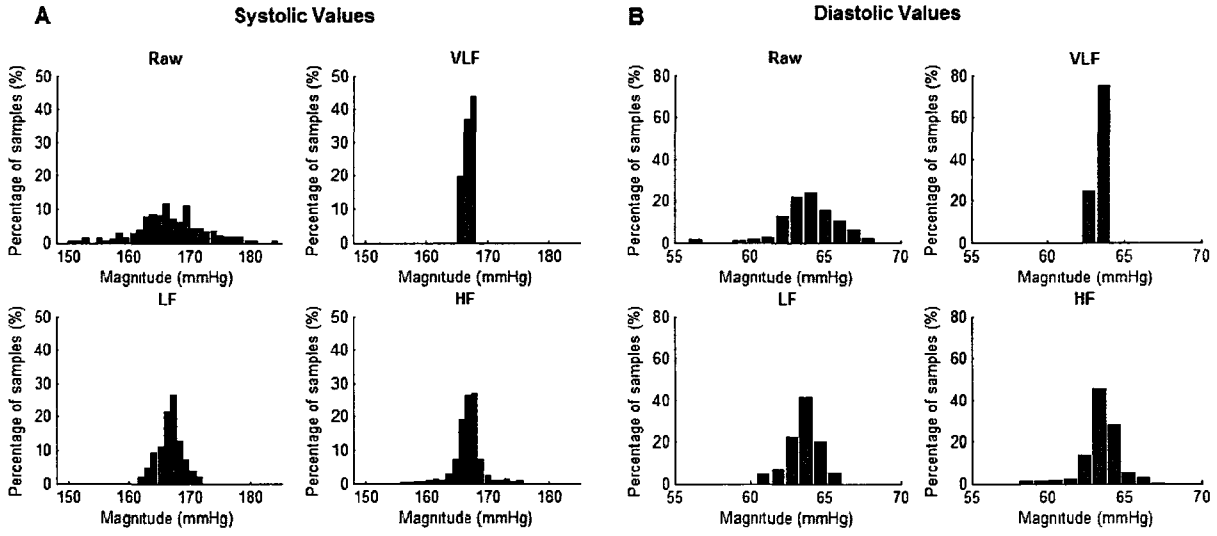


Figure 3.5 - (A) Histogram of systolic blood pressure (SBP) values and (B) diastolic blood pressure (DBP) values for an ICU patient from the PhysioNet Database. The graphs show the respective histograms of the raw signal (top left), the very low frequencies (top right), low frequencies (bottom left) and high frequencies (bottom right).

3.3 Results

3.3.1 Distribution characteristics

MGH Database - ICU patients:

Analysis of the raw BP waveforms from the ICU patients in the MGH/MF database showed that the standard deviation ranged from 1.79 to 8.52 mmHg (mean SD ± SE: 5.39±0.77 mmHg) for the SBP, and from 1.15 and 5.76 mmHg (mean SD ± SE: 3.50±0.46 mmHg) for the DBP (Table 3-1A). The percentage of peaks located beyond ±5 mmHg from the mean with the ICU patients was 33.0% of the SBP peaks and 14.9% for the DBP peaks. The values for different individuals ranged from 2.77% to 55.4% for SBP and 3.56% to 34.7% for DBP.

On average, 5.17% of the SBP peaks were outliers (ranging from 0.6% to 20.5% in individuals). Once these outliers were removed, 6 out of 10 sample signals followed a normal distribution. Similarly, on average, 12.2% of the DBP peaks were outliers (ranging from 2.39% to 26.2% in individuals). After removing the outliers, 8 out of 10 sample signals were normally distributed.

A similar analysis was performed on segments of different durations, up to 90 seconds, of the ten MGH Database signals. The segments were of length 30, 60 and 90 seconds, respectively. The statistics of the different segments were individually compared to those of the entire signal in order to identify the minimum length that would be statistically representative of the entire signal. The outcome showed that the mean systolic and mean diastolic pressure values calculated at 90 seconds vary by less than 1%, on average, from the same values calculated using the entire signal (length of 165 seconds). Below 90 seconds, the smaller the duration of the sample analyzed, the further the mean values are from the mean values obtained from the entire signal.

Table 3-1 - Average, standard deviation, skewness and kurtosis for (A) All the ICU patients and (B) All the healthy individuals. Values are means over subjects ± SE

A

		Raw	VLF	LF	HF
Systolic Pressure	Average	146.45 ± 12.07	146.44±12.08	146.51±12.06	146.45±12.08
	Standard Deviation	5.39±0.77	1.55±0.40	2.13±0.44	1.62±0.28
	Skewness	0.29±0.23	(-) 0.25±0.14	0.19±0.11	0.097±0.058
	Kurtosis	4.04±0.69	3.67±0.58	3.51±0.48	4.79±0.65
Diastolic Pressure	Average	61.01± 1.32	60.51± 21.64	60.54± 21.63	60.5± 21.64
	Standard Deviation	3.5± 0.46	1.16± 0.17	1.72± 0.32	1.24± 0.24
	Skewness	(-)0.21± 0.49	0.18± 0.22	(-)0.049± 0.08	(-)0.31± 0.29
	Kurtosis	5.97± 1.02	3.64± 0.87	5.05± 1.29	8.87± 2.13

B

		Raw	VLF	LF	HF
Systolic Pressure	Average	119.99±0.023	120.04±0.05	119.99±0.026	119.99±0.023
	Standard Deviation	4.92±0.49	1.37±0.17	1.37±0.14	0.67±0.1
	Skewness	0.1±0.23	0.066±0.054	(-)0.025±0.14	(-)0.063±0.059
	Kurtosis	3.81±0.53	3.26±0.46	4.64±1.22	4.41±0.75
Diastolic Pressure	Average	53.84±4.16	53.87±4.16	53.84±4.16	53.84±4.16
	Standard Deviation	3.39±0.17	1.25±0.10	0.96±0.11	0.53±0.089
	Skewness	0.49±0.22	0.10±0.061	(-)0.0059±0.12	0.19±0.22
	Kurtosis	4.75±0.92	3.08±0.19	5.41±1.23	13.69±4.68

Fantasia Database – Young Healthy subjects:

For healthy subjects in the Fantasia database, the standard deviation ranged from 3.02 to 7.07 mmHg (mean SD ± SE: 4.92±0.49 mmHg) for SBP and from 2.51 to 3.94 mmHg (mean SD ± SE: 3.39±0.17 mmHg) for DBP (Table 3-1B). The average percentage of peaks located beyond ±5 mmHg from the mean was 29.1% of the SBP peaks and 13.5% for the

DBP peaks. The values for different individuals ranged from 13.3% to 57.7% for SBP and 6.8% to 19.9% for DBP.

On average, 1.32% of the SBP values peaks were outliers (ranging from 0% to 4.39% in individuals). Once these outliers were removed, 5 out of 10 sample signals followed a normal distribution. As for the DBP peaks, on average, 6.51% were outliers (values ranging from 0% to 41.87%). After removing the outliers, 6 out of 10 sample signals were normally distributed.

Laboratory measurements - Healthy subjects:

For the 5 measurements taken from healthy subjects using the prototype device in our laboratory, the standard deviation ranged from 3.28 to 4.48 mmHg (mean SD ± SE: 4.24 ± 0.37 mmHg) for SBP and from 2.75 to 7.71 mmHg (mean SD ± SE: 4.88 ± 0.94 mmHg) for DBP. On average, 24.3% of the SBP peaks and 26.3% of the DBP peak were located beyond ±5 mmHg from the mean.

The percentage of outliers found was 1.66% for the SBP values and 4.22% for the DBP values. Once removed, 4 out of 5 SBP signals and 3 out of 5 DBP sample signals were normally distributed.

3.3.2 Frequency Analysis

MGH Database – ICU patients:

For the ICU patients in the MGH/MF database, the average contribution of the VLF range to the total variance (equivalent to non d.c. power) over the frequency range of 0.025 – 0.5 Hz was 28.43% for the SBP and 21.33% for the DBP. The LF oscillations contributed on average 46.59% and 51.37% to the total variance of the SBP and DBP respectively, and the HF oscillations contributed 24.98% and 27.30% to the total variance of the SBP and DBP respectively (Fig. 3.6-A). Moreover, the combined contribution of the three frequency ranges to the total variance in the raw signal is 43.40% and 63.82% for SBP and DBP respectively.

Furthermore, frequency analysis allowed us to determine the respective contribution of each of the frequency ranges of interest to the overall percentage of peaks lying beyond the ±5 mmHg margin from the mean. Averaged over the individual subjects, the SBP and DBP signals in the VLF range exceeded the ±5 mmHg margin in 3.37% and 2.87% of the cases, respectively, while the SBP and DBP signals in the LF range exceeded this margin in 5.84% and 8.48% of the cases, and the SBP and DBP signals in the HF range exceeded this margin in 3.29% and 4.72% of the cases. Significantly, the SBP signal below the VLF range exceeded the ±5 mmHg margin in 17.7% of the cases, on average.

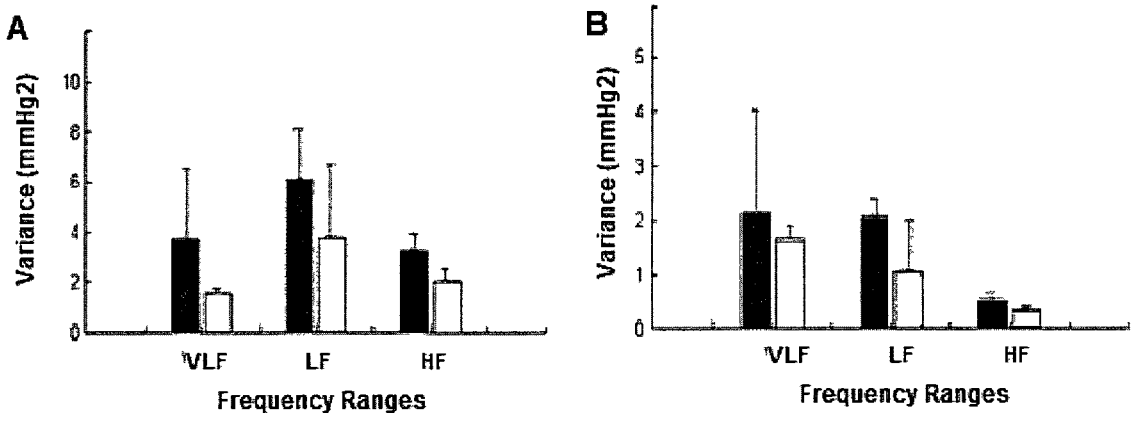


Figure 3.6 - Contribution of the three frequency regions (VLF, LF, HF) to the variance of the blood pressure variations (A) ICU patients and (B) healthy subjects from the PhysioNet Database. The dark bars represent the SBP values, the white bars refer to the DBP values. VLF, 0.025-0.05 Hz; LF, 0.05-0.15 Hz; HF, 0.15-0.5 Hz. The bars show mean variance within each frequency range over all subjects ± SE.

Fantasia Database – Young Healthy subjects:

For the healthy subjects in the Fantasia database, the VLF range – contributed on average 45.22% and 54.36% of the total variance for the SBP and DBP respectively. The LF oscillations contributed on average 43.45% and 34.17% for the SBP and DBP respectively, and the HF oscillations contributed 11.33% and 11.47% for the SBP and DBP respectively (Fig. 3.6-B). The combined contribution of the three frequency ranges to the total variance in the raw signal is 17.97% and 25.85% for SBP and DBP respectively.

Averaged over the healthy subjects, the SBP and DBP signals in the VLF range exceeded the ±5 mmHg margin in 0.67% and 0.04% of the cases, the SPB and DBP signal in the LF range exceeded this margin in 0.46% and 0.3% of the cases, and the SBP and DBP signal in the HF range exceeded this margin in 0.06% and 0.3% of the cases. Once again, the frequencies below VLF had the most frequent departures from the ±5 mmHg margin, exceeding it in 21.3% and 5.75% of the cases for SBP and DBP respectively.

Laboratory measurements - Healthy subjects:

The SBP and DBP signals were once again divided into different frequency ranges in order to identify the percentage of peaks exceeding the ±5 mmHg margin. Averaged over the measured signals, the VLF range had the highest rate of peaks exceeding this margin (20.8% for SBP and 32.5% for DBP). The SBP and DBP signals in the LF range exceeded the margin in 3.32% and 6.99% of the cases, respectively. The numbers were the lowest for the HF range where only 0.5% of the SBP and 0% of the DBP signals appeared to be ±5 mmHg away from their respective means. In these measurements, the frequencies below VLF also had a significant percentage exceeding the margin but the numbers were slightly smaller than those of the VLF frequencies (11.9% for SBP and 21.5% for DBP).

3.4 Conclusions

This chapter confirms previous observations that the beat-to-beat systolic and diastolic blood pressures undergo significant fluctuations over short periods, and quantifies the statistical characteristics of these variations. In some subjects, the standard deviation of SBP and DBP exceeded the maximum allowable error of 5 mmHg for BP measurement devices. Even in subjects for whom the standard deviation was less than 5 mmHg, the combination of intrinsic physiological variability and device error could produce measurements that are far from the average SBP and DBP in a given time period. As a result, this calls into question the reliability and utility of conventional single BP readings taken at the doctor's office or at home.

For the signals obtained from the PhysioNet database, there is an implicit assumption that the arterial pulse waveforms were recorded accurately, even though insufficient detail

is available regarding the measurement conditions. This assumption can be justified given that intra-arterial recordings are considered the gold standard in BP measurement, and in at least some studies, Finapres recordings compare favorably to those. The recordings obtained with the laboratory prototype should be considered provisional until the device is fully validated. With these caveats in consideration, our analysis indicates that physiological variability can contribute significantly to BP estimation uncertainty. Although commonly available BP measurement devices do not take physiological variability into account, a device capable of providing the measures of the mean and variability of SBP and DBP over the measurement interval could potentially alleviate the uncertainty due to biological variability.

The analysis of signals in the different frequency ranges of interest showed that there is no single source for the values exceeding the ±5 mmHg margin; all four ranges are important contributors, although the dominant contribution appears to be due to slow variations below the VLF range. It is unlikely that these variations are due to baseline drift in the short intra-arterial recordings from ICU patients that we analyzed, since these recordings are considered the gold standard for blood pressure measurement. Moreover, the Finapres recordings in healthy subjects are unlikely to be subject to baseline drift in short recordings (Ristuccia et al. 1997). Therefore it appears that the values that are distant from the mean represent actual variations in BP due to a variety of autonomic factors that operate at frequencies below the VLF range (Parati et al. 1995).

A small percentage of SBP and DBP values were identified as outliers. An outlier due to external factors (such as artifacts) should definitely be removed from the signal, whereas a physiological outlier could have diagnostic value. Future work is needed to identify the source of the detected outliers in order to correctly eliminate those due to external factors, while leaving the meaningful ones untouched.

Chapter 4. Augmented blood pressure measurement

4.1 Introduction

The blood pressure signal is highly variable and is characterized by continuous fluctuations. This chapter describes an approach that aims to augment the conventional oscillometric measurement of blood pressure by taking into account the physiological blood pressure variability (Fig. 4.1). The proposed method involves simultaneously collecting the continuous arterial pulse waveform from one arm and the oscillometric waveform from the other arm, over 90 seconds. The continuous arterial pulse waveform can be obtained noninvasively using different methods such as tonometry or optical plethysmography. In this work, it is obtained by applying constant pressure in a cuff, connected to a piezoelectric transducer. The analysis of the obtained beat-to-beat arterial pulse waveform provides important information characterizing the variability of the blood pressure. The conventional oscillometric measurement technique is applied on the other arm, producing two numbers; the conventional oscillometric systolic (SBP) and diastolic (DBP) estimates. Locating those values on the continuous waveform obtained from the first arm helps in deriving three measures that augment the oscillometric readings of blood pressure. These measures are 1) the mean SBP and DBP over the measurement interval which is arguably more representative of the BP than the oscillometric values obtained at two instants in time, 2) the standard deviation of SBP and DBP over the interval which provides information about BP variability, and 3) whether or not the oscillometric readings are outliers relative to the distribution of the readings over the interval, a finding which could be used to generate an alert (e.g. to repeat the measurement). The proposed approach was tested, and partially validated, with healthy subject recordings.

An extension of this approach is presented in the last section of the chapter. It consists of an attempt to integrate the approach into a single cuff device for enhanced practicality by deriving information about the variability directly from the oscillometric waveform.

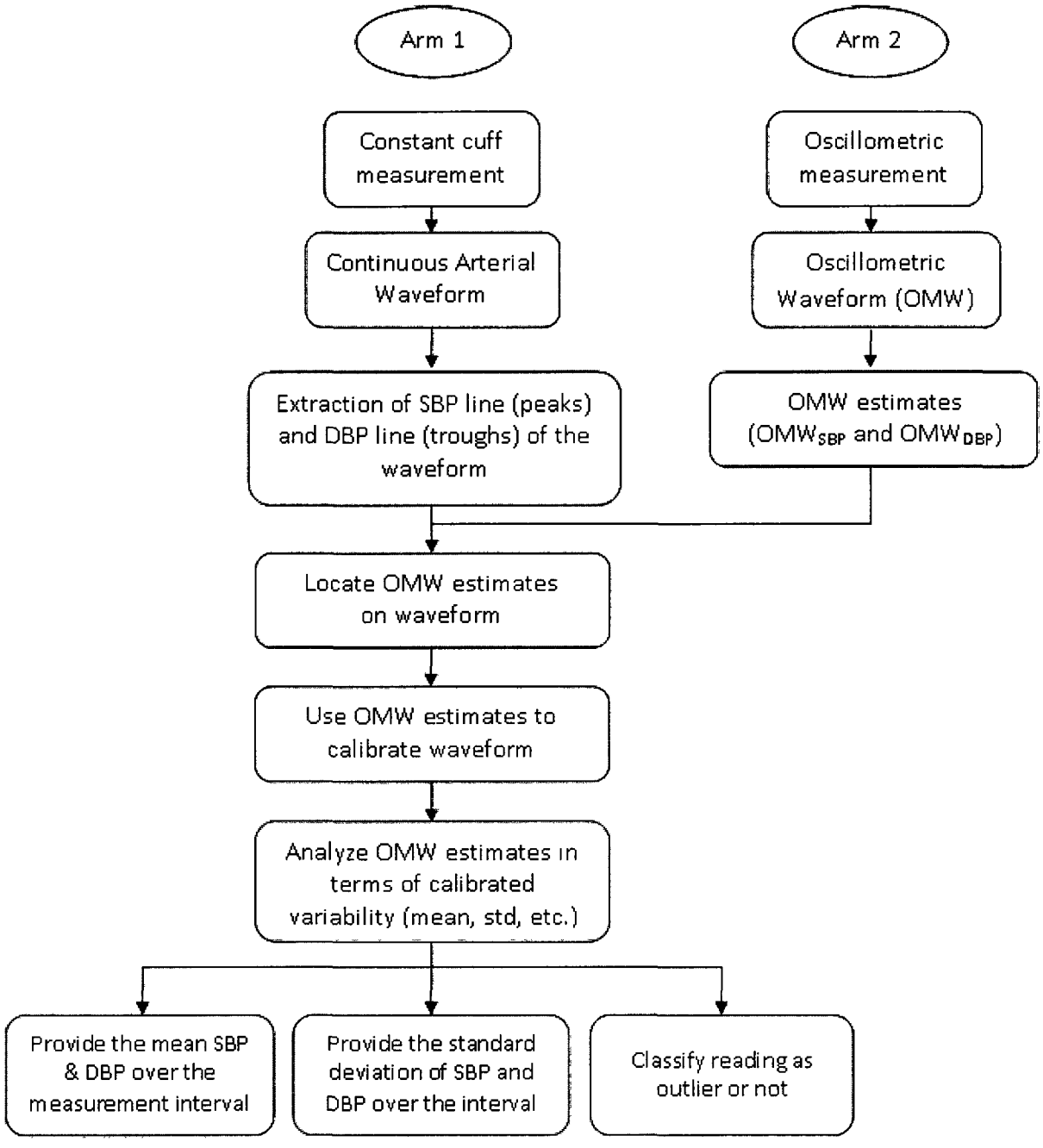


Figure 4.1- Block diagram showing the steps of the proposed approach for augmented blood pressure measurement described in this chapter.

4.2 Subjects

Fifteen adults (7 male and 8 female subjects, age ranging from 19 to 50 years) with no known history of heart disease participated in this study. All subjects provided informed consent prior to the measurement, in accordance with the guidelines of the Institutional Research Ethics Board (see Appendix C-D for the ethics approval notice and the informed consent form).

4.3 Methodology

4.3.1 Prototype device

We developed a blood pressure measurement prototype unit that includes two pressure cuffs, each connected to an analog pressure transducer. An illustrative block diagram can be found in Fig. 4.2. The Vernier pressure transducer (SenSymSDX05D4, Beaverton, OR, USA) and National Instruments™ (Austin, TX, USA) hardware and software are used to acquire the arterial pulse wave data from the two arms.

The Vernier pressure transducer operates on a DC supply voltage of 5V (Volts) and converts the mechanical vibrations exerted by the blood circulation on the cuff to an analog output voltage signal in the range of 0-5 V. The conversion factor is given in the sensor's specification sheet as the calibration slope (56.11 mmHg/V).

A first BP cuff is placed on the subject's left arm and is inflated to a constant pressure, using a manual pump, and acts as the measurement tool used to retrieve the continuous arterial pulse waveform. A second BP cuff is placed on the right arm and controlled by an automatic 6 V DC mini air pump. The pump operates with a pushbutton mounted on the prototype; once pressed, the button turns the pump on and the brachial cuff is gradually inflated and then deflated to conduct the oscillometric measurement. The pump is powered by a battery pack for convenience. The screw-controlled manual pressure release valve is connected in-line with the brachial cuff. The rotation of the screw determines the deflation rate of the cuff.

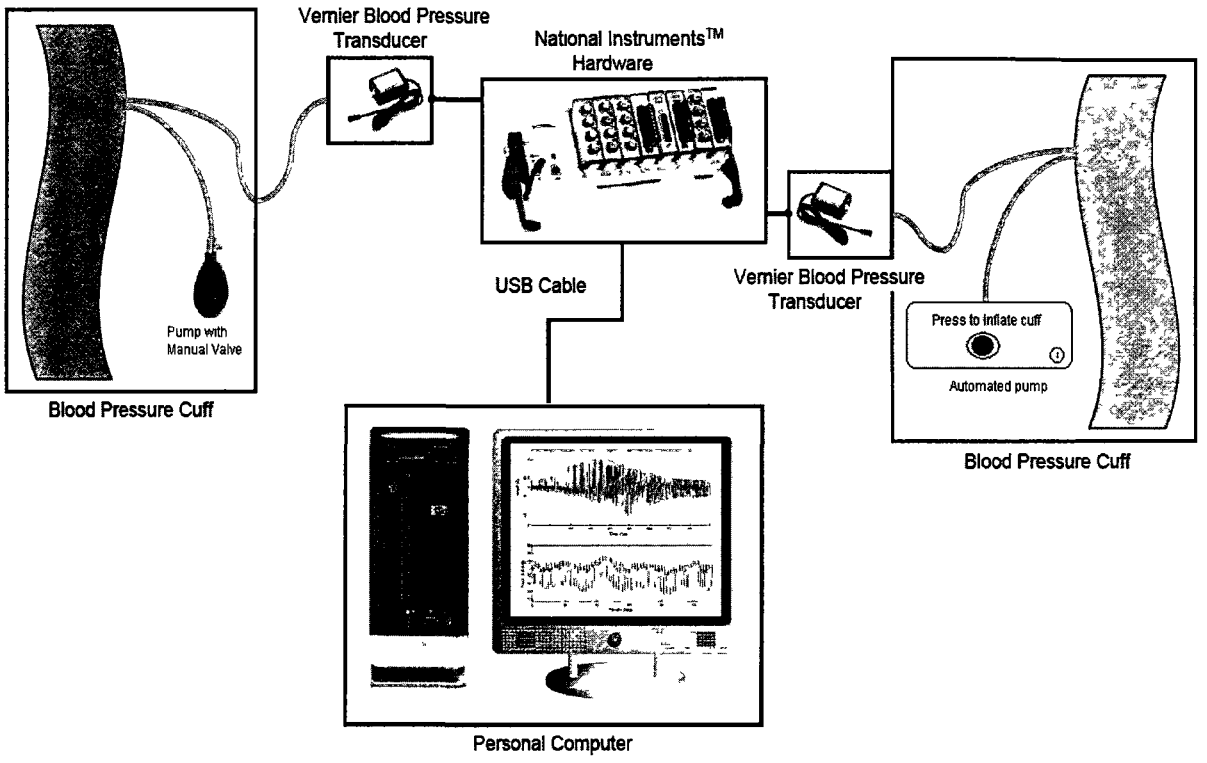


Figure 4.2 - Illustrative block diagram of the BP prototype developed in the laboratory.

The analog voltage outputs of the two transducers (corresponding to the two BP cuffs) are fed to two of the four simultaneously sampled analog input channels of the National Instruments™ C Series 9239 analog input module (NI-9239) mounted on a CompactDAQ data acquisition board. Passing through the NI-9239 unit, the analog signals are conditioned, buffered, and then sampled, at a frequency (f_s) of 1.613 kHz, by a 24-bit delta-sigma analog-to-digital converter (ADC). Prior to digitization, the signal passes through an in-built anti-aliasing filter on the data acquisition board with a cutoff frequency equal to 0.453. f_s. The quantized signals are then transmitted to a Personal Computer (PC) via a universal serial bus (USB) cable.

The voltage supply to the Vernier pressure transducers is provided from a National Instruments™ C Series 9263 4-Channel, 16-bit, ± 10 V analog output module (NI-9263) also mounted on the CompactDAQ data acquisition board. This module ensures a constant voltage supply over time.

National Instruments™ LabVIEW development environment is used for data acquisition of the constant pressure arterial waveform and the oscillometric BP signals on the PC. We developed a customized LabVIEW user interface which displays the acquired arterial pulse waveform and oscillometric signals data in real time. Signal processing, frequency and statistical analysis are applied to the signals offline using Matlab® (The MathWorks Inc., Natick, MA, USA). To minimize the effects of 60Hz and other noise components, the signals were digitally filtered using a 3rd order FIR lowpass Filter with a cutoff frequency of 30Hz prior to further analysis.

4.3.2 Reference devices

The following devices provide the reference blood pressure readings:

Biosign UFIT is a web-based test and measurement system for blood pressure assessment. The hardware consists of a wrist cuff and a small box plugged into the PC via a USB connector. This connection feeds power to the device and allows transmission of data. After acquiring the oscillometric blood pressure curve, UFIT sends the data to Biosign servers, via Internet. The results are then outputted to the monitor of the laboratory PC.

OMRON HEM-790IT is a commercial oscillometric blood pressure device intended for home use. This stand-alone device is equipped with a blood pressure cuff, a pressure transducer and a display monitor.

4.3.3 Experimental procedure

The subject is comfortably seated on a chair, and asked to relax with minimum movement. For one of the measurements, he/she is asked to breathe deeply, at a specified rate for the duration of the recording (90 seconds). The entire recording session lasts up to 60 minutes.

The first cuff is placed on the upper left arm for constant cuff pressure arterial pulse waveform measurement, the second cuff on the upper right arm for oscillometric inflation, and the UFIT wrist device is placed on the wrist of the right arm.

The UFIT is used to find the systolic and diastolic values at the start of every recording, and its cuff is kept deflated for the duration of the prototype measurement. In the case of two subjects, the UFIT server was down and Omron was used, as a replacement, to find the initial systolic and diastolic values.

The cuff on the left arm is inflated to reach a constant pressure, close to the diastolic pressure of the subject as determined by the UFIT device (subject's diastolic BP + 3 mmHg), such that the pulse and the dicrotic notch are visually confirmed to be present in the waveform. Concurrently, an oscillometric measurement is made on the other arm. In that arm, the cuff is inflated to a pressure higher than the systolic pressure as determined by the UFIT device (subject's systolic BP + 5 mmHg), and then slowly deflated at a predetermined rate (2-3 mmHg/second). Acquisition of data from the two cuffs is triggered simultaneously by the control software, and lasts 90 seconds, with the constant pressure cuff generating the continuous arterial pulse waveform and the oscillometric cuff generating SBP and DBP values.

The experiment (see Table 4-1) consists of a reference reading followed by a blood pressure recording from the two arms (oscillometric and constant pressure, in parallel). Those two steps are repeated 5 times. At the end of the session, an additional recording is performed on both arms in which the subject is asked to breathe deeply, at a predetermined rate of 8 seconds/breath (i.e. breathing frequency of 0.125 Hz). A software-generated metronome is set up on the monitor, during this recording, to help the subject maintain the required breathing frequency.

Table 4-1 – Sequence of experimental Steps

1	Place cuff with constant pressure on left arm (prototype)
2	Place oscillometric cuff on right arm (prototype)
3	Place UFIT cuff on right arm
4	Make sure subject is relaxed. Take UFIT reading (to determine boundaries of the subject's BP)
5	Take parallel recordings using the oscillometric and the constant cuffs (prototype). Measure simultaneously for 90 seconds.
6	Wait 3 minutes
7	Repeat steps (4), (5) and (6) **five times**
8	Ask subject to breathe deeply (following the metronome on the screen). Repeat steps (4), (5) and (6) one last time.

4.3.4 Waveform extraction

For each subject, we retrieve the continuous arterial pulse waveform and the oscillometric BP waveform. An example of the continuous arterial pulse waveform is shown in Fig. 4.3. A customized peak detection algorithm (explained in *section 4.3.5*) is applied to the continuous BP arterial pulse waveform in order to detect the peaks (systolic points) and the troughs (diastolic points) of the pulse waveform.

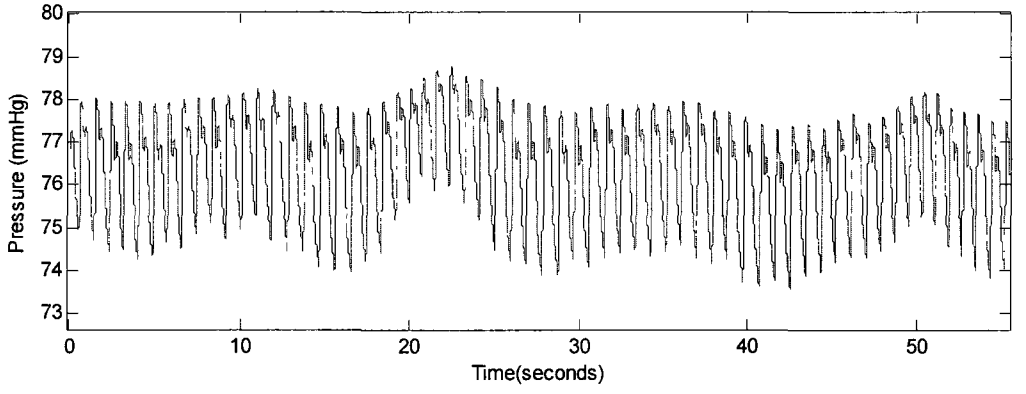


Figure 4.3 - Section of the continuous BP arterial pulse waveform

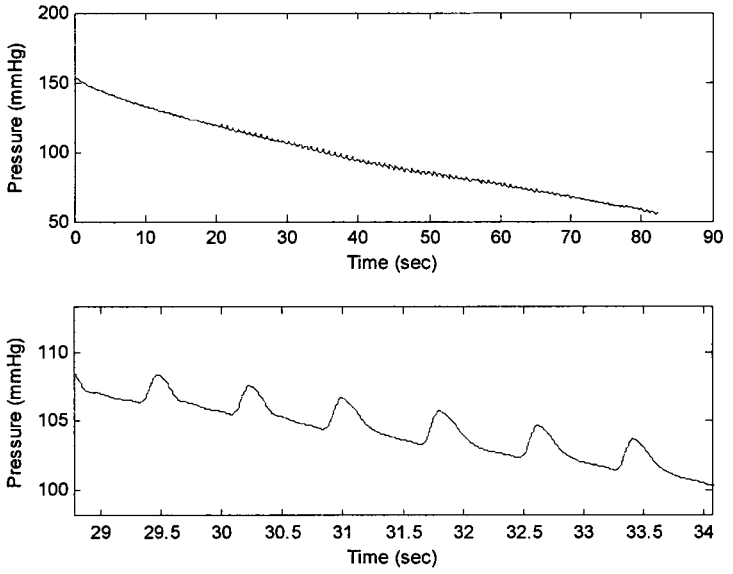


Figure 4.4- Cuff deflation curve (top graph) and a zoomed-in interval of that same curve showing the detected pulses (bottom graph).

A second order, high-pass, Butterworth filter is applied to the oscillometric deflation curve (Fig. 4.4), with a cutoff frequency of 0.1 Hz. The filter suppresses the frequency components that are related to the slowly deflating cuff pressure and allows the remaining components of the signal to pass through (Geddes et al., 1982, Sorvoja et al., 2005). These components correspond to the subject's pressure pulses that form the desired oscillometric waveform (OMW) (Fig.4.5).

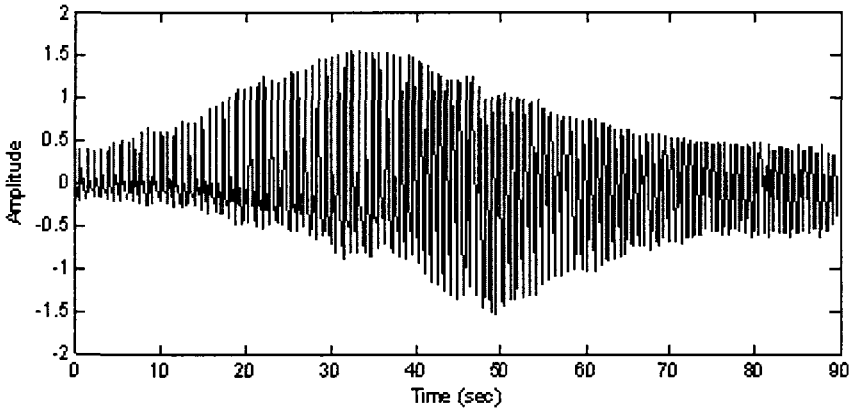


Figure 4.5 - OMW obtained after highpass filtering the transducer waveform during cuff deflation

Once the OMW is extracted, the oscillometric pulse index (OPI) is defined as the height of each pulse from baseline to peak, peak to peak, or as the area produced by

integrating each pulse (Jazbinsek et al., 2005; Ball-llovera, 2003; Gersak, et al., 2006). Each method produces a different envelope and no definitive theoretical or empirical arguments have been offered for choosing one over the other. Since the goal of this study is not to evaluate oscillometry per se, but rather to use it as a component of the proposed BP estimation approach, there was no preference as to which OPI approach to use; the 'area values' was the chosen technique to use.

The next step consisted in the linear interpolation of the envelope (shown in Fig. 4.6). The original envelope is derived from individual heartbeats, and so the signal is then sampled at a rate equivalent to the subject's heart-rate. The irregularity of the heart rate and the known heart rate variability of the signal can limit the estimation of the blood pressure to the locations of these pulses, if not interpolated. The envelope is resampled at a chosen rate of 100Hz. Interpolation allows for the calculated SBP and DBP values to be found at points in between detected peaks (Chen, 2010).

The Maximum Amplitude Algorithm (MAA) is then used to estimate the SBP and DBP values. According to the literature, it is the most popular algorithm for determining blood pressure from oscillometric waveforms (Baker et al., 1997). MAA requires, as a first step, finding the point on the envelope that corresponds to the mean arterial pressure (MAP), which is estimated to be the maximum point on the OPI and which must lie between the SBP and DBP values on the envelope. Locating this value on the deflation curve allows us to obtain the MAP value in mmHg (Fig. 4.6). In the physiological literature, MAP has been related to the SBP and DBP values using the following formula (Geddes et al., 1982):

$$MAP = DBP + \frac{1}{3} \cdot (SBP - DBP) \qquad (4.1)$$

Instead, oscillometry relies on empirically determined ratios to relate the MAP, SBP, and DBP.

Once the MAP is plotted on the OPI, it virtually divides the envelope into two sides: the left side represents the systolic side and the right side becomes the diastolic side. The MAA algorithm then utilizes systolic and diastolic characteristic ratios, determined empirically from large scale studies, to find the points that correspond to SBP and DBP. In

the literature, the systolic ratio ranges from 0.45 to 0.73 and the diastolic ratio ranges from 0.69 to 0.83 depending on the specifics of the applied MAA. The height (amplitude A) of the maximum point is multiplied by the systolic ratio (r_S) and the diastolic ratio (r_D) in order to get the amplitude of the systolic point (located on the systolic side) and the diastolic point (located on the diastolic side), respectively. The ratios used in this study are 0.55 and 0.8 for r_S and r_D, respectively. The equations used to find the SBP and DBP points, following the MAA implementation, then, are:

$$SBP = A \times r_S\,,\ DBP = A \times r_D \qquad (4.2)$$

The final stage of oscillometric estimation consists of mapping the systolic and diastolic points found on the envelope back to the deflation curve using time stamps that identify the location of the SBP and DBP on the oscillometric waveform. The SBP and DBP values are thereby obtained in mmHg (Fig. 4.6).

In our work, the parallel recording of the oscillometric and continuous BP signals result in two curves shown in Fig. 4.7.

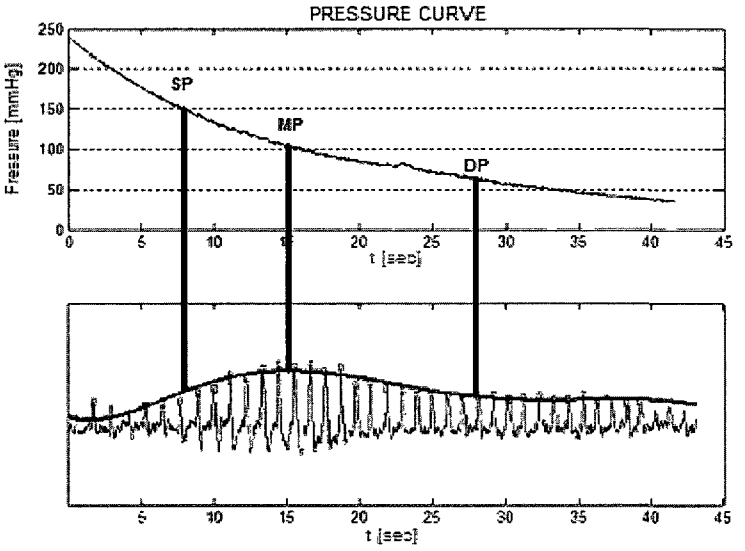


Figure 4.6 - Example of the MAA implementation **(Chen, 2010)**. The systolic, diastolic and mean values are projected from the envelope back to the deflation pressure cuff.

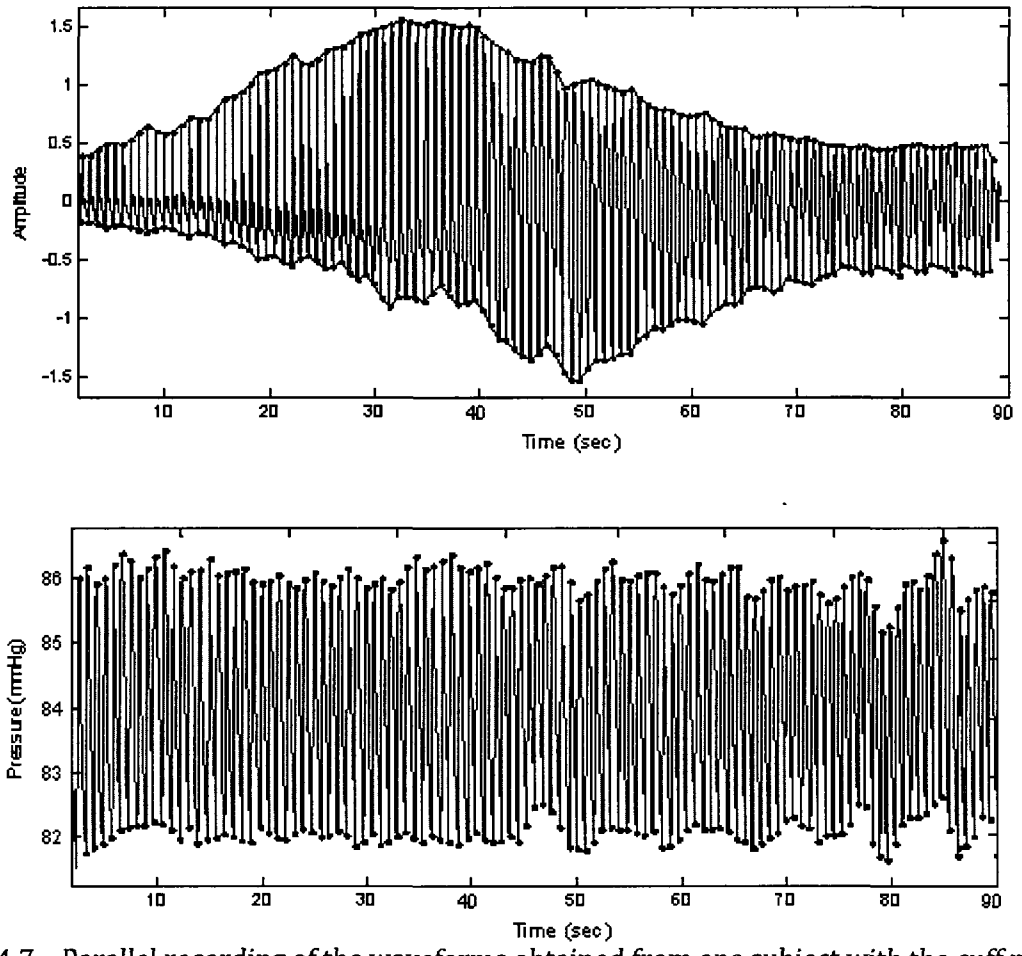


Figure 4.7 – Parallel recording of the waveforms obtained from one subject with the cuff placed on the two arms with one recording the oscillometric waveform and the other recording the continuous arterial pulse waveform, over a 90-second period.

The oscillometric algorithm explained in this section and used as the starting point of the proposed approach has been previously developed and validated in our laboratory (Chen, 2010). A variety of algorithms exist in the literature to determine the SBP and DBP from the oscillometric method. Using Biosign's commercialized UFIT device, different algorithms were evaluated, and the MAA algorithm which produced the lowest error between the estimated blood pressure and the reference readings was chosen in order to generate the oscillometric algorithm used in this study.

4.3.5 Peak Detection

In both the oscillometric and continuous pulse waveforms, the pulse begins at a minimum point and goes through a steep rise to reach a maximum to then fall, attaining the

dicrotic notch. The notch is characterized by a slight rise creating a smaller amplitude peak, followed by a drop to the minimum value, defining the end of the pulse.

The peak detection algorithm used is based on an existing method for ECG peak detection (Kohler et al., 2003) with minor alterations compensating for the shape disparity between a heart pulse and a blood pressure pulse (Chen, 2010). The pulses were determined by zero crossings; the upward and downward zero crossings are detected in order to find the beginning and the end of a pulse. A zero crossing is a point where the sign of the function changes, and is represented by a crossing of the x-axis.

The peak and troughs were defined to be the maximum and the minimum amplitude of an individual pulse, respectively. Genuine peaks had to be evenly spaced, for they correspond to the systolic phase of the heart beat, and genuine troughs had to fall in between two peaks in order to be considered in the analysis. This concept helped in recognizing mistaken identifications and allowed the algorithm to remove them from the array of peak points.

The pulse waveform signal is first filtered to facilitate the process. The first iteration consists of a 3rd order IIR Butterworth bandpass filter applied with cutoffs at 0.25 Hz and 2.5 Hz, fed forward then backward. This centers the signal at the zero-line, eliminates the high and low frequency components and removes the phase delays. The zero crossings are then detected, and the peaks are identified as the maximum values in between an upward crossing and a downward crossing and the troughs as the minimum values in between a downward and an upward crossing. A second iteration uses the detected peaks to build a bandpass filter, centered at the heart rate frequency, calculated as the mean of the peak intervals of the first iteration. The bandpass filter has cutoff frequencies at twice the standard deviation of the heart rate on each side. The cutoffs are then $[HR - 2 \times std_{HR}]$ and $[HR + 2 \times std_{HR}]$, 'HR' being the heart rate and 'std $_{HR}$' its standard deviation. The zero crossings are identified during the second iteration and the final peaks and troughs represent, once again, the maximum and minimum values in between the upward and downward crossings (Chen, 2010) (Fig. 4.8).

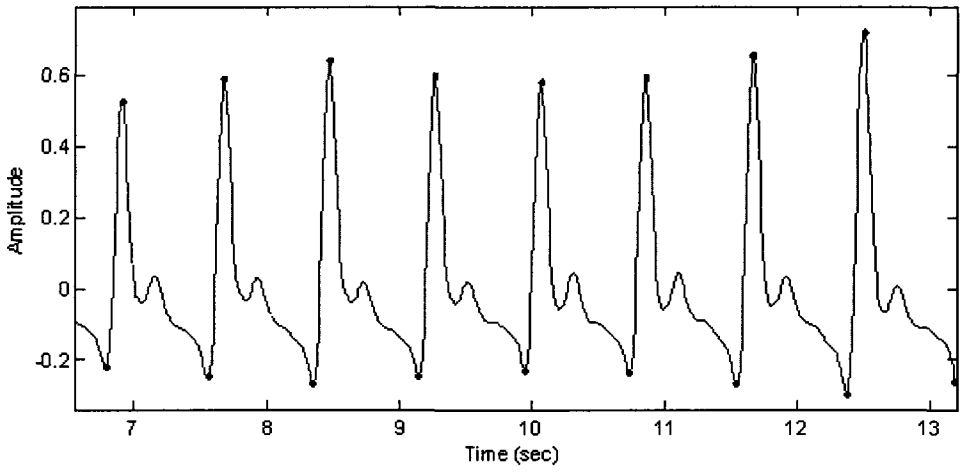


Figure 4.8 – Zoomed-in interval of the continuous BP signal, showing the detected peaks

4.3.6 SBP and DBP mapping

The systolic blood pressure corresponds to a specific heartbeat; the beat at which the blood pressure became higher than the deflating cuff pressure and the blood was capable of flowing in the brachial artery. This specific moment is accompanied with a well-identified Korotkoff sound that could be heard by trained observers using the stethoscope. Similarly, the diastolic blood pressure corresponds to a specific beat. This property represents the basis of the time mapping explained in this section.

Following the execution of the peak detection algorithm, the SBP and DBP values on the interpolated envelope of the OMW are matched to the SBP and DBP beats. This is done by finding the closest peak and trough to those values, respectively; the peak that is the closest to the SBP point on the envelope is tagged as SBP beat and the closest trough to the DBP point on the envelope is tagged as the DBP beat.

These points are then mapped, in time domain, to their respective corresponding beats on the constant pressure waveform (Fig. 4.9). The beat on the continuous waveform that occurs at the same time as the systolic beat identified by the oscillometric method will correspond to the systolic beat in our study, the same is done for the diastolic beat. This mapping method can be used to relate the oscillometric method to the auscultatory method (Fig. 2.2), but in this work, it is used to match beats from the waveforms recorded, in parallel, from the two arms.

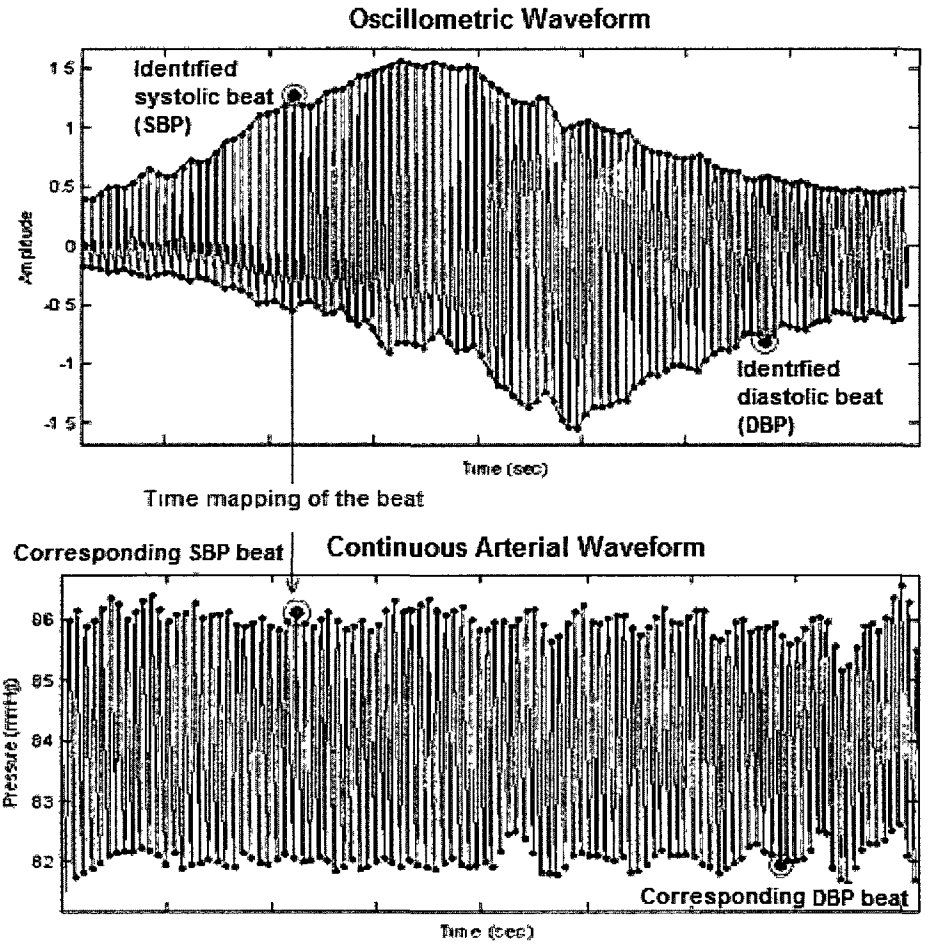


Figure 4.9 – The image on top shows the oscillometric waveform with the identified SBP and DBP peaks. The image below shows the synchronized continuous recording taken at a constant pressure and the mapped SBP and DBP peaks, from the oscillometric waveform, in time domain.

4.3.7 Calibration

The constant cuff pressure recording is uncalibrated. It is available in mmHg, centered around the value of the external pressure applied by the cuff on the subject's arm. This signal has to be calibrated in order to represent the real pressure exerted by the blood on the artery walls.

The calibration is possible at this point of the analysis (after mapping) because we now have the real (calibrated) values of the SBP and DBP points and can use these as calibration points. The calibration of the constant cuff pressure recording is done as follows (equation 4.3):

$$y_{\text{calibrated}} = \left[\frac{OMW_{SBP} - OMW_{DBP}}{uncalibrated_{SBP} - uncalibrated_{DBP}} \times (y_{\,uncalibrated} - uncalibrated_{DBP})\right] + uncalibrated_{DBP} \quad (4.3)$$

where OMW_{SBP} and OMW_{DBP} are the calibrated SBP and DBP values generated from the oscillometric method, $uncalibrated_{SBP}$ and $uncalibrated_{DBP}$, are the uncalibrated corresponding SBP and DBP points on the continuous recording, and the $y_{uncalibrated}$ and $y_{calibrated}$ indicate a given point in the continuous curve before and after calibration, respectively. Once applied, this formula results in a calibrated continuous recording (Fig. 4.10) from which we can obtain the calibrated SBP and DBP values for the duration of the measurement as well as the estimation of calibrated means, standard deviations, ranges and histograms. Calibration was conducted on every individual signal.

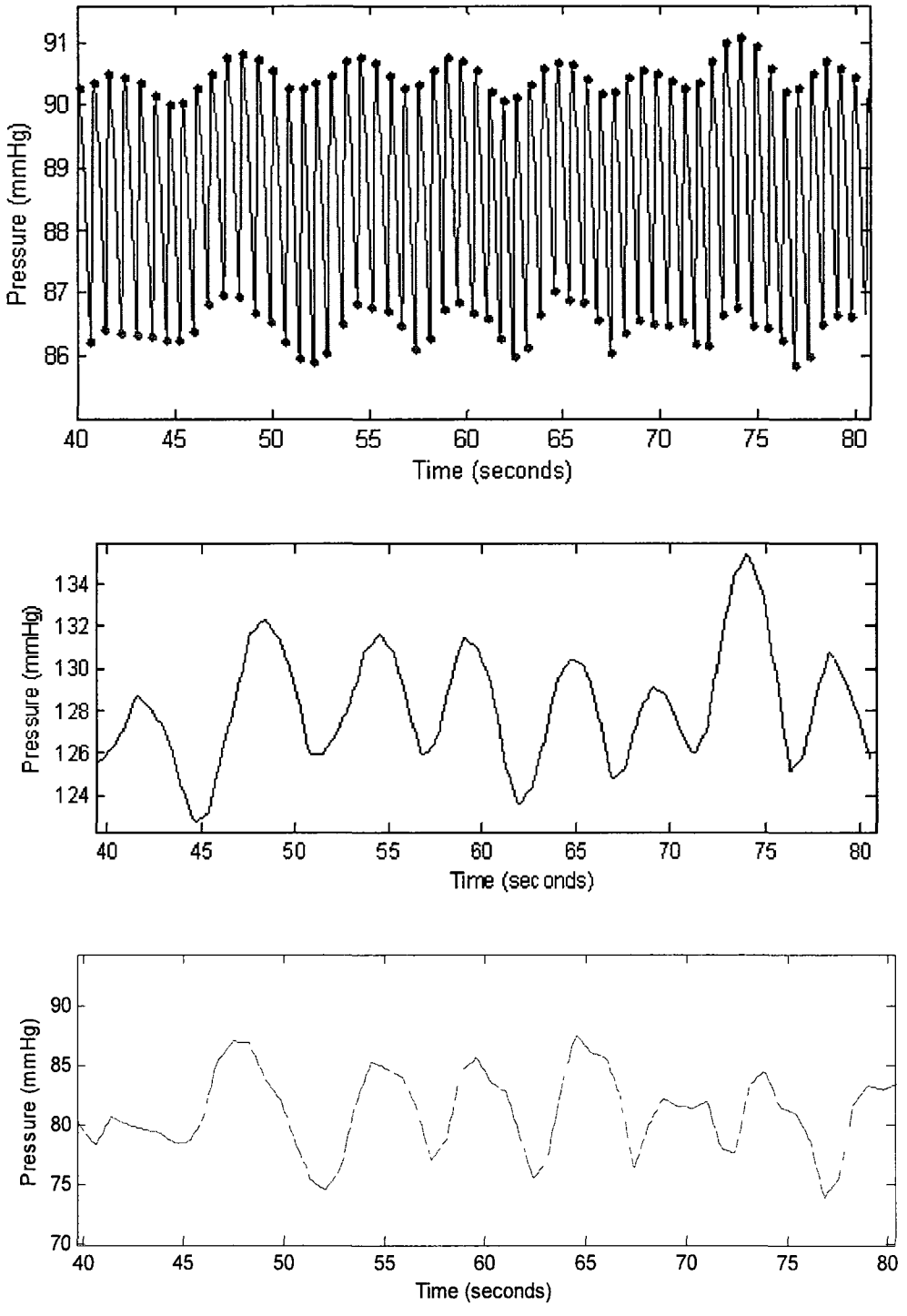


Figure 4.10 – Figure showing part of the uncalibrated continuous recording (on top). The middle graph represents the calibrated systolic peak line and the bottom graph, the diastolic peak line, after applying the calibration equation on the waveform in the top graph (Subject 120 T4).

4.4 Data Analysis

The calibrated SBP and DBP values obtained from the continuous BP recording over the duration of the measurement interval are analyzed by constructing the systolic and diastolic peak distribution histograms (as described in *Chapter 3, section 3.2.2*). The mean of the continuous SBP and DBP values in the BP waveform (INT_MEAN_{SBP} mean of the peaks over the 90-second interval of the measurement, and INT_MEAN_{DBP} mean of the troughs over the interval in time) is calculated. The variability is characterized by the standard deviation around these means (INT_STD_{SBP} and INT_STD_{SBP}). The SBP and DBP points estimated from the oscillometric measurement (i.e. OMW_{SBP} and OMW_{DBP}) are identified on the SBP and DBP histograms, respectively, in order to determine whether or not they are outliers. These three additional parameters for each of the SBP and DBP pressures augment the conventional oscillometric blood pressure measurement using information about blood pressure variability during the measurement interval.

The study collected data from 15 healthy subjects (6 readings per subject). A table (see Table A-1 in Appendix A) contains the readings for all individual subjects from the reference devices (UFIT or Omron), the respective interval means (INT_MEAN_{SBP} and INT_MEAN_{DBP}), interval standard deviations (INT_STD_{SBP} and INT_STD_{DBP}), acquired from the continuous waveform. It also contains the oscillometric estimates (OMW_{SBP}, OMW_{DBP}) and the difference between the interval means and their corresponding oscillometric values (i.e. $INT\_MEAN_{SBP} - OMW_{SBP}$ and $INT\_MEAN_{DBP} - OMW_{DBP}$).

Further statistical analysis (such as the paired t-test and Bland-Altman plots) was performed using Analyse-it® (Analyse®-it Software, Ltd, Leeds, UK).

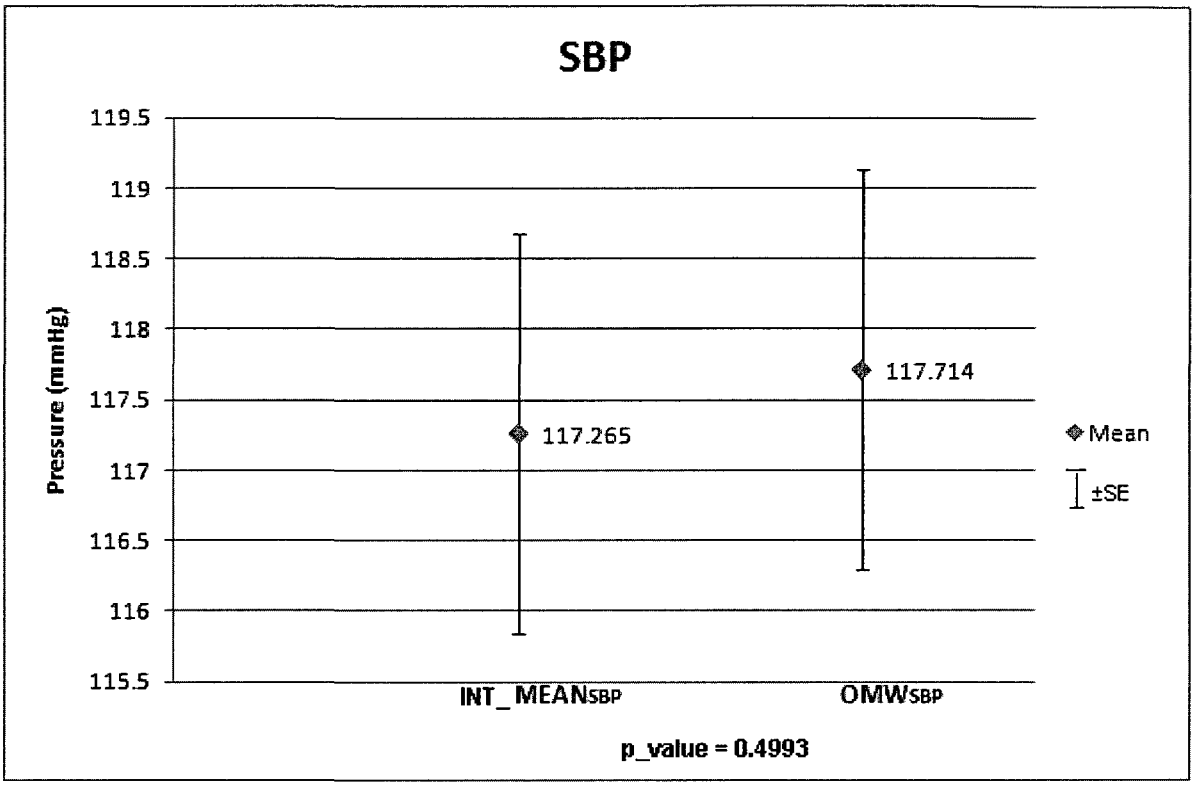
4.5 Partial validation

Definitive validation of the proposed technique requires extremely accurate intra-arterial measurements in order to verify that the estimated parameters reflect true arterial beat-to-beat SBP and DBP values. In the absence of intra-arterial recordings, we compared the SBP and DBP obtained from the two measurement techniques (i.e. INT_MEAN and OMW values), using a paired t-test (Fig.4.11), across data points from all subjects. Since the

oscillometric part of the approach went through verification in prior work and the output was comparable to the commercial device (Chen, 2010), it was used as a reference in this study. In addition to being reliable, it is practical since the methods are conducted simultaneously and on the two arms of the patient. Although the testing involves a comparison between two laboratory systems, it nonetheless provides partial validation of the proposed approach since the oscillometric method underwent independent verification.

The resulting p-values were 0.4993 for SBP and 0.8409 for DBP and the mean values were very similar (absolute mean difference = 0.449 mmHg for SBP, and 0.099 mmHg for DBP). The average INT_MEAN_{SBP} and INT_MEAN_{DBP} were 117.26 mmHg and 69.78 mmHg, respectively, and the average OMW_{SBP} and OMW_{DBP} were 117.71 and 69.88 mmHg, respectively.

The result of the t-test shows that there is no statistically significant difference between the means of the measurements obtained by standard oscillometry and the proposed method. We can then conclude that the proposed method does not introduce additional errors to the estimates of SBP and DBP when assessed over all subjects and all trials. However, in an individual subject and in a given trial, the proposed method often gives estimates that are quite different from the ones obtained by conventional oscillometry, which will be illustrated in sample cases below *(section 4.5.1)*. We will also illustrate how these augmented estimates can be more representative and more informative of the person's blood pressure.



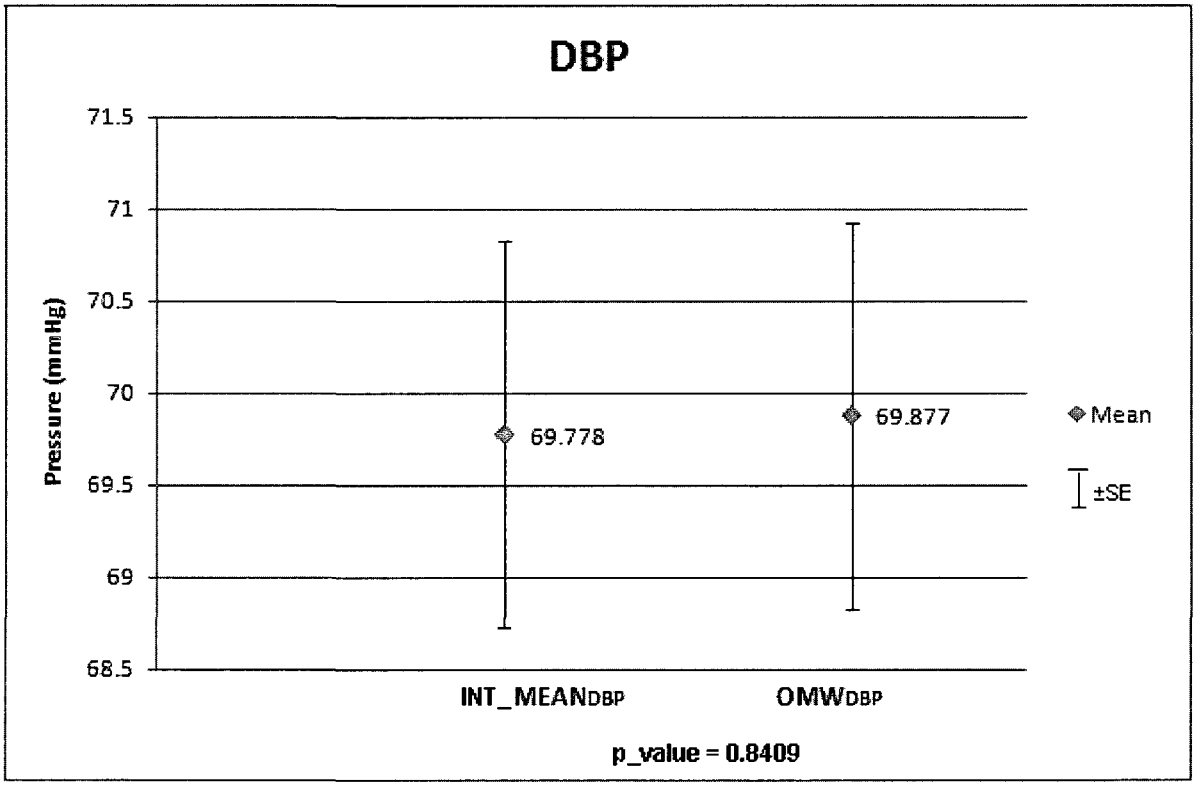


Figure 4.11 – Graphs showing the paired t-test results; average of the INT_MEAN_{SBP} ± Std Error and the OMW_{SBP} ± Std Error (top graph) and average of the INT_MEAN_{DBP} ± Std Error and the OMW_{DBP} ± Std Error (bottom graph), across all trials and all subjects.

In order to gain further insight on how well the two methods agree, the Bland-Altman test was performed. A primary application of this test is to compare two measurement methods designed to measure the same parameters (INT_MEAN_{SBP} vs. OMW_{SBP}, INT_MEAN_{DBP} vs. OMW_{DBP}). If the difference is normally distributed and if the bias is small enough, the test allows us to assume that the methods are in agreement.

The OMW_{SBP} and OMW_{DBP}, over all subjects and trials, and the INT_MEAN_{SBP} and INT_MEAN_{DBP} calculated using the continuous waveform were the variables in the test. The graphs, seen in Fig. 4.12, show the Bland-Altman agreement test output for (a) the SBP and (b) DBP values, respectively. The variables' means (mean of the two measurements, i.e. OMW and INT_MEAN) are plotted on the horizontal axis and the differences are plotted on the vertical axis, showing the amount of disagreement between the two measures, via the differences. Assuming normality, the bias was found to be insignificant in both cases (bias of 0.449 mmHg for SBP and 0.099 mmHg for DBP indicating that differences between the methods are effectively centered at zero. The proposed method is not introducing a significant trend of error compared to the oscillometric method and its results are not biased relative to oscillometric measurements. A more detailed report of the agreement tests can be found in Appendix B (Table B-1, B-2, Fig.B-1, B-2 for SBP, Table B-3, B-4, Fig.B-3, B-4 for DBP). Consequently, the Bland-Altman test performed on the data validates the agreement between the oscillometric method and the constant cuff method, when all the SBP and DBP values are taken into account.

Furthermore, the 95% limits of agreement are located at about +/- 11 mmHg. This confirms that the methods are outputting different results in individual trials. These differences are probably, at least partially, due to the underlying difference between the two compared measures: OMW represents the SBP or DBP at a random instant of time, while INT_MEAN represents the mean value of SBPs and DBPs over the whole measurement interval.

The Bland-Altman graphs below also show the outliers (in this case, values exceeding the 95% limits of agreement) and the points exceeding the ± 5 mmHg margin relative to the mean over the interval.

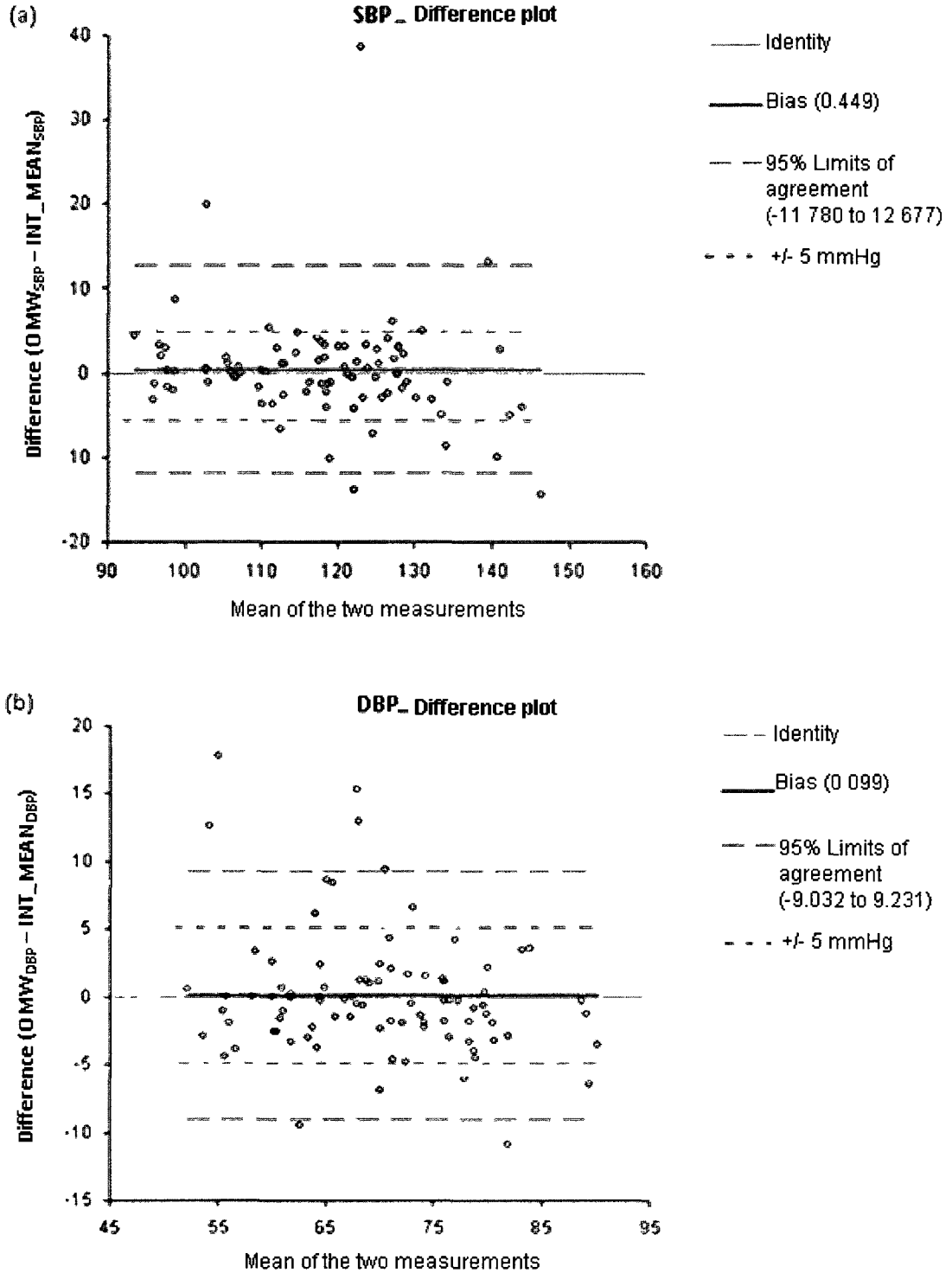


Figure 4.12 – Bland-Altman difference plot showing bias and limits of agreement between the SBP (a) and DBP (b) values estimated by the oscillometric method and the proposed method. The small bias values (bias = 0.449 (0.5%) for SBP and 0.099 (0.3%) for DBP) indicate that there is only a slight bias between the two methods.

The last part of the validation focuses on determining the degree of correlation of the BP variability between the right and left arms for the purpose of comparing the BP variability in the two arms. In order to do so, a small experiment was conducted on the 15 subjects. The data was collected by placing a cuff on both arms and by inflating the two cuffs to the same constant pressure (diastolic BP + 3 mmHg) for 60 seconds. The results showed a correlation of 98.59 ± 2.89% (mean ± standard deviation, range 90.49% – 99.9%, over 15 samples) between the interpolate peak lines signals (for SBP and DBP) acquired from both arms. This suggests that, at least in healthy subjects, the variability of the pulse waveform is synchronized and very similar in both arms.

4.6 Overall Results

Once again, as in *Chapter 3,* the percentage of oscillometric points (i.e. OMW_{SBP} and OMW_{DBP}) (1) located beyond ± 5 mmHg from the mean values over the interval and (2) that of the points located at a distance exceeding the (2σ) margin were evaluated in order to assess the contribution of blood pressure variability to measurement uncertainty. The first criterion corresponds to the maximum device accuracy error accepted by the SP10 standard (AAMI/ANSI-SP10, 2002) and the second is used to determine outliers. Locating the oscillometric values relative to the histogram could alert the user that the reading is potentially over- or underestimating their true blood pressure (represented by the mean over the measurement interval) and notifying them that a second reading may be needed to validate the first one.

On average, 82.02% of SBP readings and 85.39% of the DBP readings were within the ± 5 mmHg margin. The other 17.98% for SBP and 14.61 % for DBP (approximately 1 in 6 readings) exceeded one of the 2 margins described above.

Focusing on the ± 5 mmHg margin, and looking at the Bland-Altman graphs (Fig.4.12), 15.7% of the SBP points and 14.6% of the DBP points are found to exceed this margin. The results are in the same range as the previously obtained results from the analysis of the database signals for healthy subjects, *in Chapter 3, section 3.4.1,* showing an average of 29.1% for the SBP peaks and 13.5% for the DBP peaks located beyond ±5 mmHg from the mean. Like the results of *Chapter* 3, the outcome of the measurements described in this

chapter suggests that the natural variability results in individual beats exceeding the ± 5 mmHg margin in a substantial number of cases. Similarly, 11.24% of the SBP values and 4.49% of the DBP values were outliers, exceeding the (2σ) margin. The question remains as to how to differentiate between an artifactual value and a normal pulse that is an outlier due to high physiological variability. The question is not answered here, and the criteria that will allow us to trust/distrust a specific reading can be the subject of future investigation.

In order to gain further insight into the reliability of the reported interval means (INT_MEAN_{SBP} and INT_MEAN_{DPB}), the 95% statistical confidence interval of the mean was calculated. The estimated confidence interval of the mean over the population reflects the reliability of the 90-second interval mean estimation generated by the proposed approach. According to the *central limit theorem*, if the number of samples is large enough (usually more than 10 samples), the sample mean has a normal distribution regardless of the original distribution of the samples (Rice, 1995). In this study, the number of samples (SBP or DBP values) is comfortably large given the 90 second measurement interval. Therefore, the confidence interval with a confidence level of 95% (CI) can be defined as the mean ± $1.96\sigma/\sqrt{N}$, or approximately $\pm 2\sigma/\sqrt{N}$.

Over the 15 subjects and over all trials, the average CI's were:

$CI_{SBP} = mean_{SBP} \pm 0.99$ mmHg,

with the interval around the mean ranging from 0.28 to 5.37 mmHg

$CI_{DBP} = mean_{DBP} \pm 0.98$ mmHg,

with the interval around the mean ranging from 0.25 to 6.25 mmHg

Therefore, on average, in a given trial, we can be confident that the actual interval mean for SBP and DBP falls within less than ± 1 mmHg relative to the reported interval mean (95% of the time).

4.7 Selected cases

A few cases are used to illustrate the concept behind the augmented BP measures obtained with the proposed method, and show how it can be useful for detecting measurement outliers. Waveform graphs are shown for each case, the first identifying the measured beat in the continuous arterial pulse waveform, the second presenting calibrated interpolated peak line (for SBP or DBP), and the third identifying where the measured oscillometric value falls within the histogram of the SBP or DBP values over the measurement interval (e.g. Figures 4.13 - 415). The graphs are followed by a table that includes the conventional oscillometric measurement, the three measures provided by the proposed method, and observations on that case.

Case 1: Oscillometric DBP (OMW_{DBP}) measured at a low point, far below the mean diastolic peak value (INT_MEAN_{DBP}) during deep breathing (Table 4-2, Fig. 4.13-4.15)

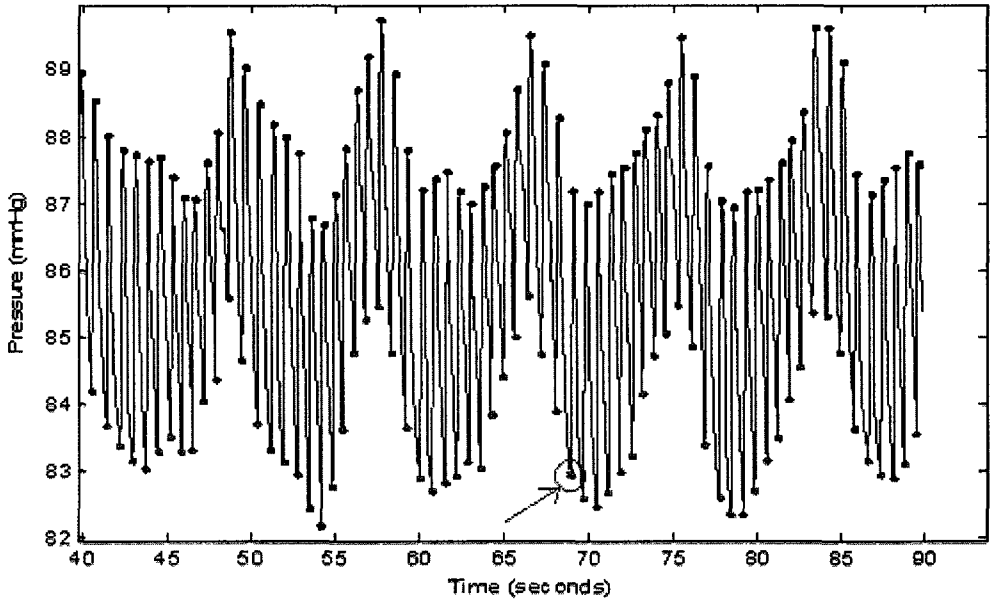


Figure 4.13 – Zoomed-in portion of the continuous recording of the subject's pulse waveform (between the 40th and 90th seconds), after applying the peak detection algorithm; the DBP measured using the oscillometric method is identified by the arrow and circle at around 69 seconds (Subject 122_T6).

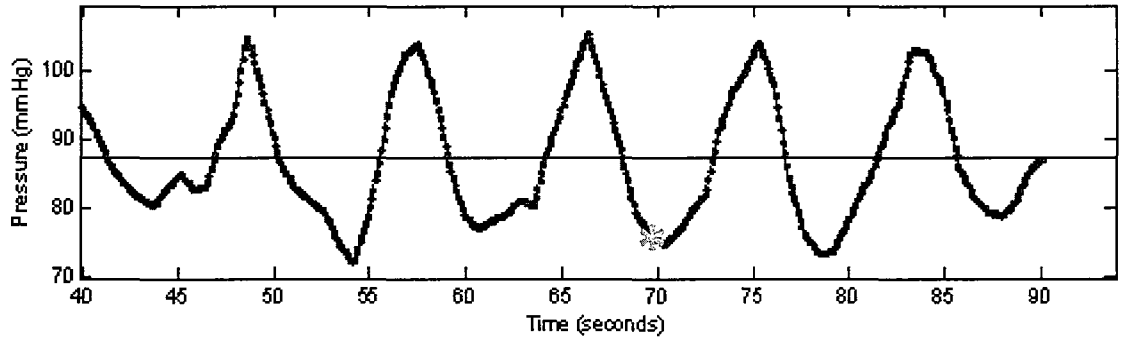


Figure 4.14 – The calibrated interpolated peak line joining the troughs of the continuous recording and the identified diastolic point (DBP) represented as a star (*) on the waveform at around 69 seconds. The horizontal line in the centre of the graph represents the INT_MEAN_{DBP} (Subject 122_T6).

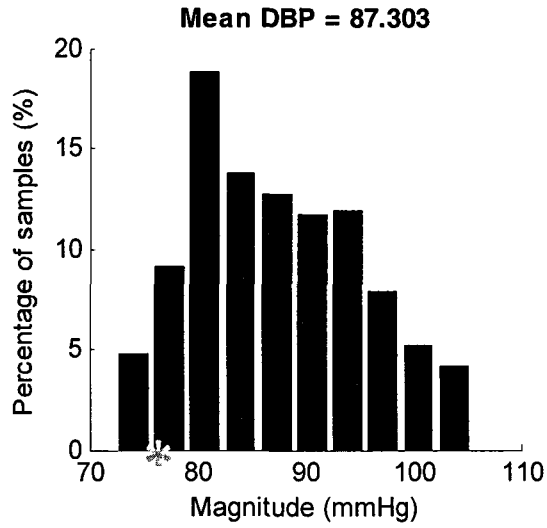


Figure 4.15 – Histogram of the distribution of the DBP values over the 90 second duration of the recording. The star (*) locates the oscillometric DBP estimate on the histogram, far from the mean (Subject 122_T6).

Table 4-2 – Data collected from case 1 (subject 122_T6)

Oscillometric Measurement	OMW_{DBP}	76.54 mmHg
Proposed Method	INT_MEAN_{DBP}	87.3 mmHg
	Confidence Interval (CI)	87.3 ± 1.58 mmHg
	INT_STD_{DBP} (σ)	7.79 mmHg
	Outlier	NO
Observations	Absolute difference (OMW_{DBP} – INT_MEAN_{DBP}) = 10.76 mmHg OMW_{DBP} is located within the (2σ) margin from the INT_MEAN_{DBP}	
Interpretation	By visual inspection, the beat at which the oscillometric DBP was estimated does not seem to be artifactual. It might be misrepresentative of the average BP over time but is accurately reflecting the BP at that instant in time. It is located at a point of high physiological variability in the fluctuating waveform.	

Case 2: Oscillometric DBP (OMW_{DBP}) measured at a high point, far above the INT_MEAN_{DBP} during normal breathing (Table 4.3, Fig. 4.16-4.18)

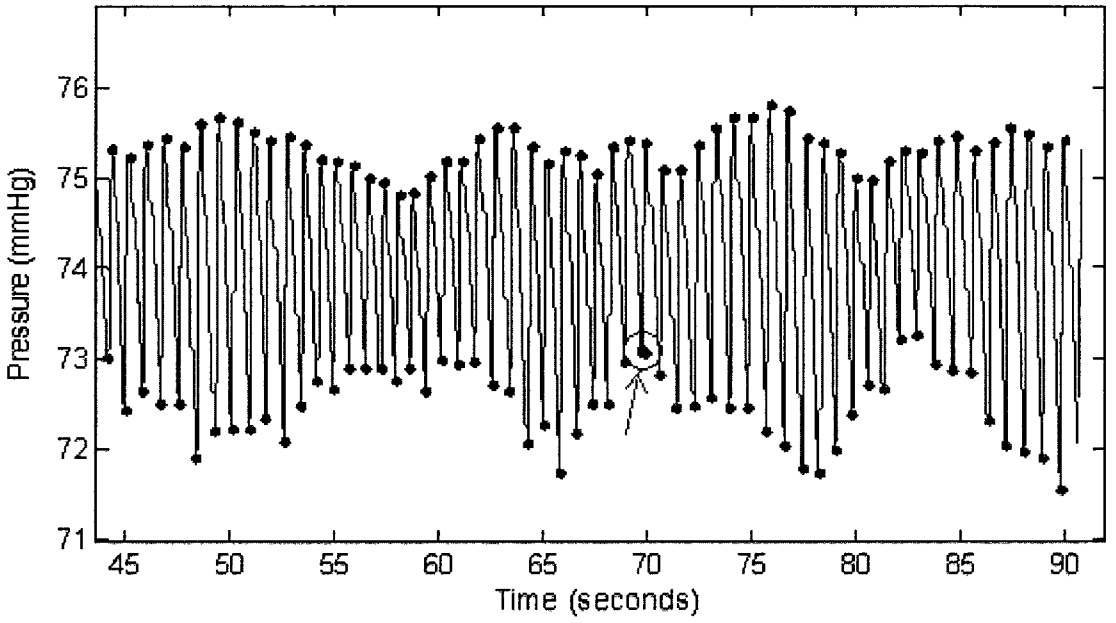


Figure 4.16 – Zoomed-in portion of the continuous recording of the subject's pulse waveform (between the 45th and 92th seconds), after applying the peak detection algorithm; the DBP measured using the oscillometric method is identified by the arrow and circle at around 70 seconds (Subject 114_T3).

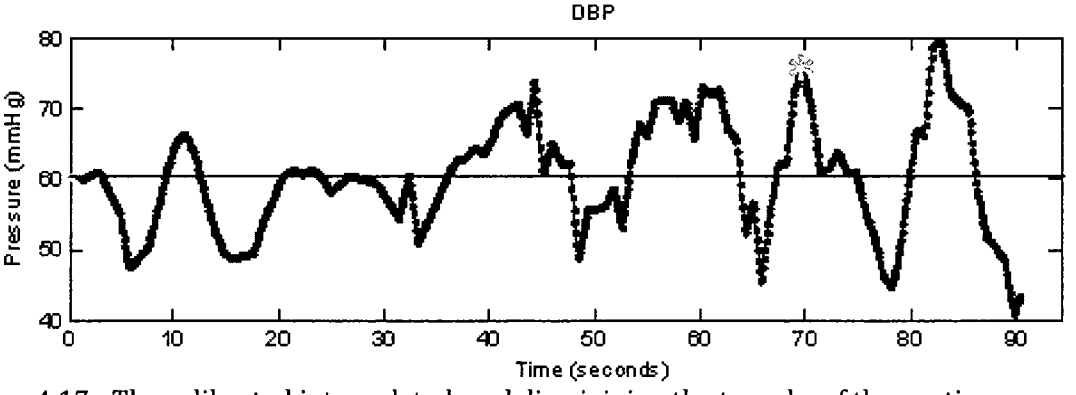


Figure 4.17 - The calibrated interpolated peak line joining the troughs of the continuous recording and the identified diastolic point (DBP) represented as a star (*) on the waveform. The horizontal line in the centre of the graph represents the INT_MEAN_{DBP} line (Subject 114_T3).

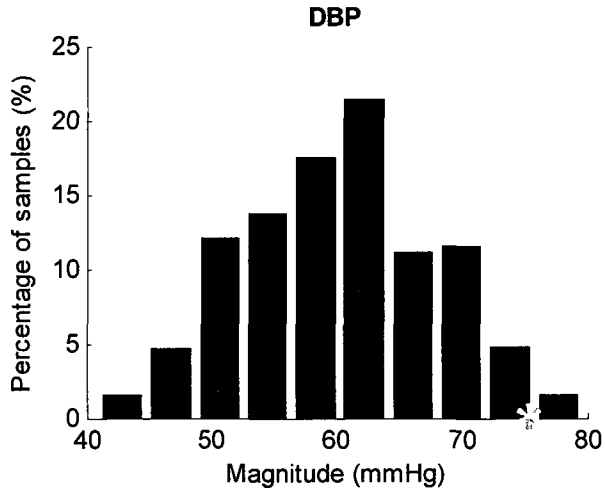


Figure 4.18– Histogram of the distribution of the DBP values over the 90 second duration of the recording. The star (*) locates the oscillometric DBP estimate on the histogram, far from the mean (Subject 114_T3).

Table 4-3 – Data collected from case 2 (subject 114_ T3)

Oscillometric Measurement	OMW_{DBP}	76.0 mmHg
Proposed Method	INT_MEAN_{DBP}	60.18 mmHg
	Confidence Interval (CI)	60.18 ± 1.6 mmHg
	INT_STD_{DBP} (σ)	7.69 mmHg
	Outlier	YES
Observations	Absolute difference (OMW_{DBP} – INT_MEAN_{DBP}) = 15.82 mmHg OMW_{DBP} is located beyond the (2σ) margin from the INT_MEAN_{DBP}	
Interpretation	According to the chosen criterion, the oscillometric value would be considered to be an outlier. By visual inspection, the beat at which the oscillometric DBP was estimated does not seem to be artifactual but related to the natural variation of the BP signal.	

Case 3: Oscillometric SBP (OMW_{SBP}) measured at a high point, far above INT_MEAN_{SBP} during deep breathing (Table 4.4, Fig. 4.19-4.21)

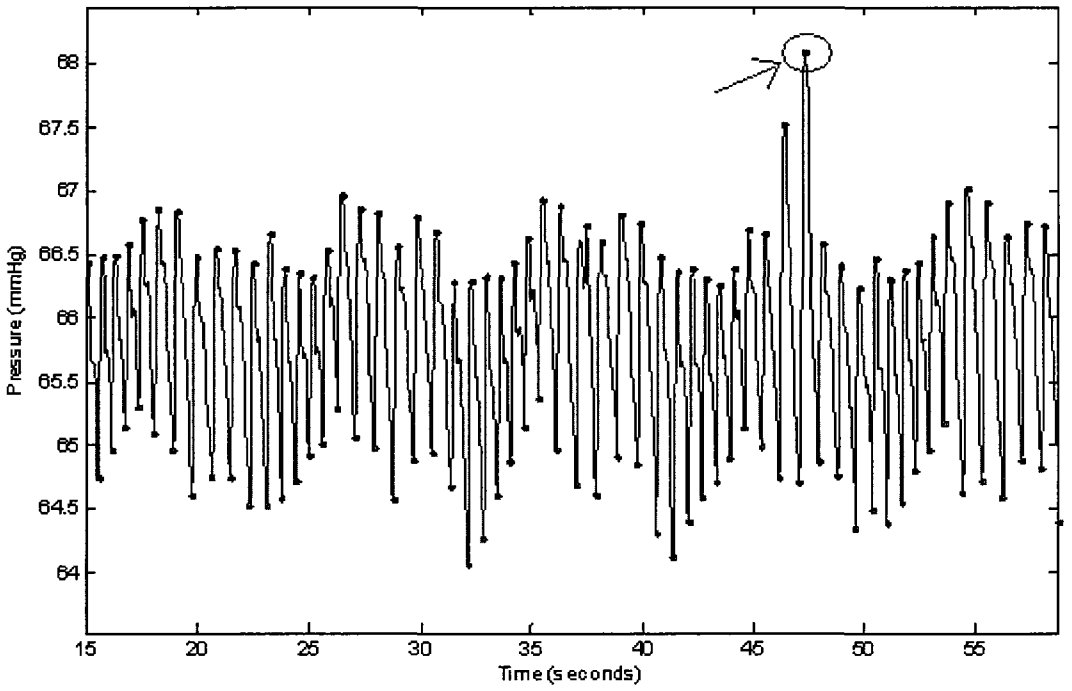


Figure 4.19 – Zoomed-in portion of the continuous recording of the subject's pulse waveform (between the 15th and 55th seconds), after applying the peak detection algorithm; the SBP measured using the oscillometric method is identified by the arrow and circle at around 47 seconds (Subject 115_T6).

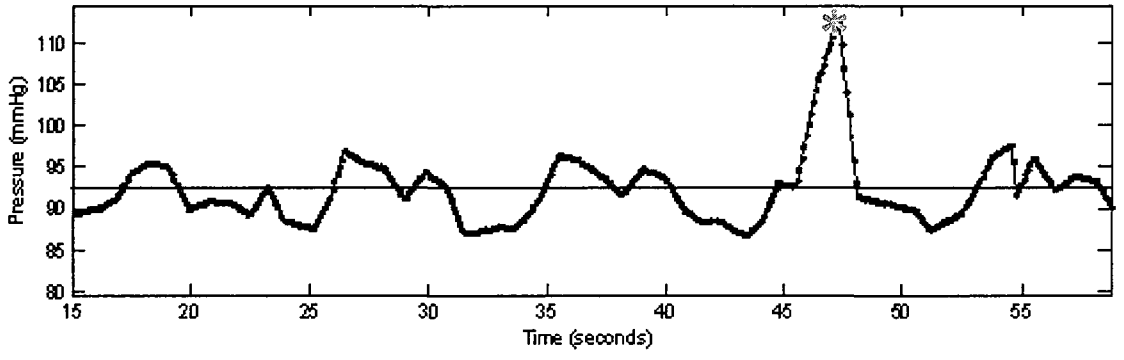


Figure 4.20 – The calibrated interpolated peak line joining the peaks of the continuous recording and the identified systolic point (SBP) represented as a star (*) on the waveform. The horizontal line in the centre of the graph represents the INT_MEAN_{SBP} line (Subject 115_T6).

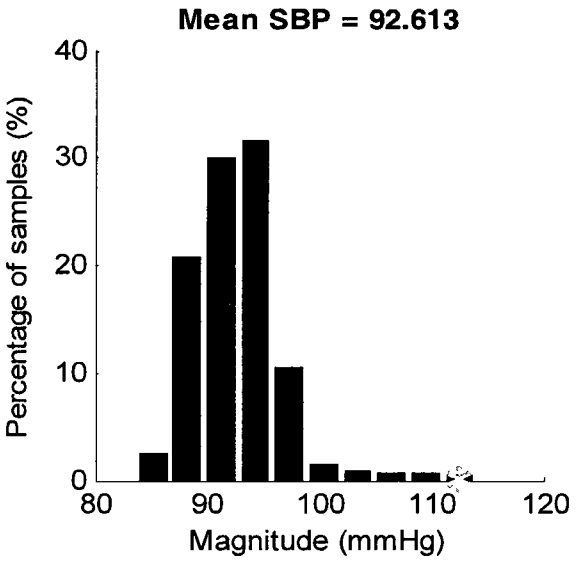


Figure 4.21 – Histogram of the distribution of the SBP values over the 90 second duration of the recording. The star (*) locates the oscillometric SBP estimate on the histogram, far from the mean (Subject 115_T6).

Table 4-4 – Data collected from case 3 (subject 115_ T6)

Oscillometric Measurement	OMW_{SBP}	112.65 mmHg
Proposed Method	INT_MEAN_{SBP}	92.61 mmHg
	Confidence Interval (CI)	92.61 ± 0.76 mmHg
	INT_STD_{SBP} (σ)	4.06 mmHg
	Outlier	YES
Observations	Absolute Difference (OMW_{SBP} – INT_MEAN_{SBP}) = 20.04 mmHg OMW_{SBP} is located beyond the (2σ) margin from the INT_MEAN_{SBP}	
Interpretation	According to the chosen criterion, the oscillometric value would be considered to be an outlier. By visual inspection, the beat at which the oscillometric SBP was estimated seems artifactual and not introduced by the regular variations. It could be the result of a movement or external artifact. This value is potentially misrepresentative of the average BP over time as well as the BP value at that instant. A repetition of the measurement would be useful.	

4.8 Extension of the proposed method: A single-cuff approach

The oscillometric waveform (OMW) is, in theory, the pulse waveform with a time-varying amplitude influenced by the deflating cuff pressure. Separating the OMW signal from the deflation curve and correcting for the distortion caused by the applied pressure on the BP pulse should result in a "flattened" pulse waveform comparable to that obtained from the continuous arterial pulse waveform recording.

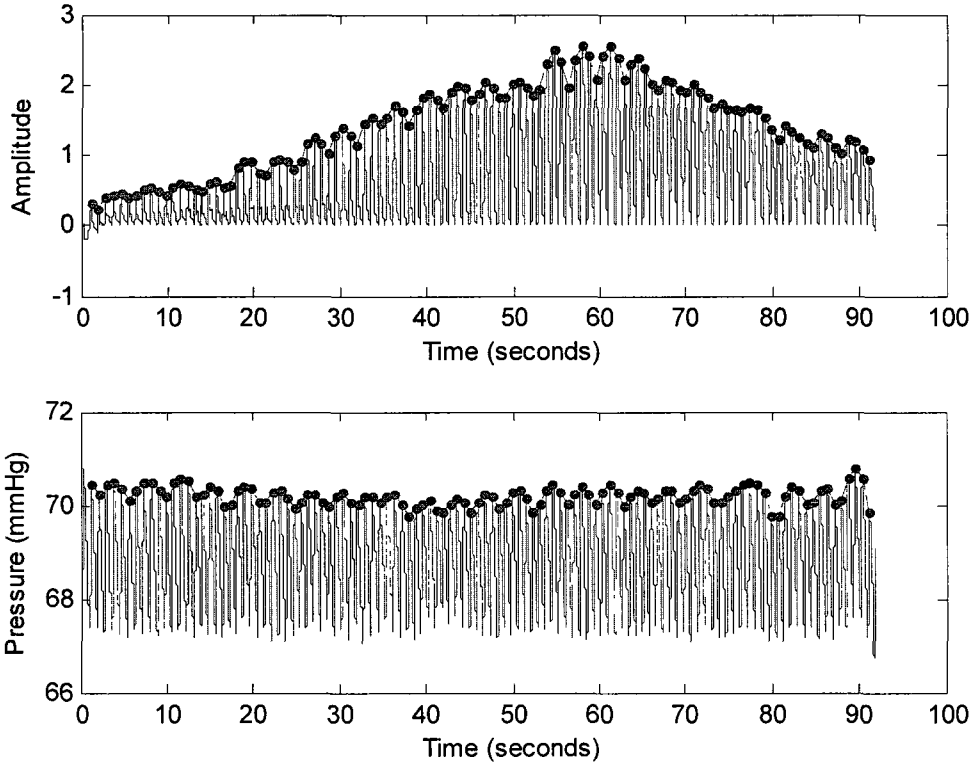


Figure 4.22 - Oscillometric waveform (top) and constant cuff continuous recording (bottom) plotted in parallel, after peak detection.

Fig. 4.22 shows the starting point of the approach. The oscillometric technique is executed on one arm. The aim is to retrieve, from the oscillometric waveform solely, a flat pulse waveform, by eliminating the effect of the deflating cuff on the arterial pressure. In this work, the continuous waveform is simultaneously recorded on the second arm, but only for the purpose of comparing and validating the output of the algorithm.

After applying the peak detection algorithm on the processed oscillometric waveform, the detected maxima (or minima in the case of diastolic) represent the systolic (or diastolic) peak line. The algorithm then finds the curve that best fits the slow trend of the

peak line by finding the coefficients of the polynomial *p(x)* of degree n that fits the data, *p(x(i))* to *y(i)*, in a least square sense.

$$p(x) = p_1 x^n + p_2 x^{n-1} + \ldots\ldots + p_n x + p_{n+1} \qquad (4.5)$$

It then returns the value of the polynomial of degree n evaluated at *x*. An example of the best curve fit is shown in Fig. 4.23.

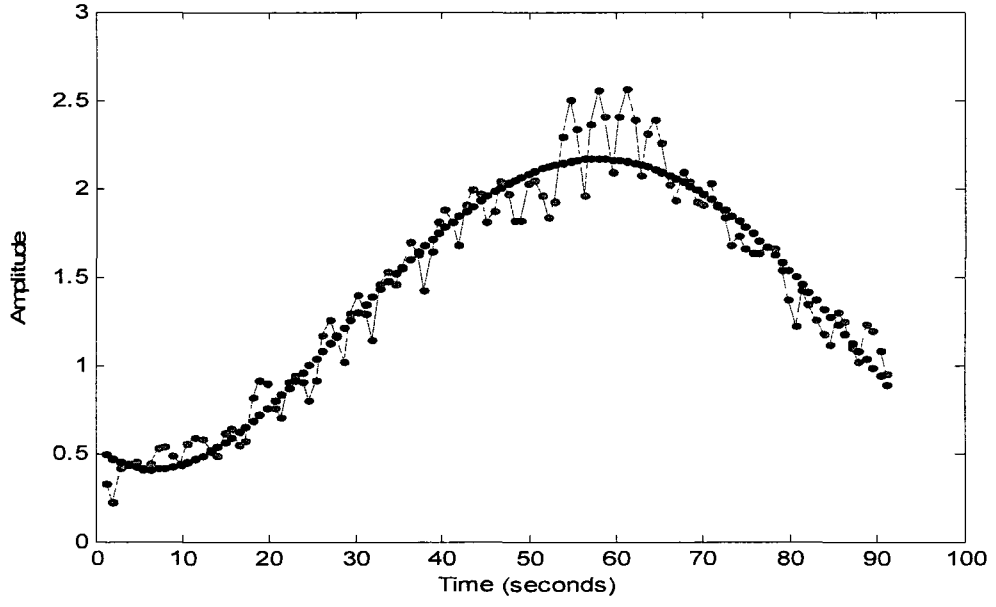


Figure 4.23 –Oscillometric peak line and its best fit curve after polynomial fitting

Subtracting the best fit curve from the oscillometric peak line results in a "flattened" oscillometric systolic peak line, shown in Fig. 4.24.

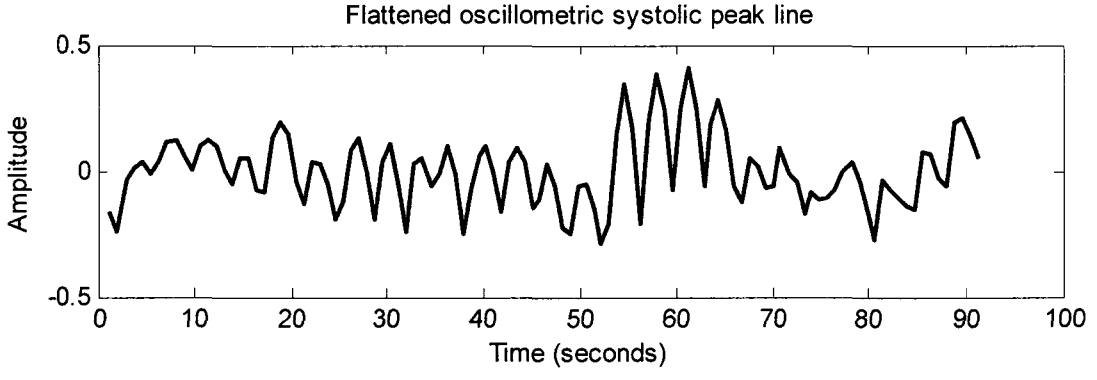


Figure 4.24 – Flattened oscillometric systolic peak line derived from a single cuff oscillometric measurement

4.8.1 Results

Considering that the main goal of the proposed method is to generate the distribution of the SBP and DBP values over the measurement interval, an attempt was made to obtain this distribution directly from the oscillometric waveform without having to use the second cuff. This extension of the proposed approach is tested by comparing the output (e.g. the "flattened" systolic peak line, Fig.4.24) to the continuous arterial systolic peak line (Fig. 4.25), obtained by interpolating the peaks of the constant cuff pressure pulse waveform, recorded using the second cuff. The 2 waveforms are overlapped for comparison in Fig. 4.26.

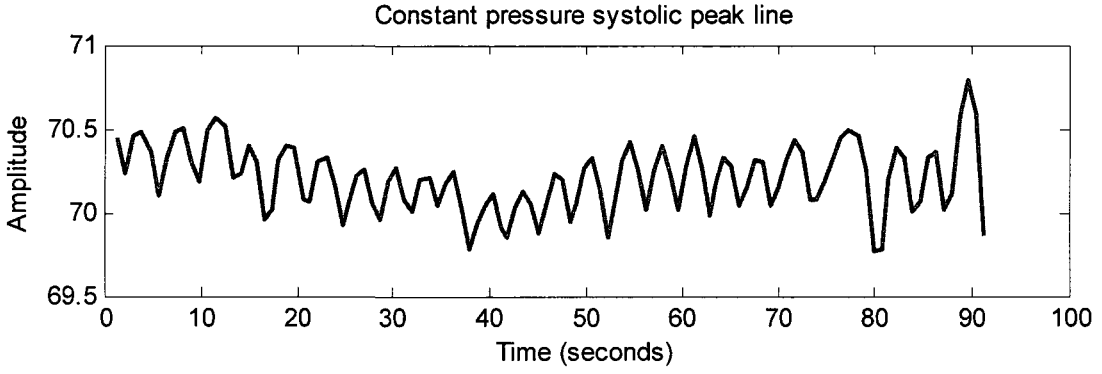


Figure 4.25 – Constant pressure systolic peak line (output of the constant cuff on the second arm)

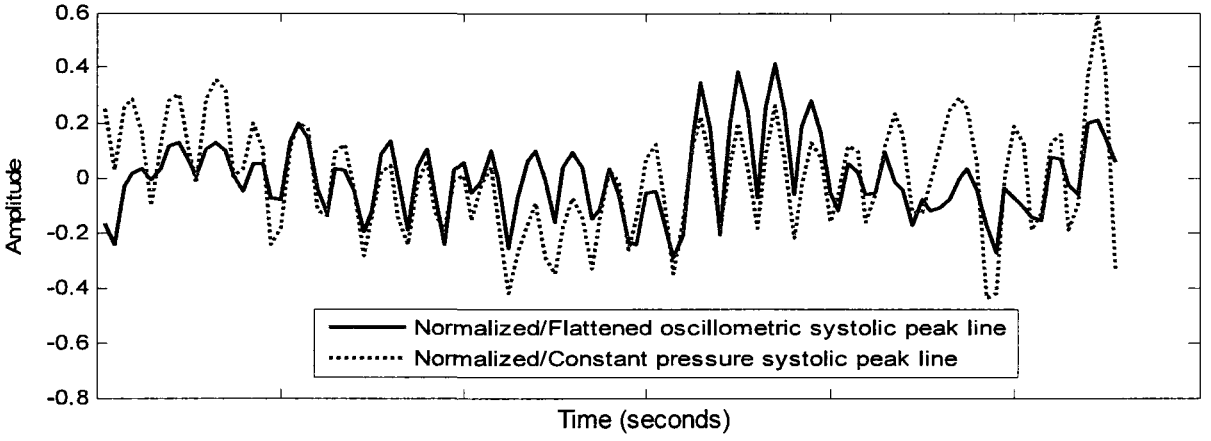


Figure 4.26 – Constant pressure waveform and "flattened" oscillometric systolic peak line superimposed (Correlation = 61.87%)

Similarly, the algorithm could retrieve the "flattened" diastolic peak line of the oscillometric waveform (Fig. 4.27).

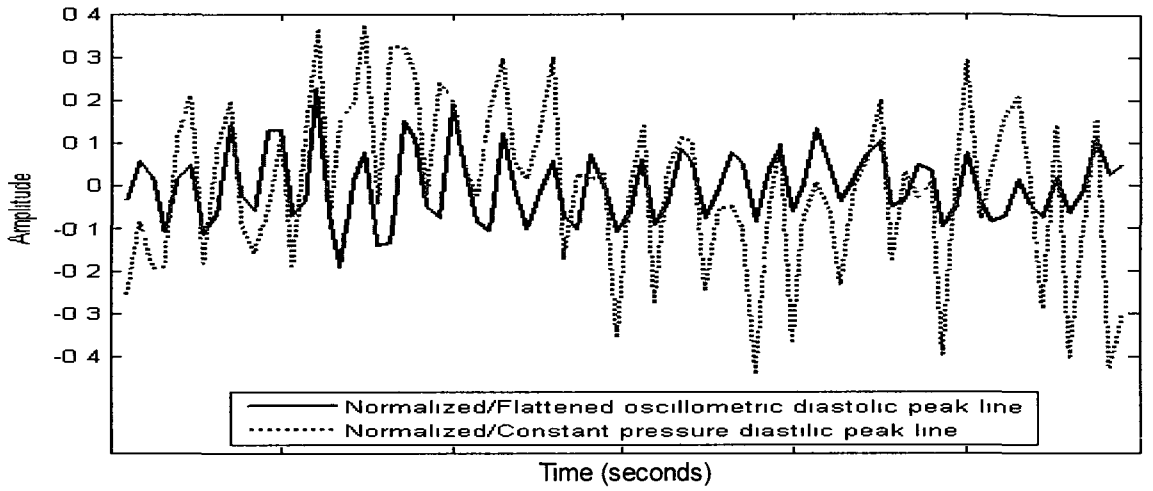


Figure 4.27 - Constant pressure and "flattened" oscillometric diastolic peak line superimposed (Correlation = 45.08%)

Although the examples shown in Figures 4.26 and 4.27 show relatively good correlation, on average, there was weak correlation between the two peak lines obtained by flattening in the oscillometric measurement and from the constant cuff pressure continuous waveform (19.17±15.66% for the systolic peak lines and 18.85±13.88% for the diastolic peak lines, values are in mean percentage ± SD). The range of the correlations was 0.38% to 74.29% for SBP and from 0.31% to 66.26% for DBP over 89 samples (6 readings per subject, 1 omitted sample). The majority of the samples (61.8% of the SBP and 59.5% of the DBP samples) showed weak correlation (below 20% correlation) between the two waveforms.

An example of a poorly correlated sample is presented in Fig. 4.28. The waveforms seem to more or less rise or fall together over the duration of the measurement; however, variable delays seem to affect one of the waveforms at various times, which significantly decrease the correlation values. These delays could be introduced by the method used to retrieve the flattened peak line from the OMW. Furthermore, the amplitude distortion seems to be greater at the beginning and the end of the flattened OMW signal in many cases; possibly due to the flattening method used. However, the change in pulse shape and amplitude in response to the pressure applied by the deflating cuff appears non-linear and could not be easily removed.

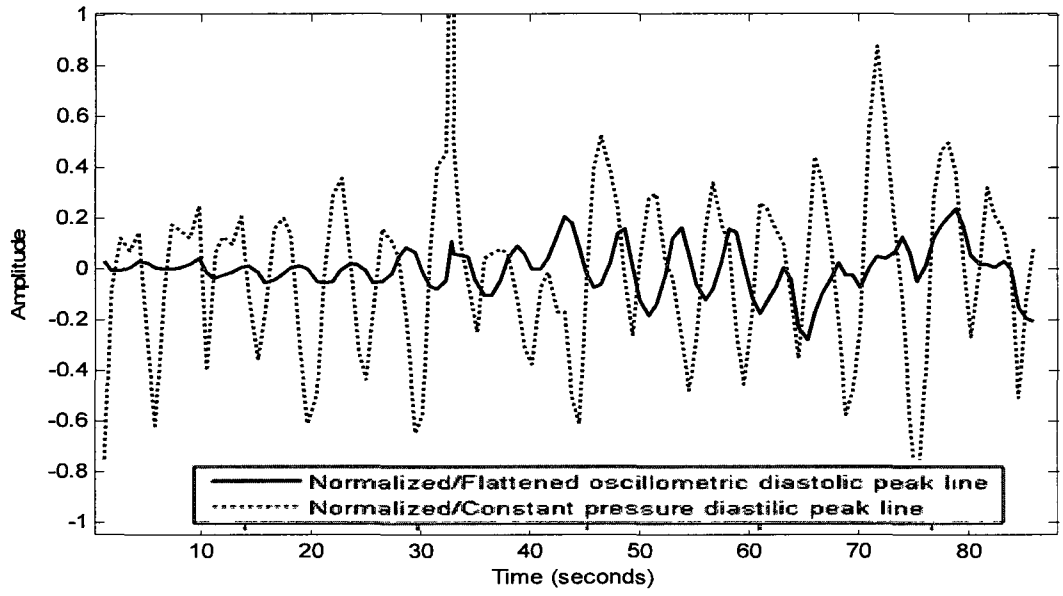


Figure 4.28 - Constant pressure waveform and "flattened" oscillometric diastolic peak line superimposed (Correlation = 1.88%)

In an attempt to improve the outcome of the single-cuff approach, an alternative approach was used to retrieve the continuous arterial pulse waveform from the oscillometric curve. Taking into consideration the non-linear amplification of the signal, algorithms were developed to multiply the amplitude of every peak of the oscillometric peak line by an amplification factor corresponding to the maximum peak amplitude value of the OMW curve divided by the amplitude of the peak in question. The results of this method were even poorer than the previously discussed approach and the distortion of the signal, after flattening, was more severe.

We speculate that a slower deflation rate in the oscillometric measurement could allow a better representation of the variability to be extracted from the oscillometric signal. Slower deflation may also help determine whether the variability in OMW is intrinsically different from that of the continuous pulse waveform or if it is modified during the extraction process. The drawback of slower deflation rate, however, is that it would lead a longer measurement interval which can be uncomfortable for the subjects.

Furthermore, different curve fitting or nonlinear detrending methods could lead to better flattening results. A nonlinear time-varying inverse filtering technique could potentially be an option since previous analysis determined the amplitude gain to be nonlinear.

4.9 Assumptions and limitations

The results of the proposed method presented in this chapter are compared to the values obtained using commercial devices (Biosign's UFIT and OMRON HEM-790IT). Ideally, the reference reading should have been the intra-arterial measurement. Given that such a complex method requiring trained personal and involving such a high-risk level is not available in the setting of this study, it is reasonable to rely on another technique (oscillometric using commercial devices in this case) for validation.

Another assumption is made when employing both arms in the analysis. The two-cuff approach assumes that the variability of a subject's blood pressure is identically reflected in both the right and left arm's waveform. By applying the same cuff pressure on both arms, our experimental results showed a very high correlation between the fluctuations of the two waveforms. Therefore, the information gathered from one arm may be used, at least in healthy subjects, together with the data collected from the second arm, to augment the estimation of the SBP and DBP values.

Being dependent on the oscillometric SBP and DBP estimates, the calibration of the continuous arterial pulse waveform might be subject to errors introduced by the oscillometric technique. The ratios used to estimate the SBP and DBP values in the oscillometric readings are found through least squares optimization (Chen, 2010). Having collected data for i subjects, let SBP_i and DBP_i be the reference SBP and DBP values generated by the commercial oscillometric device, respectively. The function $s_i(r_s)$ *and* $d_i(r_d)$ return the SBP and DBP values for a given subject i, respectively, with input systolic and diastolic ratios r_s and r_d. For a given ratio, the least squared error in a blood pressure reading across all subjects can be expressed as follows:

$$Err_{SBP} = \sum_{i=1}^{85} [SBP_i - s_i(r_s)]^2$$
$$Err_{DBP} = \sum_{i=1}^{85} [DBP_i - d_i(r_d)]^2 \quad (4.6)$$

Work has been done in order to find the ratios (r_s and r_d) that minimize the produced systolic (Err_{SBP}) and diastolic (Err_{DBP}) errors across the subjects of the experiment. The tested ratios ranged from 0 to 1. The error was evaluated empirically for the predefined set of ratios (Chen, 2010). Using a set of ratios results in a set of errors which can be considered points to which a polynomial function is fitted. The curve fitting allows for an interpolation of the points, and a minimum, representing the minimum least squared error, can then be estimated. The ratios could be much more accurate if tested over a wider range of recordings.

4.10 Conclusions

The proposed method presented in this chapter introduces a noninvasive technique that provides an augmented blood pressure measurement that includes the mean blood pressure over a 90-second period, an estimate of the variability over this period, and a determination whether or not the SBP and DBP estimated through the conventional oscillometric method are outlier values. This information cannot be obtained by means of a conventional oscillometric device.

Although definitive validation of the proposed approach can only be done by measuring the beat-to-beat BP in parallel through the gold standard invasive, intra-arterial technique, we were able to conduct partial validation through a combination of statistical comparisons between the proposed method and the conventional oscillometric technique, and by examining a few illustrative cases. The statistical comparisons showed that the proposed technique did not add significant error overall. Furthermore, the new approach did not contribute significant bias to the measurement probably due to the inter-method calibration. The examined test cases illustrated the potential value of the information

provided by the proposed method in situations where the oscillometric measurements appeared to poorly represent the subject's blood pressure.

Intrinsic physiological variability affects the blood pressure waveform and introduces fluctuations in the signal. Physiological variability and any device error would cause a significant increase of the single-measurement uncertainty in conventional oscillometry. This would be exasperated by the presence of even a small artifactual error.

In contrast, the mean SBP and DBP over the 90-second duration is a more representative value of the blood pressure, and is probably even stable over longer periods as has been established in previous analysis (*Chapter 3, section 3.3.1).*

In the case of detected outlier values, identifying whether they are due to artifacts or whether they are due to physiological variability is done visually for a few test cases in this study. However, algorithms could be potentially devised to automate the process. In that case, the proposed method would not only generate a flag that the reported oscillometric estimate is an outlier, but could ask the user to repeat the measurement or alert a clinician if needed.

The extension of the project to a single-cuff approach, if successful, would offer a more practical way to augment the blood pressure measurement, using variability information extracted from the "flattened" oscillometric blood pressure waveform. The conventional BP measurement procedure would remain completely unchanged and the developed algorithm would be in charge of collecting all the necessary data to estimate the SBP and DBP values as well as to characterize the variability of the signal over the period of the measurement. However, we have not yet been able to extract an accurate representation of BP variability from a single-cuff oscillometric waveform, and so this will be left for future work. It should be said that there are other possibilities to achieve two waveform measurements (oscillometric and continuous) that may be quite practical, and these will be discussed in the section on future work (*Chapter 5, section 5.3*).

Chapter 5. Conclusions

5.1 Summary of thesis work

The blood pressure (BP) of a human being is characterized by continuous fluctuations caused by various physiological factors and affecting the instantaneous systolic or diastolic blood pressure (SBP or DBP) readings taken at home or at the clinic. Therefore the level of confidence in conventional BP measurement is debatable in terms of its repeatability and how well it represents the person's blood pressure. The presented work is intended to address the problem by analyzing the effect of the variability on BP measurement and offering a new technique to potentially provide better and more representative measures of SBP and DBP level over a routine measurement interval.

This study evaluated the fluctuations of SBP and DBP in continuous recordings of the arterial pulse waveform over short periods of time, and quantified the statistical characteristics of these variations. It also compared them to the maximum error allowed for a BP measurement device according to current standards. As part of the analysis, the study also examined the contribution of the different frequency ranges to the BP variability. The results showed that this variability likely contributes significantly to the BP estimation uncertainty, as SBP and DBP values in a substantial proportion of heartbeats exceed ±5 mmHg relative to the mean value over the measurement interval.

The study proposes a new approach to augment the standard noninvasive SBP and DBP measurement using simultaneous recordings of oscillometric and continuous arterial pulse waveforms. The approach provides three measures to better characterize the BP: 1) The mean SBP or DBP over the measurement interval, 2) The standard deviation of the SBP or DBP over the measurement interval, and 3) An indicator as to whether or not the oscillometric estimate is an outlier. The first new measure is arguably a better representation of a person's blood pressure over the measurement interval than the SBP and DBP obtained at two random instants of time, the second characterizes the variability of SBP and DBP over the measurement interval, and the third could be useful to provide an alert to the user or to the device. In the future, it may be possible to determine if an outlier

was due to signal artifact, and so recommend repeating the measurement, or caused by an unusual physiological state.

The proposed approach was tested using a system equipped with two cuffs, each placed on one arm, and simultaneously inflated; the first cuff's pressure is kept constant while the other's deflates at a constant rate. An attempt was made to further improve the proposed approach by estimating the BP variability from a single cuff, conventional oscillometric measurement, but this extension of the approach was not very successful.

Recordings with healthy subjects using the two cuffs showed that the proposed approach does not add to the overall error and does not introduce bias relative to the conventional method. In a few illustrative cases, the proposed approach clearly showed that it could usefully augment the conventional measures of SBP and DBP which appear to poorly represent the person's BP over the measurement interval. The incorporation of this approach could augment the capabilities of existing oscillometric devices and so, could help address the unreliability and inconsistency of the BP measurements in current practice.

5.2 Contributions

The work presented in this thesis addresses the effect of natural variability in blood pressure on SBP and DBP measurements and its serious consequences on the measurement of BP.

The main contributions of this work are the following:

- Analysis of the beat-to-beat variability of SBP and DBP and characterization of this variability in relation to the maximum allowable device error as defined by current standards.
- Investigation of the contribution of the different frequency ranges of interest to BP variability and BP measurement uncertainty.
- A new proposed approach to augment the standard noninvasive SBP and DBP measurement using simultaneous recordings of the oscillometric and continuous arterial pulse waveforms, providing new measures to better characterize the subject's BP.

- A substantial contribution to the development of the prototype measurement device (hardware and software) used in the laboratory to run the experiments and test the new approach.

5.3 Future work

The progress of the project faced various limitations which could be addressed in future work. A major limitation was the restricted validation technique. The developed methodologies used the output of commercial devices as the reference readings. Instead continuous intra-arterial (invasive) recordings of beat-to-beat blood pressure would allow a more definitive validation. This does not render the work done in this thesis irrelevant, but implies that the technique probably needs further validation.

Testing on a larger population would definitely help provide more conclusive evidence for the proposed methodology; tests should be performed on patients with known medical conditions (especially those suffering from hypertension or hypotension). Furthermore, as previously mentioned, the oscillometric measurement in the study is based on ratios found through least squares optimization. This method relies on minimizing the error across a set of subjects of the experiment. The ratios would be more accurate if they were obtained from a greater number of subjects. In addition, studies could be undertaken in order to retrieve the MAP values, over time, from the continuous waveform and compare it with the oscillometric MAP value, generated using the Maximum Amplitude Algorithm (MAA). The continuous recording allows the calculation of the MAP for every single beat as well as the average MAP over the interval of measurement. This information could be useful and possibly more representative of the true varying mean arterial pressure than the reported oscillometric MAP.

Additional work is needed to improve the algorithm so that is will automatically distinguish between the outliers due to artifacts and those due to true physiological variability. Outliers due to artifacts are erroneous beats that need to be eliminated from the reading, while real unusual beats could carry important information about the subject's

health. This task could be achieved by developing a classification method and training it using simulated artifacts.

An important future extension of the work relates to the method used to obtain the continuous arterial pulse waveform. In this thesis, we obtain the blood pressure variability parameters from the continuous recording of the arterial pulse waveform at the output of a pressure cuff. Alternative cuffless approaches, such as plethysmography (*Chapter 2, section 2.4*), are possible and may be more convenient for the user.

Appendix A- Experiment Results

Table A-1 – Data collected from 15 healthy subjects containing readings from the reference devices (UFIT or Omron for subjects 111,112 and 113), the respective means (INT_MEAN_{SBP} and INT_MEAN_{DBP}) and standard deviations (INT_STD_{SBP} and INT_STD_{DBP}), acquired from the continuous waveform, and the oscillometric estimates (OMW_{SBP}, OMW_{DBP}) for 6 consecutive trials per subject.

SN	Trial #	UFIT reading		PROTOTYPE results							
		SBP	DBP	INT_MEAN SBP	INT_STD SBP	OMW SBP	Difference abs(INT_MEAN_SBP - OMW_SBP)	INT_MEAN DBP	INT_STD DBP	OMW DBP	Difference abs(INT_MEAN_DBP - OMW_DBP)
111	Reference	118	73								
	Trial 1	N/A	N/A	129 17	2 09	127 48	1 69	75 16	3 12	76 5	1 34
	Trial 2	N/A	N/A	124 44	2 95	128 59	4 15	74 5	2 61	73 16	1 34
	Trial 3	N/A	N/A	126 4	2 55	128 21	1 81	82 13	2 3	79 01	3 12
	Trial 4	N/A	N/A	131 6	2 45	128 67	2 93	75 42	3 56	76 6	1 18
	Trial 5	N/A	N/A	153 4	4 84	139 14	14 26	79 84	6 29	79 25	0 59
	Trial 6	N/A	N/A	124 55	4 24	125 85	1 3	73 53	6 65	66 68	6 85
						129.66				**75.20**	
112	Reference	91	65								
	Trial 1	N/A	N/A	112 37	3 34	113 51	1 14	71 18	2 3	68 9	2 28
	Trial 2	N/A	N/A	105 86	2 42	106 16	0 3	67 39	1 49	67 48	0 09
	Trial 3	N/A	N/A	97 32	2 44	97 87	0 55	66 59	2 34	65 13	1 46
	Trial 4	N/A	N/A	95 92	2 14	99 06	3 14	64 55	2 6	64 27	0 28
	Trial 5	N/A	N/A	102 5	2 41	102 97	0 47	64 81	2 05	62 56	2 25
	Trial 6	N/A	N/A	107 09	3 44	107 21	0 12	68 16	2 71	69 4	1 24
						104.46				**66.29**	
113	Reference	139	84								
	Trial 1	139	84	129 31	2 28	128 39	0 92	88 68	3 14	88 47	0 21
	Trial 2	151	88	123 99	3 63	130 14	6 15	73 55	4 01	68 98	4 57
	Trial 3	141	87	126 39	1 99	129 44	3 05	80 85	2 53	74 89	5 96
	Trial 4	144	86	126 38	2 64	129 55	3 17	75 26	2 84	73 05	2 21
	Trial 5	146	84	144 61	6 373	139 75	4 86	73 19	5 89	72 66	0 53
	Trial 6	110	71	116 52	4 54	119 92	3 4	68 9	6 084	71 28	2 38
						129.53				**74.89**	
114	Reference	111	72								
	Trial 1	111	72	106 42	1 24	106 09	0 33	71 85	1 05	73 53	1 68
	Trial 2	112	73	127 21	3 19	129 59	2 38	77 86	3 43	74 86	3
	Trial 3	118	78	128 4	4 94	133 57	5 17	60 18	7 69	75 48	15 3
	Trial 4	118	76	123 56	2 55	124 19	0 63	81 03	4 14	76 55	4 48
	Trial 5	114	74	128 07	4 16	121 05	7 02	78 85	6 22	81 01	2 16
	Trial 6	117	75	119 17	5 69	122 48	3 31	69 85	4 72	76 44	6 59
						122.83				**76.31**	
115	Reference	151	88								
	Trial 1	151	88	116 63	2 01	118 19	1 56	73 5	1 71	75 06	1 56
	Trial 2	N/A	N/A	116 64	8 072	115 63	1 01	79 91	4 52	76 63	3 28
	Trial 3	106	68	123 9	2 39	113 92	9 98	61 34	7 64	69 8	8 46
	Trial 4	115	72	112 05	2 45	116 95	4 9	70 01	3 3	72 1	2 09
	Trial 5	113	73	110 44	5 9	110 65	0 21	66 87	5 68	66 75	0 12
	Trial 6	108	66	92 61	4 06	112 65	20 04	64 79	4 33	61 82	2 97
						114.67				**70.36**	
116	Reference	98	59								
	Trial 1	98	59	94 24	2 25	102 99	8 75	59 89	3 59	59 96	0 07
	Trial 2	101	58	99 49	4 88	97 52	1 97	56 73	3 8	60 13	3 4
	Trial 3	101	60	98 48	6 65	97 01	1 47	61 47	5 33	59 94	1 53
	Trial 4	95	56	91 24	3 02	95 83	4 59	63 31	3 01	60 01	3 3
	Trial 5	105	60	97 38	1 99	94 32	3 06	58 05	2 8	58 08	0 03
	Trial 6	N/A	N/A	94 89	4 87	98 31	3 42	67 19	5 89	57 82	9 37
						97.66				**59.32**	
117	Reference	109	65								
	Trial 1	109	65	113 25	2 74	109 6	3 65	55 95	2 7	54 89	1 06
	Trial 2	103	63	103 46	2 4	102 5	0 96	57 73	2 71	53 41	4 32
	Trial 3	100	60	95 82	1 74	97 88	2 06	55 56	1 61	55 65	0 09
	Trial 4	102	62	96 62	2 34	95 37	1 25	56 86	2 1	54 95	1 91
	Trial 5	N/A	N/A	98 46	1 64	98 83	0 37	58 44	2 78	54 61	3 83
	Trial 6	98	58	111 84	8 83	108 24	3 6	51 77	5 22	52 41	0 64
	Trial 7 (extra)	98	58	102 39	3 51	103 05	0 66	54 99	3 19	52 1	2 89
						102.21				**54.00**	

118	Reference	122	73								
	Trial 1	122	73	111 98	5 77	113 25	1 27	60 94	5 11	67 15	6 21
	Trial 2	119	78	124 08	5 17	119 91	4 17	67 99	5 65	66 54	1 45
	Trial 3	117	71	113 08	3 8	115 64	2 56	67 61	3 27	68 84	1 23
	Trial 4	114	71	114 07	4 23	111 54	2 53	64 48	4 06	65 15	0 67
	Trial 5	115	69	119 49	4 43	117 41	2 08	68 15	3 96	67 68	0 47
	Trial 6	110	66	110 36	3 89	113 44	3 08	68 8	2 88	68 22	0 58
						115.20				**67.26**	
119	Reference	123	67								
	Trial 1	123	67	116 77	4 89	114 75	2 02	63 26	6 98	65 68	2 42
	Trial 2	127	71	128 77	7 86	115 14	13 63	47 75	8 91	60 37	12 62
	Trial 3	118	71	115 58	4 29	108 97	6 61	61 63	5 4	59 09	2 54
	Trial 4	126	74	109 84	3 02	110 24	0 4	64 35	3 96	64 4	0 05
	Trial 5	125	74	119 28	3 98	118 08	1 2	65 96	3 17	62 22	3 74
	Trial 6	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
						113.44				**62.35**	
120	Reference	138	84								
	Trial 1	138	84	104 93	1 51	106 1	1 17	89 77	2 17	88 5	1 27
	Trial 2	143	87	145 85	5 9	141 87	3 98	91 85	6 37	88 32	3 53
	Trial 3	136	82	139 5	2 47	142 44	2 94	92 51	2 7	86 13	6 38
	Trial 4	142	84	127 66	2 35	127 73	0 07	81 46	3 47	84 99	3 53
	Trial 5	148	85	135 87	3 59	130 93	4 94	82 05	4 33	85 63	3 58
	Trial 6	116	79	138 09	1 2	129 58	8 51	77 41	5 02	77 11	0 3
						129.78				**85.11**	
121	Reference	133	75								
	Trial 1	133	75	134 58	3 59	133 49	1 09	73 03	3 1	71 2	1 83
	Trial 2	111	72	117 28	1 56	119 24	1 96	74 94	2 57	70 05	4 89
	Trial 3	136	75	124 7	3 28	121 84	2 86	76 61	3 02	76 32	0 29
	Trial 4	121	73	108 12	3 19	113 64	5 52	69 34	5 57	70 51	1 17
	Trial 5	121	68	120 37	5 96	116 34	4 03	72 01	7 15	70 23	1 78
	Trial 6	126	75	103 59	1 27	142 18	38 59	60 61	8 78	69 3	8 69
						124.46				**71.27**	
122	Reference	134	89								
	Trial 1	134	89	121 36	2 24	121 25	0 11	79 07	1 23	78 32	0 75
	Trial 2	133	86	125 05	1 93	124 64	0 41	80 53	1 49	79 3	1 23
	Trial 3	133	84	121 66	2 05	123 08	1 42	81 42	1 68	79 58	1 84
	Trial 4	129	83	118 35	2 4	121 61	3 26	79 6	2 38	79 94	0 34
	Trial 5	130	83	121 93	2 18	125 36	3 43	79 23	1 83	77 43	1 8
	Trial 6	140	92	127 76	6 7	127 59	0 17	87 3	7 79	76 54	10 76
						123.92				**78.52**	
123	Reference										
	Trial 1	106	62	106 48	1 77	106 22	0 26	61 44	1 87	60 47	0 97
	Trial 2	106	62	104 31	1 74	106 21	1 9	60 48	2 49	61 14	0 66
	Trial 3	107	63	110 35	8 19	108 81	1 54	58 68	7 49	61 3	2 62
	Trial 4	110	66	106 67	2 12	106 3	0 37	61 75	2 59	61 74	0 01
	Trial 5	108	64	106 57	2 25	107 41	0 84	61 58	2 2	61 89	0 31
	Trial 6	106	64	123 66	1 64	126 44	2 78	61 35	1 82	58 85	2 5
						110.23				**60.90**	
124	Reference										
	Trial 1	121	74	116 03	2 57	119 73	3 7	76 13	2 49	75 84	0 29
	Trial 2	124	77	115 04	1 31	119 35	4 31	61 52	9 63	74 46	12 94
	Trial 3	121	76	120 33	3 12	121 2	0 87	74 9	3 77	79 17	4 27
	Trial 4	115	73	118 44	5 16	117 18	1 26	68 63	5 17	69 61	0 98
	Trial 5	121	75	119 64	4 06	118 57	1 07	83 33	4 49	80 51	2 82
	Trial 6	122	75	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
						119.21				**75.92**	
125	Reference										
	Trial 1	113	75	122 11	8 62	121 72	0 39	65 85	9 42	75 26	9 41
	Trial 2	123	77	127 18	4 5	124 27	2 91	68 72	4 66	73 1	4 38
	Trial 3	126	78	133 55	5 21	130 57	2 98	75 02	5 5	73 11	1 91
	Trial 4	128	80	127 53	2 49	125 24	2 29	80 6	3 05	76 71	3 89
	Trial 5	133	79	145 51	4 73	135 71	9 8	76 93	6 73	75 14	1 79
	Trial 6	132	78	132 79	2 27	146 02	13 23	45 98	2 68	63 77	17 79
						130.59				**72.85**	

Appendix B – Validation results

Table B-1 – Detailed Bland Altman Agreement test for the SBP values

Test	**Agreement - Altman Bland test** Systolic Blood Pressure **SBP Values** INT_MEAN_{SBP} v OMW_{SBP}	
Performed by	Karen	
n	89	(cases excluded: 1 due to missing values)
Correlation - absolute difference v average	0.20	
Bias	0.5%	
95% CI	-0.6%	to 1.6%
SE	0.55%	
t statistic	0.86	
DF	88	
p	0.3905	
SD of differences	5.2%	between single measurements
	95% Limits of agreement	95% CI
Lower	-9.7%	-11.5% to -7.8%
Upper	10.6%	8.7% to 12.5%

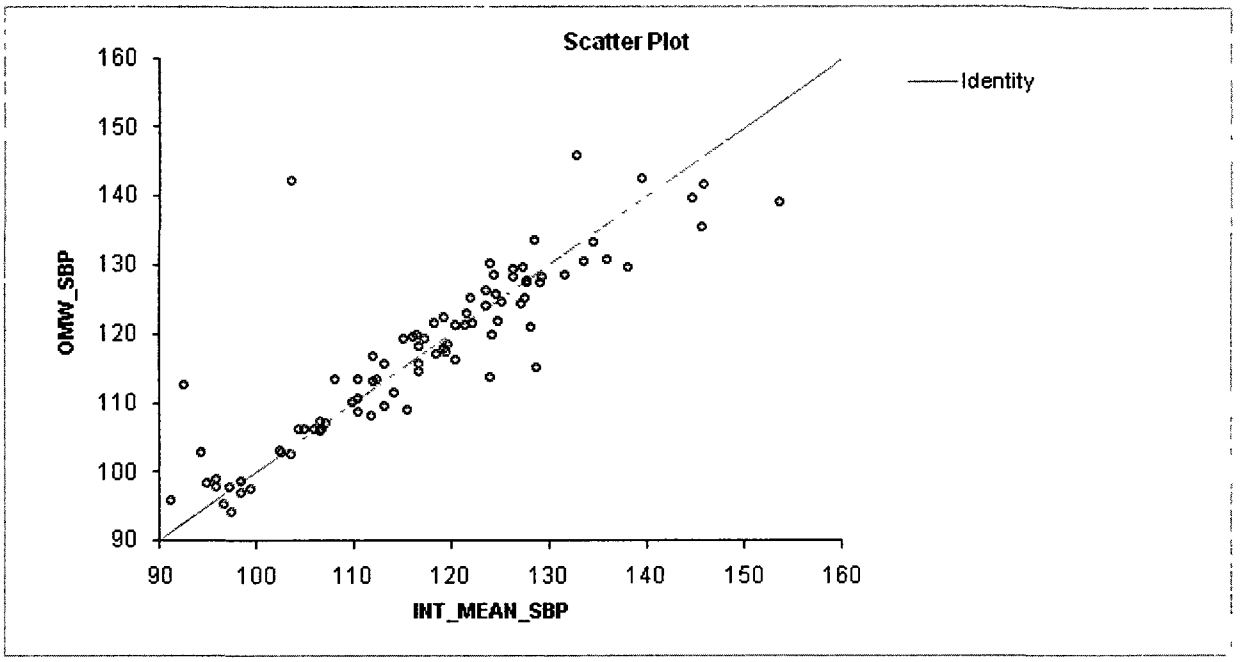


Figure B-1- Scatter plot of the OMW_{SBP} values as a function of INT_MEAN_{SBP}

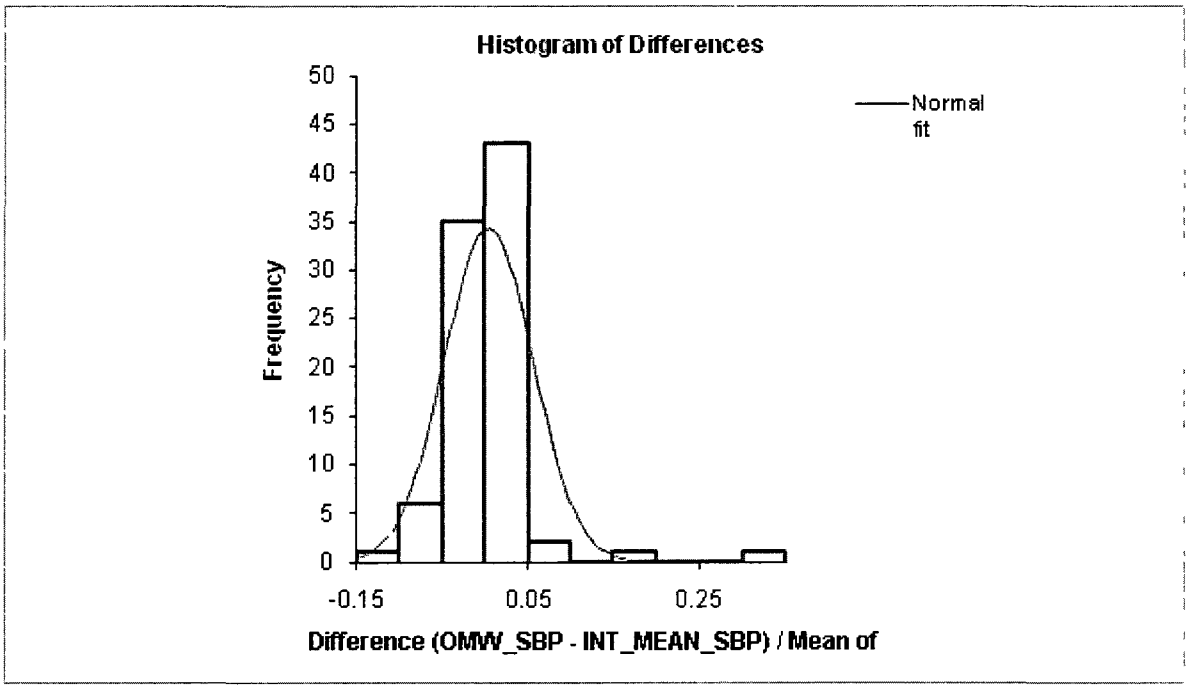


Figure B-2 – Histogram of Differences between the OMW_{SBP} and the INT_MEAN_{SBP} values over the mean of the difference

Table B-2 - Paired t-test between the mean SBP (INT_MEAN_{SBP}) values and the Oscillometric SBP values (OMW_{SBP}))

n	89	(cases excluded 1 due to missing values)

	n	Mean	SE	SD
INT_MEAN	89	117 265	1 4154	13 353
OMW	89	117,714	1,3099	12,358
Diff (INT_MEAN - OMW)	89	-0 449	0 6614	6,239

Mean difference	-0,449	
95% CI	-1 763	to 0 866
SE	0 6614	
t statistic	-0 68	
DF	88	
2-tailed p	0 4993	

Table B- 3 – Detailed Bland Altman Agreement test for the DBP values

Test	Agreement - Altman Bland test Diastolic Blood Pressure DBP Values INT_MEAN_{DBP} v OMW_{DBP}
Performed by	Karen

n	89	(cases excluded: 1 due to missing values)	
Correlation - absolute difference v average	-0.05		
Bias	0.3%		
95% CI	-1.2%	to 1.8%	
SE	0.76%		
t statistic	0.43		
DF	88		
p	0.6687		
SD of differences	7.2%	between single measurements	
	95% Limits of agreement	95% CI	
Lower	-13.8%	-16.4%	to -11.2%
Upper	14.5%	11.9%	to 17.1%

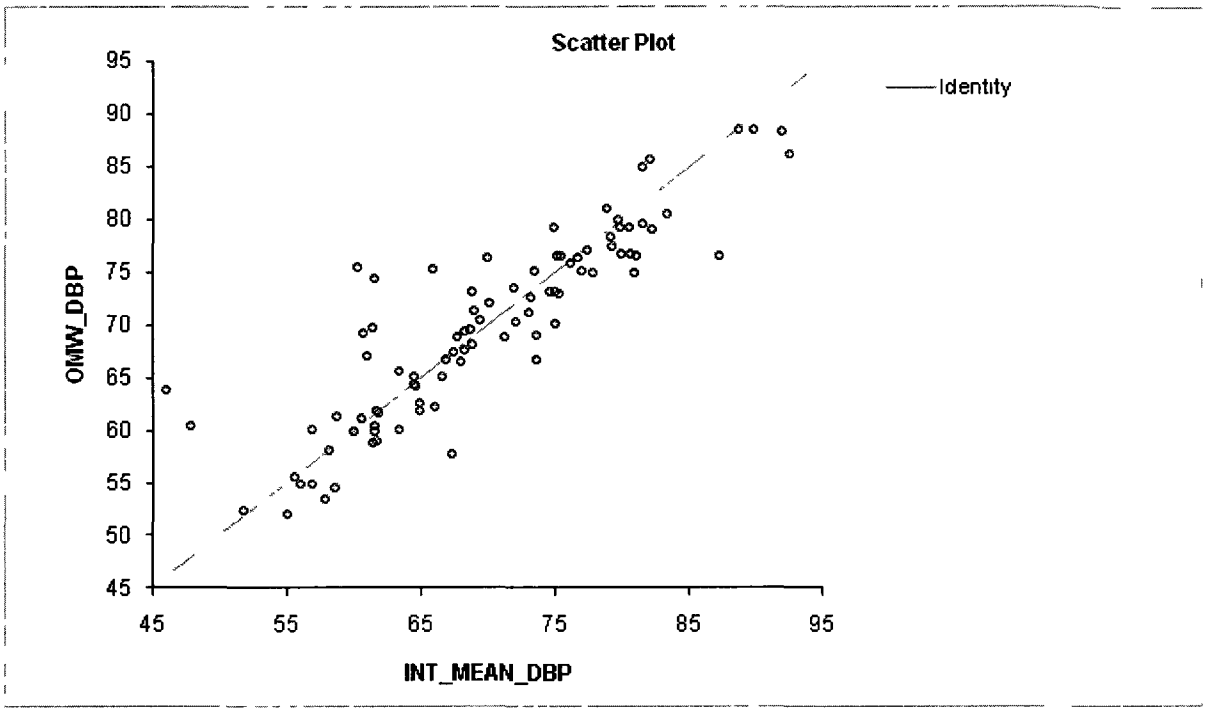


Figure B-3- Scatter plot of the OMW_{DBP} values as a function of INT_MEAN_{DBP}

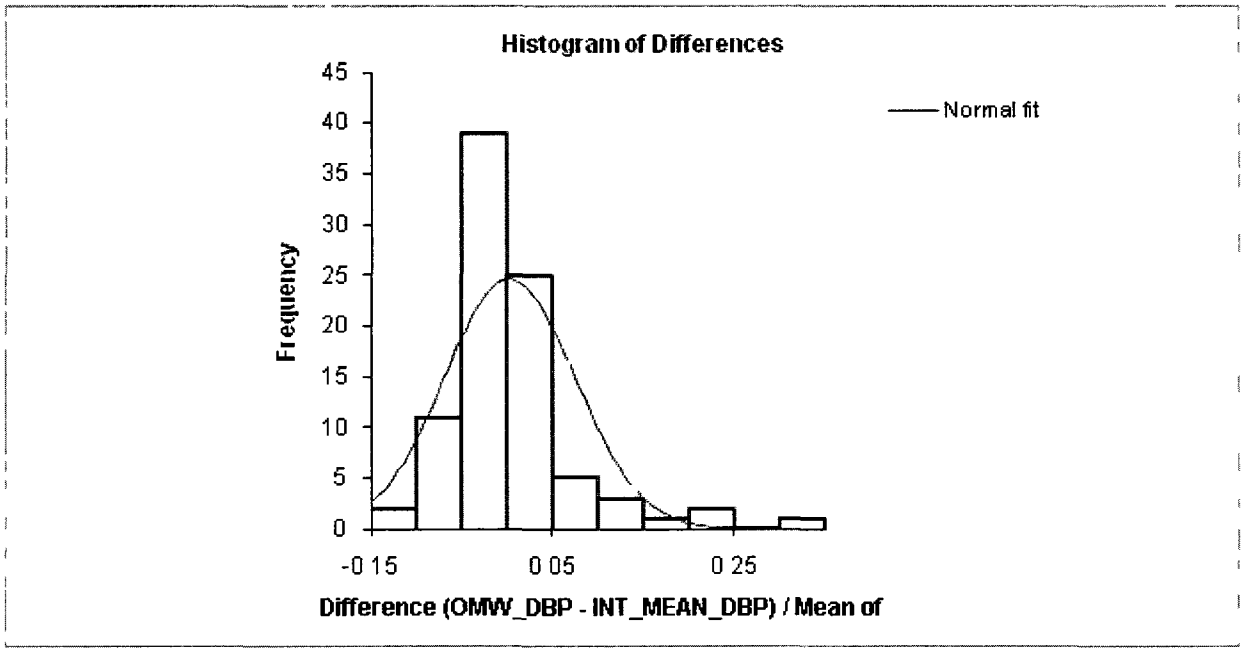


Figure B-4– Histogram of Differences between the OMW_{DBP} and the INT_MEAN_{DBP} values over the mean of the difference

Table B-4- Paired t-test between the mean SBP (INT_MEAN_{DBP}) values and the Oscillometric DBP values (OMW_{DBP}))

n	89	(cases excluded 1 due to missing values)

	n	Mean	SE	SD
INT_MEAN	89	69.778	1.0442	9.851
OMW	89	69.877	0.9400	8.868
Diff (INT_MEAN - OMW)	89	-0.099	0.4939	4.659

Mean difference	-0.099	
95% CI	-1.081	to 0.882
SE	0.4939	
t statistic	-0.20	
DF	88	
2-tailed p	0.8409	

Appendix C - Ethics approval notice

File Number: H02-10-01 Date (mm dd/yyyy): 06/09 2010

Université d'Ottawa University of Ottawa
Service de subventions de recherche et déontologie Research Grants and Ethics Services

Ethics Approval Notice

Health Sciences and Science REB

Principal Investigator / Supervisor / Co-investigator(s) / Student(s)

First Name	Last Name	Affiliation	Role
Hihmi	Dajani	Engineering / SITE	Principal Investigator
Saif	Ahmad	Medicine · Medicine	Co-investigator
Miodrag	Bolic	Engineering / Computer Science	Co-investigator
Voicu	Groza	Engineering / Computer Science	Co-investigator
Soojeong	Lee	Engineering / Computer Science	Co-investigator
Karen	Soueidan	Engineering / Computer Science	Co-investigator
Silu	Chen	Engineering / Computer Science	Student Researcher
Mohamad	Forouzanfar	Engineering / Computer Science	Student Researcher

File Number: H02-10-01

Type of Project: Professor

Title: Robust Noninvasive Blood Pressure Measurement

Approval Date (mm/dd/yyyy)	Expiry Date (mm/dd/yyyy)	Approval Type
06/09/2010	06/08/2011	Ia

(Ia: Approval, Ib: Approval for initial stage only)

Special Conditions / Comments:
N/A

1

550, rue Cumberland 550 Cumberland Street
Ottawa (Ontario) K1N 6N5 Canada Ottawa, Ontario K1N 6N5 Canada
(613) 562-5841 • Téléc. Fax (613) 562-5338
http: www.rges.uottawa.ca http: www ssrd uottawa.ca

File Number: H02-10-01 Date (mm/dd/yyyy): 06/09 2010

Université d'Ottawa University of Ottawa

Service de subventions de recherche et deontologie Research Grants and Ethics Services

This is to confirm that the University of Ottawa Research Ethics Board identified above, which operates in accordance with the Tri-Council Policy Statement and other applicable laws and regulations in Ontario, has examined and approved the application for ethical approval for the above named research project as of the Ethics Approval Date indicated for the period above and subject to the conditions listed the section above entitled "Special Conditions / Comments".

During the course of the study the protocol may not be modified without prior written approval from the REB except when necessary to remove subjects from immediate endangerment or when the modification(s) pertain to only administrative or logistical components of the study (e.g. change of telephone number). Investigators must also promptly alert the REB of any changes which increase the risk to participant(s), any changes which considerably affect the conduct of the project, all unanticipated and harmful events that occur, and new information that may negatively affect the conduct of the project and safety of the participant(s). Modifications to the project, information/consent documentation, and/or recruitment documentation, should be submitted to this office for approval using the "Modification to research project" form available at: http://www.rges.uottawa.ca/ethics/application_dwn.asp

Please submit an annual status report to the Protocol Officer 4 weeks before the above-referenced expiry date to either close the file or request a renewal of ethics approval. This document can be found at: http://www.rges.uottawa.ca/ethics/application_dwn.asp

If you have any questions, please do not hesitate to contact the Ethics Office at extension 5841 or by e-mail at: ethics@uOttawa.ca.

Germain Zongo
Protocol Officer for Ethics in Research
For Dr. Daniel Lagarec, Chair of the Health Sciences and Sciences REB

550, rue Cumberland 550 Cumberland Street
Ottawa (Ontario) K1N 6N5 Canada Ottawa, Ontario K1N 6N5 Canada
(613) 562-5841 • Télec. Fax (613) 562-5338
http://www.rges.uottawa.ca http: www.ssrd.uottawa.ca

Appendix D – Informed Consent Form

Blood Pressure Measurement in Healthy Subjects

The research project is being conducted by professors Hilmi Dajani, Voicu Groza, and Miodrag Bolic at the School of Information Technology and Engineering of the University of Ottawa. (Tel. (613) 562-5800, ext. 6217).

Purpose: This informed consent form is to make sure that you understand the nature of your involvement in this study, and to obtain your informed consent to participate in this study.

Procedure: You will be comfortably seated on a chair, and asked to stay relaxed with minimum movement. For one of the measurements, you will be asked to breath at a specified rhythm for the duration of the recording (90 seconds). A first cuff will be placed on one arm for constant BP measurement, a second cuff on the other arm for oscillometric inflation and the U-FIT wrist device on the wrist of the arm holding the oscillometric cuff. The entire recording session will last up to 60 minutes.

Subject description: Healthy adults with no known history of heart disease will be included.

Risks to participating: There is no danger or risk to health associated with this study. All procedures have been pre-tested and they have been used routinely for many years in hospitals, clinics, and laboratories.

Withdrawing from the study: Your participation in this study is voluntary. You may withdraw from the study at any time, by verbally informing the investigator or any of the researchers, even after signing the form. There will be no consequences following this action. If you have any concerns with regards to the ethical conduct of the study, you may contact the Protocol Officer for Ethics in Research, University of Ottawa, Tabaret Hall, 550 Cumberland Street, Room 159, Ottawa, ON K1N 6N5, tel. (613) 562-5841, email: ethics@uottawa.ca.

Compensation: You will not receive monetary compensation for this study.

Confidentiality: Any information, about you, collected during the study will be kept strictly confidential. Your name will not be associated with the collected data in any way. While the results will appear in student's dissertations and may also be published, you will not be identified.

The data collection will be conducted by Dr. Dajani, his graduate students, research fellows, or his research assistant. The records will be kept on computer files. The files will be password-protected. The data will be kept in Dr. Dajani's office when not in use and will be conserved for a maximum period of 10 years, after which the computer files will be deleted.

In closing: With your participation, you will be given a copy of this consent form. At the conclusion of the study, should you wish, you will be provided with a summary of the results. You may ask questions at any time, even after signing this consent form.

Signatures: I have read the above description of the study and understand the conditions of participation. My signature indicates that I agree to participate in the study.

Please indicate if you want to receive a summary of your results (please write YES or NO):

_____

Name of participant (please print name here):

_____

Participant's Signature:

_____ **Date:**

Researcher's Signature:

_____ **Date:**

2/2

References

AAMI/ANSI-SP10. (2002). *Manual, Electronic or Automated Sphygmomanometers.* ANSI (Americal National Standards Institute), AAMI (Association for the Advancement of Medical Instrumentation), Arlington.

Ahmad, S., Bolic, M., Dajani, H., Groza, V., Batkin, I., Chen, S., et al. (2010). Prototype of a Novel Integrated Blood Pressure and Electrocardiogram Device for Multi-Parameter Physiologic Monitoring. *I2MTC conference paper.* Texas, USA.

Ahmad, S.; Chen, S.; Soueidan, K.; Batkin, I.; Bolic, M.; Dajani, H.; Groza, V. (2010). A prototype of an integrated blood pressure and electrocardiogram device for multi-parameter physiologic monitoring. *I2MTC.* Ottawa.

Amoore, J. N. (2006). Extracting Oscillometric Pulses from the Cuff Pressure: Does it Affect the Pressures Determined by Oscillometric Blood Pressure Monitors? *Blood Pressure Monitoring , 11*, 269-279.

Ando, S., Dajani, H. R., & Floras, J. S. (1997). Frequency domain characteristics of muscle sympathetic nerve activity in heart failure and healthy humans. *Am J Physiol Regulatory Integrative Comp Physiol , 273*, 205-212.

Baker, P. D., Westenskow, D. R., & Kuck, K. (1997). Theoretical Analysis of Non-Invasive Oscillometric Maximum Amplitude Algorithm for Estimating Mean Blood Pressure. *Medical and Biological Engineering , 35*, 271-278.

Ball-llovera, A. (2003, September). An Experience in Implementing the Oscillometric Algorithm for the Non-Invasive Determination of Human Blood Pressure . *Proceeding of the 25th Annual Internation Conference of the IEEE Engineering in Medicine and Biology Society .*

Banet, M. J., & Visser, H. (2007). *Patent No. US 7,238,159 B2.* San Diego, California/USA.

Bobrie, G., Genes, N., Vaur, L., Clerson, P., Vaisse, B., & Mallion, J. (2001). Is "isolated home" hypertension as opposed to "isolated office" hypertension a sign of greater cardiovascular risk? *Arch Intern Med , 161*, 2205-2211.

Chen, S. (2010). *Improving algorithms for oscillometric blood pressure estimation by suppressing breathing effects.* MASc Thesis, Electrical and Computer Engineering, University of Ottawa, School of Information Technology and Engineering.

Clark, C. E., & Powell, R. J. (2002). The differential blood pressure sign in general practice: prevalence and prognostic value. *Family Practice , 19* (5), 439-441.

Dajani, H. R., & Leung, R. S. (2008). The measurement of blood pressure during sleep. *Proceedings of the IEEE International Workshop on Medical Measurement and Applications (MeMeA)*, (pp. 120-123). Ottawa.

Ding, C.-Y., Huang, C.-N., Yu, F.-M., & Chung, H.-Y. (2007). Continuous Blood Pressure Measurement System Based on Low Cuff Pressure Approach. *SICE Annual Conference 2007, Kagawa University*, (pp. 779-782). Japan.

Eguchi, K., Yacoub, M., Jhalani, J., Gerin, W., Schwartz, J., & Pickering, T. G. (2007). Consistency of Blood Pressure Differences Between the Left and Right Arms. *Archives of Internal Medicine , 167.*

Elghozi, J. L. (2008). Variabilité à court terme de la pression artérielle: physiologie et pharmacologie. *Annales Pharmaceutiques Françaises , 66*, 158-168.

Erlanger, J. (1916). Studies in Blood Pressure Estimations by Indirect Methods I. The Mecahnism of the Oscillatory Criteria. *American Journal of Physiology , 39*, 401-446.

Geddes, L. A., Voelz, M., Combs, C., Reiner, D., & Babbs, C. F. (1982). Characterization of the Oscillometric Method for Measuring Inderect Blood Pressure. *Annals of Biomedical Engineering , 10*, 271-280.

Gerin, W., Schwartz, A. R., Schwartz, J. E., Pickering, T. G., Davidson, K. W., Bress, J., et al. (2002). Limitations of current validation protocols for home blood pressure monitors for individual patients. *Blood Pressure Monitoring , 7* (6).

Gersak, G., Batagelj, V., & Drnovsek, J. (2006). *Oscillometric Virtual Instrument for Blood Pressure Measurement.* XVIII Imeko World Congres, Rio de Janeiro, Brazil.

Global Neighbourhood. (n.d.). Retrieved 06 20, 2010, from The circulatory system: http://www.globalneighbourhood.org/k-presentation.php

Gloster, J., & Perkins, E. S. (1963). The validity of the Imbert-Fick law as applied to applanation tonometry. *Exp. Eye Res , 2*, 274-283.

Gosse, P. (2002). Blood pressure should be measured in both arms on the first consultation. *Journal of Hypertension , 20*, 1045-1046.

Gould, B. A., Hornung, R. S., Kieso, H. A., Altman, D. G., & Raftery, E. B. (1985). Is the Blood Pressure the Same in Both Arms? *Clinical Cardiology , 8*, 423-426.

Handler, J. (2009). The importance of accurate blood pressure measurement. *The Permanente Journal , 13* (3).

Hansen, S., & Staber, M. (2006). Oscillometric blood pressure measurement used for calibration of the arterial tonometry method contributes significantly to error. *European Journal of Anaesthesiology , 23*, 781-787.

Jazbinsek, V., Luznik, J., & Trontelj, Z. (2005, November). Non-Invasive Blood Pressure Measurements: Separation of the ARterial Pressure Oscillometric Waveform from the Deflation Using Digital Filtering. *IFBME Proceedings of EMBEC'05 .*

Jones, D. W., & Hall, J. E. (2008). Hypertension - Pathways to success. *Hypertension, Editorial , 51*, 1249-1251.

Jones, D. W., & Hall, J. E. (2008). Pathways to Success. *Hypertension , 51*, 1249-1251.

Kimble, K. J., Darnall, R. A., Yelderman, M., Ariagno, R. L., & Ream, A. K. (1981). An automated oscillometric technique for estimating mean arterial pressure in critically ill newborns. *Anesthesiology , 54*, 423-425.

Klabunde, R. E. (2007). *Cardiovascular Physiology Concepts.* Ohio: Lippincott Williams & Wilkins.

Kohler, B. U., Hennig, C., & Orglmeister, R. (2003). QRS detection using Zero Crossing Counts. *Progress in Biomedical Research , 8*, 138-145.

Laitinen, T., Hartikainen, J., Niskanen, L., Geelen, G., & Lansimies, E. (1999). Sympathovagal balance is major determinant of short-term blood pressure variability in healthy subjects. *Am J Physio Heart Circ Physio , 276*, H1245-H1252.

Lau, E., Kaczorowski, J., Karwalajtys, T., Dolovich, L., Levine, M., & Chambers, L. (2006). Blood pressure awareness and self-monitoring practices among primary care elderly patients. *Canadian Pharmacists Journal CPJRPC , 139* (6), 34-41.

Lee, J. Y., Kim, J. K., & Yoon, G. (2002). Digital Envelope Detector for Blood Pressure Measurement Using an Oscillometric Method. *Journal of Medical Engineering & Technology , 26*, 117-121.

Lewington, S., Clarke, R., Qizilbash, N., Peto, R., & Collins, R. (2002). Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet , 360*, 1903-1913.

Maestri, R., Pinna, G. D., Robbi, E., Capomolla, S., & La Rovere, M. T. (2005). Noninvasive measurement of blood pressure variability: accuracy of the Finometer monitor and comparison with the Finapres device. *Physiological measurement , 26*, 1125-1136.

Manios, E., Vemmos, K., Tsivgoulis, G., Barlas, G., Eleni, K., Spengos, K., et al. (2007). Comparison of noninvasive oscillometric and intra-arterial blood pressure measurements in hyperacute stroke. *Blood Pressure Monitoring , 12* (3), 149-156.

Marey, E. J. (1876). Pression et vitesse du sang. . *Physiologie Experimentale* .

Matthys, K. S., Kalmar, A. F., Struys, M. M., Mortier, E. P., Avolio, A. P., Segers, P., et al. (2008). Long-term pressure monitoring with arterial applanation tonometry: A non-invasive alternative during clinical intervention? *Technology and Health Care , 16*, 183-193.

Matthys, K., & Pascal, V. (2002). Development and modelling of arterial applanation tonometry: A review. *Technology and Health Care , 10*, 65-76.

McCombie, D. B., Reisner, A. T., Asada, H. H., & Shaltis, P. (2008). *Patent No. US 2008/0039731 A1.* Boston/USA.

McGhee, B. H., & Bridges, M. E. (2002). Monitoring Arterial Blood Pressure: What you may not know. *Critical Care Nurse , 22*, 60-79.

Moraes, J., Cerulli, M., & Ng, P. S. (1999, September). Development of a New Oscillometric Blood Pressure Measurement System. *IEEE Computers and Cardiology* , 467-470.

Ng, K. G., & Small, C. F. (1994). Survey of Automated Noninvasive Blood Pressure Monitors. *Journal of Clinical Engineering , 33*, 452-475.

Ng, K. G., Ting, C. M., Yeo, J. H., Sim, K. W., Peh, W. L., Chua, N. H., et al. (2004). Progress on the development of the MediWatch ambulatory blood pressure monitor and related devices. *Blood Pressure Monitoring , 9*, 149-165.

Nichols, W. W., & O'Rourke, M. F. (1998). *McDonald's Blood Flow in Arteries: Theoretical, experimental and clinical principles* (Fourth Edition ed.). London, Britain: Arnold, Hodder Headline Group.

O'Brien, E. T., Petrie, J. C., Littler, W. A., & de Swiet, M. (1986). The British Hypertension Society Recommendations on blood pressure measurement. *British Medical Journal , 293*, 611-615.

Omboni, S., Parati, G., Frattola, A., Mutti, E., Di Rienzo, M., Castiglioni, P., et al. (1993). Spectral and sequence analysis of finger blood pressure variability. Comparison with analysis of intra-arterial recordings. *Hypertension , 22*, 26-33.

Parati, G., Bilo, G., Vettorello, M., Groppelli, A., Maronati, A., Tortorici, E., et al. (2003). Assessment of overall blood pressure variability and its different components. . *Blood Pressure Monitoring , 8*, 155-159.

Parati, G., Saul, J. P., Di Rienzo, M., & Mancia, G. (1995). Spectral analysis of blood pressure and heart rate variability in evaluating cardiovascular regulation. A critical appraisal. *Hypertension , 25*, 1276-1286.

Peterson, W. D., Skramsted, D. A., & Glumac, D. E. (2005). *Phoenix Ambulatory Blood Pressure Monitor Project* . University of Minnesota, Mayo Memorial Building, Minnesota.

PhysioNet: The Research resource for complex physiological signals. (n.d.). (PhysioNet) Retrieved January 25, 2010, from PhysioNet: http://physionet.org/physiobank/database/#multi

PhysioNet: The Research resource for complex physiological signals. (n.d.). (Physionet) Retrieved January 25, 2010, from http://physionet.org/physiobank/database/#multi

Pimenta, E., Oparil, S., (2009). Role of aliskiren in cardio-renal protection and use in hypertensives with multiple risk factors. *Vascular Health and Risk Management* 5 (1), 453-463.

Pickering, T., Hall, J., Appel, L., Falkner, B., Graves, J., Hill, M., et al. (2005). Recommendations for Blood Pressure Measurement in Humans and Experimental Animals. Part1: Blood Pressure Measurement in Humans. *Hypertension , 45*, 142-161.

Ramsey, M. (1991). Blood Pressure Monitoring: Automated Oscillometric Devices. *Journal of Clinical Monitoring and Computing , 7*, 55-67.

Reisner, A., Shaltis, P. A., McCombie, D., & Asada, H. H. (2008). Utility of the photoplethysmogram in circulatory monitoring. *Anesthesiology , 108*, 950-958.

Ristuccia, H. L., Grossman, P., Watkins, L. L., & Lown, B. (1997). Incremental bias in Finapres estimation of baseline blood pressure levels over time. *Hypertension , 29*, 1039-1043.

Russia

Shelley, K., & Shelley, S. (2001). Pulse oximeter waveform: photoelectric plethysmography. In C. L. Lake, R. L. Hines, & C. D. Blitt, *Clinical Monitoring: Practical Applications for Anesthesia and Critical Care* (pp. 420-428). Philadelphia: W.B.Saunders Company.

Shock, N. W., & Ogden, E. (1939). *The differences between blood-pressure measurements obtained simultaneously on the two arms.* University of California, Division of Physiology of the Medical School and the Institute of Child Welfare, Berkeley.

Slome, C., Scotch, N., Abramson, J. H., & Gampel, B. (1959). Variations in Blood Pressure in the Two Arms of Urban Africans. *American heart Journal , 58* (1).

Sorvoja, H. (2006). *Noninvasive Blood Pressure Pulse Detection and Blood Pressure Determination.* University of Oulu, Electrical and Information Engineering, Infotech Oulu.

Sorvoja, H., Myllyla, R., Karja-Koskenkari, P., Koskenkari, J., Lilja, M., & Kesaniemi, A. (2005). Accuracy Comparison of Oscillometric and Electronic Palpation Blood Pressure Measuring Methods Using Intra-arterial Method as a Reference. *Molecular and Quantum Acoustics , 26*, 235-260.

Soueidan, K.; Dajani, D. R.; Bolic, M.; Groza, V.; Chen, S. (2010). Characterization of the statistical variability of systolic and diastolic blood pressure. *Canadian Medical and Biological Engineering Conference (CMBEC'33).* Vancouver.

Soueidan, K.; Dajani, H. R.; Bolic, M.; Groza, V.; Chen, S. (2010). The effect of blood pressure variability on the accuracy of measured systolic and diastolic pressures. *International Workshop on Medical Measurements and Applications (MeMeA 2010).* Ottawa.

Stergiou, G. S., Lourida, P., Tzamouranis, D., & Baibas, N. M. (2009). Unreliable oscillometric blood pressure measurement: prevalence, repeatability and characteristics of the phenomenon. *Human Hypertension , 23*, 794-800.

Syeda, B., Gottsauner-Wolf, M., Denk, S., Pichler, P., Khorsand, A., & Glogar, D. (2003). Arterial compliance: a diagnostic marker for atherosclerotic plaque burden? *American Journal of Hypertension , 16*, 356-362.

Task force of the European Society of Cardiology the North American Society of pacing electrophysiology. (1996). Heart rate variability, Standards of meausrement, physiological interpretation, and clinical use. *Circulation , 93*, 1043-1065.

(2004). *The Seventh Report of the Joint National Committee on Prevention, Detection, and Treatment of High Blood Pressure.* National Institutes of Health (National Heart, Lung, and Blood Institute), U.S Department of health and human services. National High Blood Pressure Education Program.

Turner, K. (2000). *Arterial Blood Pressure Monitoring: An Introduction.* St Vincent's Hospital, Intensive Therapy Unit, USA.

Uusitalo, A., Laitinen, T., Vaisanen, S., Lansimies, E., & Rauramaa, R. (2004). Physical training and heart rate and blood pressure variability: a 5-yr randomized trial. *Am J Physiol Heart Circ Physiol , 286*, H1821-H1826.

Webster, J. G. (Ed.). (1998). *Medical Instrumentation, Application and Design.* USA, CANADA: John Wiley & Sons, Inc,.

Weiss, B. M., Spahn, D. R., Rahmig, H., Rohling, R., & Pasch, T. (1996). Radial artery tonometry: moderately accurate but unpredictable technique of continuous non-invasive arterial pressure measurement. *British Journal of anaesthesia , 76*, 405-411.

Weisstein, W. (2010, January 26). Normal Distribution at MathWorld.

Yang, B.-H., Zhang, Y., & Asada, H. H. (2002). *Patent No. US 6,413,223 B1.* Cambridge/USA.

Yelderman, M., & Ream, A. D. (1979). Indirect measruement of mean blood pressure in the anesthetized patient. *Anesthesiology , 50*, 253-256.